IMPAACT P1072
(DAIDS ID 10638)
Safety and Immunogenicity of a Live, Attenuated, Rotavirus Vaccine (RotaTeqTM) in HIV-Infected and Uninfected Children Born to HIV-Infected Mothers

A Multicenter, International Trial of the
International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains the current IMPAACT P1072 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #1, dated 09 January 2012
- Letter of Amendment #2, dated 30 January 2013
- Letter of Amendment #1, dated 03 October 2012
- Protocol Version 3.0, dated 10 November 2011
RE: CLARIFICATION MEMO #1 for P1072: “Safety and Immunogenicity of a Live, Attenuated Rotavirus Vaccine (RotaTeq™) in HIV-1 Infected and Uninfected Children Born to HIV-1 Infected Mothers” Version 3.0 (11/10/2011)

TO: IMPAACT Principal Investigators, Study Coordinators & Pharmacists at Sites Participating in IMPAACT P1072

FROM: P1072 Protocol Team

This is Clarification Memo #1 for IMPAACT P1072: “Safety and Immunogenicity of a Live, Attenuated Rotavirus Vaccine (RotaTeq™) in HIV-1 Infected and Uninfected Children Born to HIV-1 Infected Mothers” Version 3.0, dated November 10, 2011.

This Clarification Memo can be obtained from the P1072 protocol specific web page (http://www.impaactgroup.org/). The document is located under the section titled “Current Protocol Related Documents”.

This memo provides clarification to the discrepancy between the availability of rotavirus vaccine and the licensure of rotavirus vaccine in a specific country. These two events may occur several months to years apart. Exclusion criterion 4.34 states that “Subjects cannot be enrolled from any site at which rotavirus vaccine is available and is being administered”, while Section 6.6, describes ‘Guidelines for Managing Subjects in Countries Where RotaTeq™ Licensure Occurs During the Study’.

Please note that to comply with exclusion criterion 4.34, the text in Section 6.6 has been amended and should read as follows:

6.6. Guidelines for Managing Subjects in Countries Where RotaTeq™ Licensure Occurs
Rotavirus Vaccine becomes Available and is Being Administered during the Study

The protocol currently limits the study to sites where rotavirus vaccine is NOT available and being administered. In the situation where any rotavirus vaccine becomes available for administration RotaTeq™ licensure is obtained in a specific country while study subjects are participating in the study, the following guidelines will go into effect:

- No new subjects at that site will be enrolled into P1072.
- In conjunction with DAIDS, the team will provide instructions to the site(s) regarding how to un-blind on an individual basis. The only subjects who will be unblinded will be those who have not yet exceeded the upper age limit recommended for receiving the vaccine.
- Subjects on study who are in the PLACEBO group will receive non-study-supplied rotavirus vaccine as per national (or site) implementation if their age permits them to receive vaccine (NOTE: there are recommended limitations on upper age and specified interval). Subjects will then continue to be followed as
Subjects on study who are in the VACCINE group will complete the vaccine series per national (or site) implementation and will continue to be followed as per the protocol schedule of evaluations in Appendices IA (HIV-infected) or IB (HIV-uninfected).

Where applicable, unblinding lists for each site will be distributed as outlined in the IMPAACT Unblinding SOP (SDM-4001-01). [This document can be accessed by going to the IMPAACT website (http://www.impaactgroup.org); the user name is impaact, the password is cure. Under “Member Area,” select SOPs and Guidelines, and under Statistical Data Management section, choose SDM-4001-01.]

Every effort should be maintained by site personnel to keep study team members blinded to treatment assignment and prevent dissemination of information for these subjects.

If there are any questions, please do not hesitate to contact P1072 core team at actg.p1072cmc@fstrf.org. Thank you for your continued participation in the IMPAACT P1072 study.
DATE: January 30 2013

RE: LETTER OF AMENDMENT #2 FOR P1072, Version 3.0, dated 11/10/2011

"Safety and Immunogenicity of a Live, Attenuated, Rotavirus Vaccine (ROTATEQ™) In HIV-Infected and Uninfected Children Born To HIV-Infected Mothers"

DAIDS ES #  10638

TO: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1072

FROM: IMPAACT P1072 Protocol Team

___________________________________________________________________________

THE FOLLOWING INFORMATION IMPACTS THE P1072 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

UPON RECEIVING FINAL IRB/EC AND ANY OTHER APPLICABLE REGULATORY ENTITY (RE) APPROVAL(S) FOR THIS LoA, SITES SHOULD IMPLEMENT THE LoA IMMEDIATELY. SITES ARE STILL REQUIRED TO SUBMIT A LoA REGISTRATION PACKET TO THE DAIDS PROTOCOL REGISTRATION OFFICE (PRO) AT THE REGULATORY SUPPORT CENTER (RSC). SITES WILL RECEIVE A REGISTRATION NOTIFICATION FOR THE LoA ONCE THE DAIDS PRO VERIFIES THAT ALL THE REQUIRED LoA REGISTRATION DOCUMENTS HAVE BEEN RECEIVED AND ARE COMPLETE. A LoA REGISTRATION NOTIFICATION FROM THE DAIDS PRO IS NOT REQUIRED PRIOR TO IMPLEMENTING THE LoA. A COPY OF THE LoA REGISTRATION NOTIFICATION ALONG WITH THIS LETTER AND ANY IRB/EC CORRESPONDENCE SHOULD BE RETAINED IN THE SITE’S REGULATORY FILES.

_______________________________________________________________________________________

This memo is to inform you of recent developments related to RotaTeq™, which is administered in P1072. The following new adverse events have been identified during post-approval use of RotaTeq from reports to the Vaccine Adverse Event Reporting System (VAERS). Reporting of adverse events to VAERS following immunization is voluntary, and the number of doses of vaccine administered is not known; therefore, it is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to vaccine exposure using VAERS data. In post-marketing experience, the following adverse events have been reported following the use of RotaTeq:

Immune system disorders:
Anaphylactic reaction

Skin and subcutaneous tissue disorders:
Angioedema

Therefore, Section 1.12 ‘Rotavirus Vaccines’ has been updated with the above information. Additionally, the informed consent has been modified to include the following statements:

WHAT ARE THE RISKS OF THE STUDY?

Vaccine Risks:
The common side effects that may be expected with RotaTeq™ are: fever, vomiting, irritability, and diarrhea.

In the studies done so far, the side effects of RotaTeq™ have generally been mild. Three studies of over 70,000 infants showed that the vaccine was generally well tolerated.

Other less common side effects have been reported, **these include anaphylactic reaction and angioedema.** but none of them have been shown to be caused by the vaccine. The study doctor or staff can discuss these with you. There may be other side effects or risks that are not known at this time. The effect of the vaccination on your child’s HIV infection or chance of acquiring HIV infection are not known; however, we will closely follow all children in the study to become aware as soon as possible if this happens.

When a baby is infected with rotavirus from the environment, the virus is often found in the stool and passed on to others in this manner. A baby that receives the rotavirus vaccine may have the vaccine virus present in the stool for prolonged periods, which is something that we are testing. The vaccine virus in the stool may also be passed on and may possibly cause rotavirus infection in other non-vaccinated family members.

Germs other than rotavirus can also cause vomiting and diarrhea. The study vaccine is directed only against the rotavirus germ and not against the other germs. Your child may have diarrhea caused by rotavirus or one of the other germs.

While your baby is on this study it is very important that you and other family members wash your hands after handling your baby’s diapers to reduce the chance of spreading rotavirus to others.

You must tell your study doctor or nurse before enrolling in any other clinical trials while your child is on this study.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.
DATE: October 3rd, 2012

RE: LETTER OF AMENDMENT #1 FOR P1072, Version 3.0, dated 11/10/11

“Safety and Immunogenicity of a Live, Attenuated, Rotavirus Vaccine (ROTATEQ™) In HIV-Infected and Uninfected Children Born To HIV-Infected Mothers”

DAIDS ES # 10638

TO: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1072

FROM: IMPAACT P1072 Protocol Team

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THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

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Following an SMC review and recommendation, the P1072 team is proposing to implement the following changes:

1. Remove balanced enrollment.

   Currently enrollment of HIV-positive individuals has to be at the same rate as enrollment of HIV-negative individuals. We propose to remove this restriction so that participants can be enrolled, whether they are HIV infected or uninfected, thus allowing the team to fully enroll the HIV-uninfected arm (n=160 infants).

   This will affect the following section:

   Section 8.3 – Randomization and Stratification

2. Remove accrual limit for HIV-infected infants with CD4% ≥20%.

   Currently there is an accrual limit of 80 infants with CD4% ≥20% (stratum 2a). The study was never powered to detect differences by CD4% stratum within the HIV-infected group and given the difficulty in finding infants with lower CD4%, we propose to remove this enrollment restriction.
This will affect the following sections, where the accrual limit by CD4 stratum is mentioned:

- Schema – Stratification
- Section 3.0 – Study Design
- Section 8.4 – Sample Size and Accrual

3. Sample Informed Consent for Mothers

Based on a recent monitor’s citing of an informed consent violation at a site, it has come to the attention of the Protocol Team that the parental statement embedded in the P1072 protocol and informed consent is not sufficient and that a separate informed consent should have been obtained from the mother. Since version 1.0, private, identifiable information, including CD4 counts, ARV medication history, and intercurrent diarrheal illnesses is being collected from the infant’s mother which makes the mother a participant in the research. Legally effective informed consent needs to be obtained from the mother, as required under the HHS regulations at 45 CFR 46.116. Unfortunately, until recently, no one identified the infant’s mother as a participant in the research. DAIDS OPCRO has been consulted and indicated that it will not be necessary to re-consent all the prior participants who: (a) have been enrolled and are (b) already off study, unless required by your IRB/EC. All participants enrolled prospectively from when your IRB/EC’s approval is obtained will need a separate mother’s informed consent before medical information can be obtained from her the infant’s mother. Those still on study at the time of approval by your IRB/EC will need to be re-consented with the informed consent for the mother.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.
SHORT TITLE FOR THE STUDY: Rotavirus Vaccine (RotaTeq™) Study

INTRODUCTION

You are being asked to allow you and your baby to take part in this research study because when the mother of a baby is infected with the human immunodeficiency virus (HIV), the baby may also be infected with HIV. Children who are HIV-1 infected, and are currently taking anti-HIV medications or are going to start taking anti-HIV medications as well as those who are HIV-uninfected, are being asked to take part in this study. This study is sponsored by the National Institutes of Health (NIH) in the United States of America. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you and your baby will be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Rotavirus is the leading cause of severe diarrhea in infants and young children throughout the world. Almost every child in the world is infected with rotavirus by 3 to 5 years of age. Rotavirus infection in infants can lead to severe vomiting, diarrhea and dehydration. Research in South Africa and the United States has shown that the symptoms of rotavirus diarrhea may be worse in HIV-1 infected patients that have other medical problems such as poor nutrition or other infections, and rotavirus infection may interfere with their nutrition.

Many infants in Africa who will be getting this vaccine (called RotaTeq™) have HIV-1 infection, and there is not enough information on how HIV-1 infected children will respond to this vaccine.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

At each of your baby’s study visits, you will be asked some questions about your health, where you get your water from, what you fed your baby since his/her birth, any anti-HIV medications you may be taking, as well as if you had any diarrhea in between study visits.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You / your child will receive no known benefit from being in this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 320 children, and their mothers will take part in this study; 160 HIV-1 infected and 160 HIV-uninfected children.

HOW LONG WILL I BE IN THIS STUDY?
You will be in this study for as long as your baby remains in the study; typically about 8 months.

WHAT OTHER CHOICES DOES I HAVE BESIDES THIS STUDY?

You may choose to not to participate in this study. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. 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 records may be reviewed by the US Food and Drug Administration (FDA), (insert name of site) IRB/EC, US National Institutes of Health (NIH), NIAID, US Office of Human Research Protections (OHRP), study staff, study monitors, the drug company supporting this study (Merck & Co., Inc.) and their designees.

WHAT ARE THE COSTS TO ME?

You will not be expected to pay for any study related visits.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study or take your baby out of the study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your baby's health, welfare or willingness to stay in this study. Let the study staff know if you want the results of the study.

WHAT DO 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 subject, contact:
  • name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
  • telephone number of above
SIGNATURE PAGE

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’s Signature and Date

____________________________  ______________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

____________________________
Study Staff Conducting
Consent Discussion (print)

____________________________
Study Staff Signature and Date

____________________________  ______________________________
Witness’ Name (print)    Witness’s Signature and Date
(As appropriate)
SAFETY AND IMMUNOGENICITY OF A LIVE, ATTENUATED ROTAVIRUS VACCINE (RotaTeq™) IN HIV-1 INFECTED AND UNINFECTED CHILDREN BORN TO HIV-1 INFECTED MOTHERS

A Limited Center, International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

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

Pharmaceutical Support Provided by:
Merck & Co., Inc.

IND # 13,979

IMPAACT Complications
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Protocol Vice Chair: Werner Schimana, M.D.
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NICHD Medical Officer: George Siberry, M.D., M.P.H.
Clinical Trials Specialist: Elizabeth Petzold, Ph.D.

Version 3.0
FINAL
November 10, 2011
All questions concerning this protocol should be sent via e-mail to actg.teamp1072@fstrf.org. Questions concerning patient management should be sent to the Core Team (actg.p1072cmc@fstrf.org). Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1072@fstrf.org. All decisions requiring immediate attention, i.e. within 48 hours, will be made by the Protocol Investigators at the international sites. This study will not be conducted at US sites. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail rscsafetyoffice@tech-res.com or call 1-800-537-9979 or 301-897-1709, or fax 1-800-275-7619 or 301-897-1710. To order study agent, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, contact the Data Management Center at sdac.random.desk@fstrf.org.

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## List of Commonly Used Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette-Guerin Vaccine</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CCHMC</td>
<td>Cincinnati Children’s Hospital Medical Center</td>
</tr>
<tr>
<td>CMI</td>
<td>Cell-mediated immunity</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>DHHS</td>
<td>Department of Health &amp; Human Services</td>
</tr>
<tr>
<td>DTwP</td>
<td>Diptheria, Tetanus toxoid, killed whole-cell Pertussis Vaccine</td>
</tr>
<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
</tr>
<tr>
<td>EIA</td>
<td>Enzyme ImmunoAssay</td>
</tr>
<tr>
<td>EndoCAB</td>
<td>Endotoxin Core Antibodies</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization (WHO)</td>
</tr>
<tr>
<td>GALT</td>
<td>Gut-Associated Lymphoid Tissue</td>
</tr>
<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titer</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
</tr>
<tr>
<td>HepB</td>
<td>Hepatitis B Vaccine</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus Influenza Type B Vaccine</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>LBP</td>
<td>Lipopolysaccharide Binding Proteins</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral Poliovirus Vaccine</td>
</tr>
<tr>
<td>PPD</td>
<td>Pharmaceutical Product Development</td>
</tr>
<tr>
<td>RSC</td>
<td>Regulatory Support Center</td>
</tr>
<tr>
<td>RRV-TV</td>
<td>Rhesus Rotavirus Tetravalent Vaccine</td>
</tr>
<tr>
<td>SADR</td>
<td>Suspected Adverse Drug Reactions</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>sCD-14</td>
<td>Soluble CD-14</td>
</tr>
<tr>
<td>SCID</td>
<td>Severe Combined Immunodeficiency</td>
</tr>
<tr>
<td>SMC</td>
<td>Study Monitoring Committee</td>
</tr>
<tr>
<td>SNA</td>
<td>Serum Neutralizing Antibody</td>
</tr>
<tr>
<td>US HHS</td>
<td>United States Department of Health &amp; Human Services</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Summary of Changes
Safety and Immunogenicity of a Live, Attenuated Rotavirus Vaccine (RotaTeq™) in HIV-1 Infected and Uninfected Children Born to HIV-1 Infected Mothers, Version 3.0, dated November 10, 2011

All changes in this version appear in boldface type. Major changes are listed below. Editorial changes, including corrections of typographical errors and other changes required to update information not affecting regulatory issues or the Sample Informed Consent may also be included. Information from Letter of Amendment #1 (6/14/10), Letter of Amendment #2 (8/20/10), Letter of Amendment #3 (11/09/10) and Clarification Memo #1 (2/17/11) are included.

1) The team roster has been updated.
2) Protocol Team Roster – the following text has been added: “Questions concerning patient management should be sent to the Core Team (actg.p1072cmc@fstrf.org).”
3) The investigator roster has been updated.
4) Schema, Section 3.0, Section 8.3 & Section 8.52 - The CD4 stratification of the HIV-1 infected subjects at entry has been changed to:
   - Stratum 2a – CD4 ≥20%
   - Stratum 2b – 15% ≤ CD4 < 20%
5) Section 1.13 - Transmission of vaccine-derived (RotaTeq™) rotavirus was reported in a recent paper; this new information has been added.
6) Section 1.13 - Based on post-marketing reports of gastroenteritis in infants with Severe Combined Immunodeficiency (SCID), the US package insert was updated; as such, the text has been updated in the rationale.
7) Section 1.2 - Due to the completion of a clinical trial with RotaTeq™ in Asia and Africa, Merck has provided updated safety information which has been added throughout the section.
8) Section 3.0 – The following text has been clarified: “...to determine the presence of HIV-1 DNA (or RNA) in the blood of the infant...”
9) Section 3.0, Section 4.18 and Schedule of Evaluations (Appendix IA, footnote #16) - At the direction of the SMC, “ALL HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ART) before, or at the time of, administration of the 1<sup>st</sup> dose of study vaccine/placebo. NOTE: It is <u>not</u> acceptable for subjects to take a prescription home with them to start ARV therapy on the day of vaccination” has been added.
10) Section 3.1, 3<sup>rd</sup> paragraph – The following text has been revised: “Either HIV-1 DNA PCR or HIV-1 RNA PCR will be collected at screening. HIV-1 RNA (infected) or HIV-1 DNA (uninfected) will also be determined on blood drawn just prior to the first dose of vaccine/placebo (Entry).”
11) Section 3.1, 4<sup>th</sup> paragraph – The following text has been added: “Additional testing for other potential pathogens may be conducted.”

10
12) Section 4.22 – The following text has been added: “Subjects must be <32 weeks of age at the time of the 3rd vaccine/placebo dose.”

13) Section 4.32 – The following text has been deleted and all subsequent sections have been re-numbered: “Receipt of any blood or blood products since birth or prior to receiving any dose of study vaccine or planned, during the duration of the study.”

14) Section 4.35 – The following text has been added: “Any condition, which would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.”

15) Section 4.36 – The following text has been added: “Any other condition, situation, or clinically significant finding (other than HIV infection) that, in the investigator’s opinion, would interfere with study participation, or interpretation.”

16) Section 4.37 - The following text has been added: “Subjects with a known history of SCID or intussusception.”

17) Section 4.41; Section 6.3; Section 8.51; Section 8.52 – The text has been revised to state: “More than 20% of subjects (or more than four if less than 20 have been enrolled) in any stratum have experienced ≥ grade 3 possibly/probably/definitely vaccine-related adverse events.”

18) Section 4.6 – The enrollment procedure language has been updated at the direction of the DAIDS RSC.

19) Section 5.11 – The text in this section has been re-structured and re-worded for clarity.

20) Section 5.12 – Addition of text describing the requirement for a visual check of the vaccine pouch prior to administration.

21) Section 5.2 – The following text has been added: “In the manufacturing process for RotaTeq™, a porcine-derived material is used, DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq™ PCV-1 and PCV-2 are not known to cause disease in humans.”

22) Section 5.3 (2nd paragraph) and sample informed consent (Appendix III) – Antiretroviral therapy will NOT be provided as part of the study medications has been added. These medications will be provided via local access programs or through standard of care.

23) Section 5.3 (4th paragraph) – The following text has been revised: “All unused study vaccine must be returned to the NIAID CRPMC after the study is completed or terminated, or managed as directed by the NIAID procedures on handling unused study products.”

24) Section 6.1; Section 6.2; Section 8.5: “The following text has been revised: “Toxicities will be graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December, 2004, Clarification August 2009, which is available on the RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance).”
25) Section 6.2 (1st paragraph); Section 6.2 (7th paragraph) – The following text has been added: “Additional testing for other potential pathogens will be conducted.”

26) Section 6.2 (2nd paragraph); footnote #4 in Schedule of Evaluations (Appendix IA) – At ALL scheduled/unscheduled study visits (including clinic/office or home visits), a directed history and clinical exam, including an abdominal exam to exclude any signs of intussusception, should be carried out. Sites are also encouraged to follow-up on tests/investigations (e.g. X-rays) that are ordered on a study participant to ensure that the participant was able to complete them.

27) Section 6.2, (7th paragraph) – Amount of stool to be collected has been corrected to 6ml to be consistent with the Schedule of Evaluations.

28) Section 6.6 – Guidelines for Managing Subjects in Countries Where RotaTeq™ Licensure Occurs During the Study.

The following text has been added to describe how to manage subjects on study in a country that obtains licensure during the study.

“The protocol currently limits the study to sites where rotavirus vaccine is not licensed. In the situation where RotaTeq™ licensure is obtained in a specific country while study subjects are participating in the study, the following guidelines will go into effect:

- No new subjects at that site can be enrolled into P1072.
- In conjunction with DAIDS, the team will provide instructions to the site(s) regarding how to un-blind on an individual basis, ONLY the affected subjects who are within the age range where they could receive the full series of three vaccinations.
- Subjects on study who are in the PLACEBO group will receive study vaccine as per national (or site) implementation if their age permits them to receive vaccine (NOTE: there are recommended limitations on upper age and specified interval). Subjects will then continue to be followed as per the protocol schedule of evaluations in Appendices IA (HIV-infected) or IB (HIV-uninfected).
- Subjects on study who are in the VACCINE group will complete the vaccine series per national (or site) implementation and will continue to be followed as per the protocol schedule of evaluations in Appendices IA (HIV-infected) or IB (HIV-uninfected).
- Where applicable, unblinding lists for each site will be distributed as outlined in the IMPAACT Unblinding SOP (SDM-4001-01).

[This document can be accessed by going to the IMPAACT website (http://www.impaactgroup.org); the user name is impaact, the password is cure. Under “Member Area,” select SOPs and Guidelines, and under Statistical Data Management section, choose SDM-4001-01.]
• Every effort should be maintained by site personnel to keep study team members blinded to treatment assignment and prevent dissemination of information for these subjects.

29) Section 6.4 – The text has been updated: “Possibly/probably/definitely vaccine-related toxicity that requires permanent study drug discontinuation as defined in Section 6.1.”

30) Section 7.1; Section 7.2; Section 7.3; Section 7.4 - The Expedited Adverse Event (EAE) reporting language has been updated.

31) Section 8.212; Section 8.62 - The text has been updated to state: “A positive response is defined as a ≥3-fold rise over pre-vaccine levels at least 14 days after the third vaccination.”

32) Section 8.221; Section 8.222 – The following text has been revised: “The presence of vaccine-virus strains in the stools will be assessed by the following assays: Enzyme ImmunoAssay (EIA) rotavirus antigen detection, testing for infectious virus (e.g. Florescent Focus Assay (FFA), RT-PCR specific for specific for rotavirus gene 6, which codes for the VP6 protein.”

33) Section 8.221; Section 8.222 – The following text has been added: “Additional molecular characterization of rotavirus strains and testing of specimens for other potential pathogens may be conducted.”

34) Section 8.4, Table 3 – The heading in column 3 has been changed: “Annual Immunogenicity benefit of RotaTeq™ (Arm 1-2).”

35) Section 8.5, paragraph 1 – The text has been updated as follows: “The SMC will conduct two early unblinded interim safety analyses (see Section 8.52) and yearly unblinded reviews….. Data summaries will be by treatment group.”

36) Section 8.5, paragraph 3 – The text has been updated as follows: “It will be important to only trigger unscheduled safety reviews by the SMC if adverse event rates are higher than the expected….”

37) Section 8.5 – The text has been updated to reflect the change from 26 weeks to 34 weeks for the maximal duration after initial dosing for each subject participating in Protocol P1072.

38) Section 8.51 – The text has been revised as follows: “If at any time the Core Team determines…….the study may be suspended pending a thorough investigation by the SMC.”

39) Section 8.52, Table 4 - The headings in columns 2-5 have been changed to state: “≥Grade 3”

40) Section 8.62, 2nd paragraph – The text has been changed to state: “Summaries of differences in the geometric mean titer (GMT) between the pre and post-vaccine levels are will be presented with confidence intervals. Correlations of changes in titer levels (on the log_{10} scale) from GMT between pre to and post vaccine levels will be calculated between IgA ELISA responses.”

41) Section 9.2 – NIH has been added to the entities that have to give written permission of the subject for clinical information to be released.
42) Section 11.0 – Biohazard containment guidelines and hyperlink have been updated.

43) The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events reference has been updated throughout the protocol.

44) References to the RCC (Regulatory Compliance Center) and website links have been updated to the Regulatory Support Center (RSC) throughout the protocol.

45) Appendix I - For clarification purposes, the Schedule of Evaluations has been separated into two schedules:

   Appendix IA – Schedule of Evaluations for HIV-1 Infected Infants
   Appendix IB – Schedule of Evaluations for HIV-1 Uninfected Infants

Appendix IA and IB have also been amended to reflect the following changes:

a. A DNA PCR for HIV nucleic acid is the preferred test at screening. However, if only an RNA test is available, this is acceptable (Appendix IA, footnote 14; Appendix IB, footnote 13).

b. The amount of stool to be collected should be 6ml rather than 6mg. Additionally, stool specimens are no longer required to be split into two cryovials for shipment. Stool should be stored and shipped in the fecal tubes provided by Merck. As such, footnote #5 has been updated to state: “Stool specimens: Refer to the LPC. Minimum of 6mL required. Plastic containers (large fecal tubes with scoops) will be provided for collection and shipment of stool samples.” (Footnote 5)

c. The number of subjects who will have PBMC collected and cryopreserved has been increased to 100 for HIV-1 infected infants and 100 for HIV-1 uninfected infants (Footnote 7)

d. Dried Blood Spots (DBS) should now be collected at the following visits:
   
   HIV-Infected: Dose # 1 day 0 (Entry)
   HIV-Uninfected: Dose # 1 day 0 (Entry), Dose # 2 day 0 and Dose # 2 day 21

e. Footnote 15 (Appendix IA) and footnote 14 (Appendix IB) have also been clarified to state that each filter paper card will contain 5 filled blood spots, rather than 2 spots.

f. If only one test result is available to document the subject being HIV-positive (from the screening result or other documented test), the investigator may proceed with enrolling the subject and should use the Entry (Dose #1 Day 0) blood draw to perform an HIV RNA PCR test for HIV infection. The site DOES NOT have to perform the test before enrollment but blood for this test must be collected prior to administration of the study vaccine (Appendix IA - footnote 8)

g. At the Dose 3, Day 14 visit, if the infant weighs less than 5kg, the indicated tests should be omitted and only the anti-rotavirus antibody
and PBMCs for CMI should be drawn. The omitted tests should be drawn at the Dose 3, Day 42 visit instead. (Appendix IA – footnotes 11 & 12; Appendix IB – footnotes 10 & 11)

h. Appendix IA, footnote 17 has been added: “If HIV-1 DNA PCR is unavailable at screening, HIV-1 RNA PCR may also be used.”

46) Appendix II – Planned Laboratory Testing on Collected Specimens – this Appendix has been added to the protocol.

47) Appendix III - Informed Consent Form: The following text has been added:
   a. **Introduction**
   The following text has been added: “Children who are HIV-1 infected, and are currently taking anti-HIV medications or are going to start taking anti-HIV medications as well as those who are HIV-uninfected, are being asked to take part in this study.”

   b. **Why is this study being done?**
   The following text has been added: “If the vaccine becomes available in your country while your child is participating in this study, your child will NOT be taken off study, unless you request that your child stop participating. Those children receiving placebo will receive active vaccine if they are eligible. Those children receiving active vaccine will complete the vaccine series. Your child will then be followed on study on the normal schedule described below.”

   c. **What does my baby have to do if he/she is in the study?**
   **First Vaccine**
   The following text has been revised: “On the day that your infant receives his/her first vaccine, a stool specimen will be collected to test for the presence of rotavirus in the stool or if there are any antibodies in your baby’s bowels. Tests for other germs in the stool may also be done. In addition, about 1½ teaspoons (7.5 mL) of blood will be taken to measure your baby’s antibodies to the rotavirus. **Additional tests related to the rotavirus vaccine may also be done.**”

   **Second Vaccine**
   “Just before the second vaccine, if your baby is not HIV-infected, a drop of his/her blood will be collected for testing at a later date.” “In addition, if your baby is not HIV-infected, another drop of your baby’s blood will be collected on a piece of paper at day 21 after the second dose of vaccine for later testing.”

   **Third Vaccine**
   “Your child’s blood may also be drawn for HIV testing on days 14 or 42 after the third vaccine.”

   d. **What are the risks of the study?**
   The following text has been added: “When a baby is infected with rotavirus from the environment, the virus is often found in the stool and passed on to others in this manner. A baby that receives the rotavirus vaccine may have the vaccine virus present in the stool for
prolonged periods, which is something that we are testing. The vaccine virus in the stool may also be passed on and may possibly cause rotavirus infection in other non-vaccinated family members.”

e. What are the costs to me?
The following text has been added: “The anti-HIV medications your baby is taking will not be provided by the study.

48) Appendix IV – Background and Rationale for P1072.
The following text has been added:
a. Ensuring That Subjects Will Not be Denied Access to Care.
The following text has been added: “This information is included in the exclusion criteria and management procedures described in detail in section 6.6 entitled: “Guidelines for Managing Subjects in Countries Where RotaTeq™ Licensure Occurs During the Study.”
b. Minimizing Risks to Subjects - (1st paragraph)
“Per Letter of Amendment #3 (November 9, 2010), all HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ARV) before, or at the time of, administration of the 1st dose of study vaccine/placebo. It is not acceptable for subjects to take a prescription home with them to start ARV therapy on the day of, and following, vaccination.”
c. Minimizing Risks to Subjects - (4th paragraph)
“Additionally, as of October 2011, 96 subjects have enrolled into the P1072 protocol. To date, none of these subjects have experienced any severe gastroenteritis events following vaccination(s).”
SCHEMA

SAFETY AND IMMUNOGENICITY OF A LIVE, ATTENUATED ROTAVIRUS VACCINE (RotaTeq™) IN HIV-1 INFECTED AND UNINFECTED CHILDREN BORN TO HIV-1 INFECTED MOTHERS

DESIGN: Phase II, randomized, double-blind, placebo controlled.


POPULATION: Children age ≥2 weeks to <15 weeks at time of screening, born to an HIV-1 infected mother. The screening must be completed so that the first dose of vaccine can be administered when the subject is between ≥4 to <15 weeks of age.

STRATIFICATION: HIV-1 infection status of the infant will be determined at screening by HIV-1 DNA (or RNA) testing. Lymphocyte subsets (including CD4 count and CD4%) in blood will also be obtained at screening on all infants. On the basis of the screening tests, subjects will be stratified into 4 strata:

<table>
<thead>
<tr>
<th>Stratum</th>
<th>CD4%</th>
<th>Number</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV-1 Uninfected</td>
<td>N=160</td>
<td>80 Vaccine 80 Placebo</td>
</tr>
<tr>
<td>2a</td>
<td>HIV-1 Infected</td>
<td>CD4≥20%</td>
<td>N=80</td>
</tr>
<tr>
<td>2b</td>
<td>HIV-1 Infected</td>
<td>15%≤CD4&lt;20%</td>
<td>N=60</td>
</tr>
<tr>
<td>2c</td>
<td>HIV-1 Infected</td>
<td>CD4&lt;15%</td>
<td>N=20</td>
</tr>
</tbody>
</table>


REGIMEN: Subjects will receive three doses (2.0 mL each) of either a live attenuated rotavirus vaccine (RotaTeq™) or placebo. The first dose will be given when subjects are between ≥4 to <15 weeks of age and subsequent doses will be given at intervals of 4 to 10 weeks. The third dose must be administered by 32 weeks of age. Subjects will be followed for adverse events after the first and second doses and for 6 weeks after the third dose.

STUDY DURATION: Approximately 6 weeks after the last subject receives the last dose of study vaccine.

OBJECTIVES:

Primary

1. To evaluate the safety of any dose of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.

2. To evaluate the immunogenicity of a 3-dose regimen of RotaTeq™ in HIV-1 infected and uninfected children born to HIV-1 infected mothers, as measured by serum anti-rotavirus IgA ELISA and serum neutralizing antibody [SNA] responses to serotypes G1, G2, G3, G4, and P1A[8].

Secondary

1. To evaluate the fecal shedding of RotaTeq™ strains after each dose of RotaTeq™ given to HIV-1 infected and uninfected children born to HIV-1 infected mothers.

2. To evaluate the relationship of anti-rotavirus serologic immune responses to CD4 cell count and/or CD4%, plasma RNA or DNA, and antiretroviral therapy (ART) after a 3-dose regimen of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.

3. To evaluate the safety of any dose of RotaTeq™ given to HIV-1 uninfected children born to HIV-1 infected mothers.

4. To compare the incidence of HIV-1 infection at the last study visit between those receiving rotavirus vaccine and placebo among the infants who were not HIV-1 infected at enrollment.
Exploratory

1. To evaluate the relationship between virus shedding and rotavirus-specific SNA antibodies, copro-antibodies, and cell-mediated immunity (CMI) against rotavirus vaccine serotypes in recipients of the rotavirus vaccine.

2. To evaluate IgA and IgG copro-antibodies and CMI responses against rotavirus serotypes contained in the vaccine in HIV-1 infected versus uninfected infants born to HIV-1 infected mothers.

3. To compare in HIV-1 infected recipients of rotavirus vaccine or placebo the CD4% at the last study visit and the change in CD4% from the first study visit to the last study visit.

4. To assess how microbial translocation changes in response to vaccination with RotaTeq™ relative to placebo in HIV-1 infected and HIV-1 uninfected infants.

5. To evaluate the relationship of mucosal and cell-mediated immune responses to CD4 cell count and/or CD4%, plasma RNA or DNA, and ART after a 3-dose regimen of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.
1.0 INTRODUCTION

1.1 Background

1.11 Rotavirus Disease Burden

Rotavirus is the leading cause of severe diarrhea in infants and young children, accounting for 45% of severe diarrhea disease in both developed and developing countries.\(^1,2\) Virtually all children throughout the world are infected with rotavirus by the time they are 3 to 5 years old, regardless of socioeconomic status or environmental conditions.\(^2\) Annually, rotavirus causes approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations, and 352,000 to 592,000 deaths (median, 440,000 deaths) in children less than 5 years of age, of which approximately 90% of hospitalizations and 99% of deaths occur in developing countries.\(^1\)

Although rotavirus infection is not more common in HIV-1 infected children, it complicates their care and interferes with their nutrition. The morbidity of these infections can be greater in HIV-1 infected children when there is concomitant wasting, malnutrition, and/or opportunistic infections. A survey of five Pediatric AIDS Clinical Trials Group (PACTG) international sites indicated that the symptoms of rotavirus diarrhea were often more marked in their HIV-1 infected patients (PACTG survey of international sites; 2003). In Cape Town, South Africa, 13-55% of hospital admissions for diarrhea-associated dehydration were caused by rotavirus infection and the severity tended to be greater in malnourished children. The proportion of rotavirus-infected children with co-morbid HIV infection reflected the HIV prevalence in the community.\(^3\) In Durban, South Africa, HIV-1 infected children admitted to the hospital with diarrheal disease have multiple co-morbidities and a subsequent high mortality rate.\(^3\)

In the United States (US) the combined hospitalizations, physician visits, and expense of childhood rotavirus infection were sufficient to justify a universal recommendation to administer a rotavirus vaccine for prevention of this disease.\(^4,5\)

1.12 Rotavirus Vaccines

After more than 15 years of development and clinical trials, the live-attenuated rhesus rotavirus tetravalent vaccine (RRV-TV), called
RotaShield™, was licensed by the US Food and Drug Administration (FDA) in August, 1998. In July 1999, after nearly 1.5 million doses had been administered, the Centers for Disease Control recommended postponing any further RRV-TV administration due to the association of the vaccine with intussusception (a rare form of bowel obstruction in which one segment of bowel becomes enfolded within another segment), and RRV-TV was removed from the market in October 1999.\(^6\)\(^7\)

Merck & Co., Inc.’s live rotavirus vaccine, RotaTeq\(^{TM}\), is a pentavalent combination vaccine of five human-bovine reassortant rotavirus strains (WI79-9, SC2-9, WI78-8, BrB-9, and WI79-4 – designated as G1, G2, G3, G4, and P1, respectively for simplicity). The G1, G2, G3, and G4 reassortant rotavirus strains contain the four rotavirus G serotypes (G1-G4) known to cause >85% of all rotavirus gastroenteritis worldwide, and the P1 rotavirus reassortant strain contains the most common P serotype (P1A) associated with rotavirus gastroenteritis.\(^4\) Three doses are administered orally, with the first dose being given at age ≥4 to <15 weeks and subsequent doses following at 4 to 10-week intervals. In Phase II trials, RotaTeq\(^{TM}\) was generally well tolerated with no statistically significant vaccine-related increase in the incidence of fever, vomiting, diarrhea, and irritability relative to placebo.\(^8\)\(^9\) Phase II trials showed that RotaTeq\(^{TM}\) prevented ~100% of severe rotavirus disease and ~70% of any rotavirus disease regardless of severity.\(^9\) In Phase III clinical trials, RotaTeq\(^{TM}\) prevented approximately 98% of severe rotavirus gastroenteritis and approximately 74% of rotavirus gastroenteritis of any severity caused by the rotavirus serotypes in the vaccine. RotaTeq\(^{TM}\) was also generally well tolerated with respect to all adverse experiences including the adverse experiences of special clinical interest for this vaccine, diarrhea, fever, irritability, and vomiting.\(^10\)\(^11\) Data from a large-scale clinical trial (approximately 70,000 subjects) to evaluate the safety of RotaTeq\(^{TM}\) with respect to intussusception showed that the vaccine did not increase the risk of intussusception relative to placebo during the 42-day period after any dose;\(^10\)\(^11\) there were 6 cases in the group that received vaccine and 5 cases in the placebo group (relative risk = 1.6; 95% CI: 0.4, 6.4), and there was no temporal clustering or relationship to dose number as had been observed with RRV-TV.\(^10\)\(^11\) In addition, the Phase III clinical trials also showed that RotaTeq\(^{TM}\) was generally well tolerated with respect to other adverse experiences. There was a slight increase in mild diarrhea or vomiting during the week after a dose of RotaTeq\(^{TM}\); the incidence of fever and irritability was comparable
among recipients of RotaTeq™ and placebo recipients. Fecal shedding of vaccine-virus strains occurs in a low proportion of subjects and occurred almost exclusively during the week after dose 1. In the Phase III studies in which fecal shedding of vaccine-virus strains was evaluated, 8.9% of subjects shed vaccine after dose 1 and only 1 subject shed vaccine after dose 3.\(^{(11)}\)

The efficacy, immunogenicity, and safety of RotaTeq™ when administered concomitantly with licensed pediatric vaccines were also evaluated in Phase III trials, which included diphtheria, tetanus toxoid and pertussis, inactivated poliovirus, Haemophilus b conjugate, hepatitis B, and pneumococcal conjugate vaccines. RotaTeq™ was generally well tolerated, immunogenic, and efficacious when administered concomitantly with these vaccines.\(^{(10)}\) In addition, the immunogenicity of the licensed pediatric vaccines was unaffected by RotaTeq™. Finally, in the large pivotal trial there was a 96% reduction in hospitalizations, an 86% reduction in physician visits, and a 94% reduction in emergency visits for rotavirus-related diarrhea in vaccinees as compared with placebo recipients.\(^{(12)}\) An attenuated G1P1A[8] human rotavirus vaccine, Rotarix™ (GlaxoSmithKline [GSK]), is licensed in many countries.\(^{(13)}\) This vaccine will not be used in the current trial.

RotaTeq™ was licensed by the FDA on February 3, 2006. The Advisory Committee on Immunization Practices (ACIP) recommended on August 11, 2006 that it be administered to all infants in the United States.\(^{(14)}\) The ACIP has recently extended the recommended upper age limit for instituting RotaTeq™ to <15 weeks.

### 1.13 Safety Considerations for HIV-1 infected Children in the Developing World

The safety of RotaTeq™ will need to be demonstrated in HIV-1 infected infants given the relatively high prevalence of HIV-1 in some developing countries. Based on the biological properties of the vaccine strains, it is anticipated that RotaTeq™ will be well tolerated in HIV-1 infected infants despite the fact that it is a live virus vaccine. The human-bovine reassortants are naturally attenuated for humans, replicating relatively poorly in the intestinal tract. Studies conducted in the United States, Latin America, and several countries in Africa showed that the natural course of rotavirus disease is similar in HIV-1 infected and uninfected infants.\(^{(15-20)}\) The severity of symptoms, duration of hospitalization and age at presentation does not appear to differ by HIV-1 infection status overall, but may be enhanced when there are preexisting conditions
such as malnutrition or other infections. Shedding of rotavirus occurs for up to 3 weeks after onset of symptoms in a higher proportion of HIV-1 infected than uninfected infants; however, the shedding was asymptomatic.\(^{(15)}\)

Live oral rotavirus vaccines are known to be shed in stools. A recent paper reports on a single occurrence of transmission of vaccine-derived rotavirus from a vaccinated infant to an older, unvaccinated sibling that resulted in symptomatic rotavirus gastroenteritis requiring emergency department care (21). This single occurrence was detected among an active surveillance population of >141,000 children younger than five, which, as the authors note, "suggests that it is not a common phenomenon." This is the first reported confirmed occurrence vaccine-derived rotavirus transmission associated with RotaTeq™.

The risk of transmission for RotaTeq™ is considered to be very low as both the quantity and frequency of vaccine virus shed among healthy recipients of RotaTeq™ are known to be low. Shedding was evaluated among a subset of subjects in the large-scale Phase III clinical trial. The data showed that RotaTeq was shed in low quantities in the stools of 32 of 360 vaccine recipients tested after dose 1, 0 of 249 vaccine recipients after dose 2, and in 1 of 385 vaccine recipients after dose 3. Transmission of vaccine virus from vaccine recipients to unvaccinated contacts was not evaluated in the clinical program. The risk of transmission of vaccine virus could be further mitigated by scrupulous hygienic practices.

The risk of transmission may be increased from immunocompromised contacts, such as HIV-1 infected individuals. However, it is very likely that shedding of wild-type rotavirus to others in the environment presents a greater risk than shedding of vaccine strain. Rotavirus vaccine is naturally attenuated in humans; therefore, the risk and the clinical consequences of transmission are anticipated to be relatively low.

Merck & Co., Inc. made changes to the U.S. Physician Prescribing Information for RotaTeq™ to include the information that infants with Severe Combined Immunodeficiency Disease (SCID) should not receive RotaTeq™ (see exclusion criterion 4.37). This was based on post-marketing reports of gastroenteritis associated with vaccine virus in infants who were vaccinated with RotaTeq™ before they were
diagnosed with having SCID (22). SCID is extremely rare and caused by a very serious genetic defect that has been estimated to affect 1:100,000 to 1:500,000 live births. SCID is the most severe of all recognized immuno-deficiencies – it is characterized by the absence of T- and B-cell function from birth. Without bone marrow transplantation or enzyme replacement therapy, children with SCID usually die within the first year of life. Given that HIV-1 is a less severe immunodeficiency and based on the biological properties of the vaccine strains as well as previous data that showed that the natural course of rotavirus disease is similar in HIV-1 infected and uninfected infants, it is anticipated that RotaTeq™ will be well tolerated in HIV-1 infected infants.

Another factor that supports the safety of RotaTeq™ in HIV-1 infected infants is the tolerability of oral poliovirus vaccine (OPV) in this population. OPV is a live vaccine that replicates much more robustly in the intestinal tract than RotaTeq™. The World Health Organization (WHO) estimates indicate that >750,000 doses of OPV have now been administered to HIV-1 infected infants with no evidence of an increased risk of vaccine-associated paralytic poliomyelitis. Even in resource-poor countries, unexplained paralysis in infants who received OPV would be noticed. OPV has much greater pathogenic potential and is known to revert to disease-producing variants, whereas this is not a possibility for RotaTeq™.

In sub-Saharan Africa where breast-feeding is critical for infant survival, nearly 40% of new HIV-1 infections in children occur through breast-feeding (24). The overall rate of postnatal HIV-1 transmission through breast-feeding is estimated to be 16% among infants continuing to breast-feed into the second year of life. (25) The risk of transmission to the infant is approximately 14% in women with established infection and 29% among those with primary HIV-1 infection. (25) Most of the HIV-1 transmission through breast-feeding occurs during the first 14-weeks of life (70% of infections), but the risk continues as long as breast-feeding continues. Two randomized clinical trials showed that breast-milk transmission of HIV-1 can be reduced with extended daily dosing of nevirapine (26). In the PEPI-Malawi study, the cumulative risk of postnatal infection between birth and 14 weeks was estimated at 8.4% among HIV-1 exposed, breast-fed, infants who received a single dose of nevirapine at birth and one week of post-natal zidovudine compared to 2.8% in the extended-prophylaxis groups receiving daily nevirapine with or without zidovudine. The overall net difference of approximately 5%
between the extended-prophylaxis groups and the control group was maintained at 24 months of age. Together, these data support that most of the HIV-1 infections related to breast-feeding occurs by 14-weeks of age, with a substantially lowered risk beyond that age. Whether the administration of oral viral vaccines increases breast-milk-associated HIV-1 transmission is unknown, and will be examined in the context of this study. Although research in this area is rapidly evolving, opportunities to interdict this transmission at the study sites are currently limited by prevailing cultural norms and resources. The Protocol Team will regularly review this problem on Team calls and will encourage adoption of proven methods for preventing transmission by breastfeeding route – such as exclusive breastfeeding and prolonged use of antiretrovirals in the post-natal period – so that they can be adopted when feasible. The protocol is flexible in including such changes in post-partum management of infants born to HIV-1 infected mothers. While changes in management during the study may complicate the final analyses, these changes will be encouraged, and analyses will be adjusted to compensate for them.

P1072 will not enroll infants in the US because of the small number of HIV-1 infected infants available for the trial, and the necessity for studying the rotavirus vaccine in HIV-1 infected and HIV-1 uninfected infants in similar environments, typical of developing countries, with respect to available medical care, environmental pathogens, and co-administration of OPV.

1.14 Bacterial translocation and gut integrity in HIV-1 infected infants

In HIV-1 infected adults, the gut-associated lymphoid tissue (GALT) is rapidly depleted during the acute phase of the infection and its integrity remains compromised in patients on HAART.(27) Recently, Brenchley and colleagues(28) reported that levels of lipopolysaccharide (LPS), and related proteins, LPS binding proteins [LBP] and soluble CD14 [sCD14], and endotoxin core antibodies (EndoCAb IgM) are elevated in HIV-1 infected persons and decrease with HAART. LPS measures the translocation of luminal bacterial products, and therefore provides a way of assessing the integrity of the gut in HIV-1 infected persons at different stages of HIV-1 infection and its treatment. Furthermore, these soluble factors are thought to be directly related to the chronic immune activation seen in HIV-1 infected persons. A single study of LPS levels in HIV-1 infected European children(29) indicates that LPS levels are significantly higher among HIV-1 infected children compared to
uninfected children. Among the children treated with HAART, LPS levels remained stable for up to two years, but continued to increase among the virologic non-responders. This protocol provides an opportunity to investigate microbial translocation among HIV-1 infected and uninfected African infants. In the context of this trial in which live attenuated oral rotavirus vaccine or placebo will be given to breast-fed African infants between ≥ 4 and ≤ 32 weeks of age, we will evaluate the extent of microbial translocation among the four infant groups targeted.

1.15 Cell Mediated Immunity

The importance of rotavirus-specific T cells in protection against rotavirus infection results from the help that T cells provide B cells for antibody production and from the antiviral activity of T cells themselves. HIV-1 infected individuals have poor antibody responses to microbial antigens and vaccines. HIV does not infect B cells, but it decreases their function by several mechanisms, including the diminution of CD40/CD40L-mediated T cell help. For example, HIV-1 infected children who develop CMI in response to hepatitis A vaccine have higher antibody titers in response to vaccination. In the mouse rotavirus model, CD40/CD40L-mediated CD4 T cell help is necessary for persistence of protective anti-rotavirus antibody levels after immunization, confirming the role of T cell help in anti-rotavirus antibody production.

Comprehensive studies of rotavirus infection in mice showed that CD8-mediated viral clearance is equally as important as antibody-mediated protection. In addition to CD8, CD4 cells also contribute to protection against murine rotavirus infection.

Less is known about the role of CMI in protection against rotavirus infection in humans. Children who recover from acute rotavirus gastroenteritis develop rotavirus-specific CMI. Studies of RotaTeq™ in immunocompetent children showed that neutralizing antibodies against rotavirus were detected only in 70% of the vaccinees, whereas 98% of the vaccinees were protected against severe rotavirus infection and 74% against any type of infection caused by the serotypes contained in the vaccine. Vaccine-induced protection of seronegative individuals suggests a role for CMI.
Based on the profound T cell destruction and dysregulation caused by HIV infection, there is reason to believe that T cell dysfunction results in significant interference with the response to the rotavirus vaccine in HIV-1 infected children. Kaufhold et al. developed a robust IFN\(\gamma\) ELISPOT assay using the attenuated rotavirus vaccine strains.\(^{(53)}\) Using CD8-depletion coupled with the assay described by Kaufhold et al., we will measure CD4- and CD8-mediated responses to rotavirus vaccination in HIV-1 infected and HIV-1 exposed, but uninfected children.

1.2 Study Rationale

**Benefit of a rotavirus vaccine for HIV-1 infected infants.** It is very likely that RotaTeq\(^{TM}\) will succeed in preventing morbidity and mortality from rotavirus gastroenteritis in children in the developing world, and will thereby facilitate the care of HIV-1 infected infants, especially those debilitated by malnutrition, wasting, and opportunistic infections. It is also likely that the vaccine will reduce the rotavirus-related burden on the local health care system. In order to achieve these potential benefits, it is necessary to demonstrate that RotaTeq\(^{TM}\) will be safe and immunogenic in HIV-1 infected infants, especially since factors other than HIV-1 infection, such as differences in host populations, other associated health conditions, intestinal co-infections, and other epidemiological factors in developing countries could affect immunogenicity and vaccine safety as measured by serious adverse events and acquisition or progression of HIV-1 infection.

**WHO recommendations** WHO recently recommended that all infants receive a rotavirus vaccine in early infancy \(^{(54)}\). However, this recommendation cannot be immediately implemented and is intended to be achieved when major feasibility issues can be resolved. The reasons that this protocol should proceed are:

a. The WHO recommendations are based on very limited information concerning the safety and immunogenicity of rotavirus vaccine in HIV-1 infected children.

b. The information available was obtained with Rotarix\(^{TM}\) – a monovalent human rotavirus-derived strain that is fundamentally different from RotaTeq\(^{TM}\) – a bovine-based pentavalent vaccine. Thus, information on safety and immunogenicity for RotaTeq\(^{TM}\) cannot be assumed from the information available from Rotarix\(^{TM}\).

c. There may be clinical (based on country- and regional-specific epidemiology) advantages of RotaTeq\(^{TM}\) over Rotarix\(^{TM}\).
d. The information available to the WHO does not specify the nature of any interaction between vaccine responses and HIV-1 treatment status.

e. The information available from the Rotarix™ study does not directly address the potential effects of that (or any) rotavirus vaccine on acquisition of HIV-1 infection by HIV-1 exposed, but uninfected infants being nursed by their HIV-1 infected mothers. This will be investigated in P1072.

f. P1072 will provide important new information before the WHO recommendations are adopted by countries and funding agencies and before rotavirus vaccine is available to all infants.

Administration of rotavirus vaccine with OPV. Most providers in developing countries continue to administer OPV to all infants, including those with HIV-1. Concomitant administration of RotaTeq™ with OPV was not studied in any of the Phase III clinical trials of RotaTeq™. However, the safety and immunogenicity of RotaTeq™ when administered concomitantly with OPV were evaluated recently.(55) Concomitant administration of RotaTeq™ and OPV was generally well tolerated and did not interfere with the immunogenicity of each of the poliovirus types 1, 2, or 3, suggesting that the efficacy of OPV, when given concomitantly with RotaTeq™, would not be affected. Similar to other rotavirus vaccines (RotaShield™ and Rotarix™), concomitant administration of RotaTeq™ with OPV may reduce the serum anti-rotavirus IgA geometric mean titer (GMT), but in contrast to other rotavirus vaccines,(56) the seroresponse rates of RotaTeq™ remain high (>93%) and consistent with rates observed in previous studies demonstrating high (100%) vaccine efficacy against severe rotavirus gastroenteritis.(23)

Merck clinical study Protocol 015 (Efficacy, Safety and Immunogenicity of RotaTeq™ Among Infants in Asia and Africa) was recently completed (57;58). Infants in Protocol 015 were administered rotavirus vaccine in the setting of concomitant use of the Expanded Programme on Immunization (‘EPI’) vaccines including OPV. Results from the study showed that RotaTeq™ was well tolerated when given concomitantly with other routine pediatric vaccines, including OPV, of the EPI schedule. The results from the study also demonstrated that RotaTeq™ was efficacious against naturally-occurring severe rotavirus gastroenteritis (57;58).

Routine HIV testing was not standard of care in the developing world countries participating in an earlier Merck Study (Protocol 015) in Africa and Asia. However, HIV testing was offered to all participants (~1300) in Kenya. In total, there were 30 infants confirmed to have HIV
infection (19 received RotaTeq™ and 11 received placebo). For evaluation of safety, subjects in Protocol 015 were followed for serious adverse experiences for 14 days following any vaccination and for vaccine-related serious adverse experiences and deaths until the end of the study. Among all HIV-infected participants with safety follow-up identified in Kenya, 5 vaccine recipients (26.3%) and 1 placebo recipient (10.0%) reported a serious adverse experience occurring within the 14-day follow-up period after any vaccination. Among the serious adverse experiences within 14 days following any vaccination, only 1 was identified as vaccine-related by the reporting investigator. The subject developed gastroenteritis on Day 12 post-dose 2. In addition, there was 1 subject who reported a vaccine-related serious adverse experience, gastroenteritis, outside of the 14-day follow-up period on Day 15 post-dose 3. (58)

Overall, 11 deaths occurred during the study among HIV-infected participants in the total Kenyan cohort. Of these, 8 deaths occurred among the vaccine recipients and 3 deaths occurred among placebo recipients. Causes of death determined in these subjects included HIV infection, therapeutic agent toxicity (subject was being treated with sulfamethoxazole/trimethoprim and unspecified herbal medication), gastroenteritis, pneumonia, meningitis, febrile infection, tuberculosis, dehydration and dysentery. None were considered related to the vaccine. Given the relatively high prevalence of HIV-1 in some developing countries and the limited amount of data from Protocol 015, further evaluation is warranted. P1072 is critical to evaluation of the safety of RotaTeq™ in HIV-1 infected infants.

Availability of study information prior to universal rotavirus vaccination at each site.

The administration of the live rotavirus vaccine in this trial is likely to be associated with a favorable risk/benefit ratio, since almost all children in the study locations will develop wild-type rotavirus infection early in childhood (mostly in infancy), and these wild-type rotavirus infections will very likely result in more signs and symptoms than will be caused by infection with the vaccine strain. The evidence base resulting from this trial will be an essential step in advocating for widespread use of RotaTeq™ in HIV-1 infected children in developing countries. In addition, establishing the safety of the vaccine in HIV-1 infected children will support requests to donors (e.g. President's Emergency Plan for AIDS Relief; the Global Fund to Fight AIDS, Tuberculosis, and Malaria) to pay for it as part of preventive care for HIV-1 infected children. Furthermore, RotaTeq™ has been pre-qualified by the World Health Organization (WHO) for use in Latin American and European countries. In 2010, WHO prequalification of
RotaTeq™ for Africa and Asia was achieved based on the results of an industry-sponsored multi-site efficacy trial in those regions, thus making RotaTeq™ eligible for procurement by the Pan American Health Organization (PAHO), UNICEF and other United Nations agencies. Countries eligible for the Global Alliance for Vaccines and Immunization’s (GAVI) financial support for the introduction of new and underused vaccines will have the potential to access RotaTeq™ through the GAVI system. Alternative rotavirus vaccines are likely to be available, as well. However, the implementation of these plans within each country will take time. It is anticipated that access to vaccine for the general public in most of the countries participating in this study will not be realized in the near future.

Issues related to choice of placebo groups (see Appendix IV for additional details).

During this study some HIV-1 uninfected infants will receive placebo. In the countries in which this study is undertaken there is currently no administration of rotavirus vaccine (which is not licensed for use in these countries). Thus, placebo recipients will be managed in accordance with the standard of care in the countries targeted. No element of this standard will be withheld because of study participation. The enrollment of placebo recipients will not place them at any added risk of significant or irreversible harm.

In order to determine the precise adverse event rate and accurately determine rotavirus-specific immune responses in HIV-1 infected infants it is necessary to have two placebo-controlled cohorts – one with and one without HIV infection for the following reasons:

(1) Evaluating the relationship of adverse events to the administration of rotavirus vaccine in HIV-1 infected infants requires a control group of HIV-1 infected infants as a comparator. These groups will be assigned randomly and without investigator input so as to insure that the groups are as comparable as possible with regard to other factors potentially affecting study outcomes.

(2) The safety and immunogenicity of rotavirus vaccine in HIV-1 infected infants should also be evaluated against the safety and immunogenicity in HIV-1 exposed (uninfected) infants, to determine the impact of HIV status on any toxicity and immunologic boost related to vaccine administration. Having a placebo-control for each of these cohorts will enable comparison of the changes over placebo between the HIV-1 infected and the HIV-1 exposed (uninfected) groups.
(3) It is especially important that data from HIV-1 exposed (but not infected) infants be obtained in developing countries, where background rates of adverse events (unrelated to any intervention) may be increased. This information cannot be obtained from historical controls available from developed countries. A simple observational study would determine adverse events and immune responses in vaccinees, but would not ensure comparability in the treatment groups for other factors related to the study outcomes, thus potentially biasing the conclusions. A case control study would also be subject to unappreciated biases; would be difficult to conduct in countries where the vaccine is widely administered; and impossible to conduct in countries where the vaccine is not available. An equivalence design, to investigate similarity between Rotarix™ and RotaTeq™, would require an impractically large number of vaccinated infants and the conclusions could be hard to interpret as so little is currently known about Rotarix™ in HIV-1 infected infants.

(4) It is important to determine potential adverse effects of rotavirus vaccine given to HIV-1 uninfected infants who are breastfed by their HIV-1 infected mothers. This information can only be obtained if there is a control group of HIV-1 exposed (but uninfected) children who do not receive rotavirus vaccine.

(5) The inclusion of placebo-controlled arms is relevant to the host countries because this design will provide them with the most useful information for making decisions about including this vaccine in routine care protocols for HIV-1 infected children.

Other issues related to administration of rotavirus vaccine to HIV-1 infected infants in Africa. Similar to other rotavirus vaccines (RotaShield™ and Rotarix™), concomitant administration of RotaTeq™ with OPV may reduce the serum anti-rotavirus IgA geometric mean titer (GMT), but in contrast to other rotavirus vaccines,(56) the seroresponse rates of RotaTeq™ remain high (>93%) and consistent with rates observed in previous studies demonstrating high (100%) vaccine efficacy against severe rotavirus gastroenteritis.(23)

Immunogenicity of RotaTeq™ was previously studied in Phase III clinical trials by measuring SNA responses against the serotypes included in the vaccine and serum anti-rotavirus IgA responses. Serum anti-rotavirus IgA responses, usually reflective of response to vaccine and a surrogate marker of protection against mucosal pathogens, were consistently high across all populations tested (>93% in Latin America and Taiwan; >95% in Korea; and >99% in the European Union [EU] and the US), whereas the seroresponse rates of SNA responses to G1, G2, G3, G4, and P1A ranged
from ~75%, ~39%, ~23%, ~63%, and ~60%, respectively, in the EU and the US.

This protocol will only investigate the safety and immunogenicity of the rotavirus vaccine in infants born to HIV-1 infected mothers, and is not designed to measure efficacy. The study's primary objectives are to evaluate safety after any dose of RotaTeq™ in HIV-1 infected subjects and to evaluate the immunogenicity of a 3-dose regimen of RotaTeq™ in both HIV-1 infected and HIV-1 uninfected subjects. The study arms will be stratified by CD4%. Secondary objectives include evaluating safety in HIV-1 uninfected subjects and evaluations of fecal shedding in HIV-1 infected and HIV-1 uninfected subjects. Immune responses to vaccines are lower in HIV-1 infected children compared with HIV-1 uninfected children. Although there are no adequate studies of vaccine responses in HIV-1 infected infants, the data from older children showed that the HIV-1 viral burden is the strongest predictor of poor response to vaccines. Since HIV-1 infected infants typically have very high HIV-1 plasma RNA (≥100,000 copies/ml), it is reasonable to assume that they will mount sub-optimal responses to the rotavirus vaccine. These data, combined with the failure of many HIV-1 uninfected infants to develop SNA, suggest that there will be an even greater discordance between SNA and clinical response in HIV-1 infected children.

The design of this study will also allow the protocol team to study some factors that influence gut integrity in early HIV-1 infection, such as HIV-1 infection status, viral load and CD4 counts and/or CD4%, immunizations, immune activation, and rotavirus-specific immune responses.

All subjects will receive three doses of study vaccine or its matching placebo. The first dose will be administered at age ≥4 to <15 weeks. The rationale for administration of the first dose of RotaTeq™ as early as 4 weeks of age in the P1072 study, rather than as early as 6 weeks as indicated in the package insert is twofold:

1) To increase synergy with routine childhood vaccination schedules in the developing world countries, which use EPI schedules of 4, 8, 12 weeks dosing for OPV and DTwP.

2) Emerging data suggest that natural rotavirus infection occurs earlier in the developing world setting than is generally observed in the USA and Europe. Thus earlier vaccination against rotavirus is likely to provide increased benefit in these developing world countries.
Data from infants who received the first dose of RotaTeq™ prior to 6 weeks of age was also collected in Merck Protocol 015. Among the subjects enrolled in Africa, 1102 infants less than 6 weeks old received at least one dose of RotaTeq™ (N=535) or placebo (N=567) without unexpected reports of serious adverse events. The incidence of serious adverse experiences was comparable between treatment groups in this subgroup. A total of 4 (0.7%) infants who received RotaTeq™ and 4 (0.7%) infants who received placebo had one or more serious adverse events. Vaccine-related serious adverse events were also comparable between treatment groups (1 each).

Since WHO guidelines recommend administration of ART as soon as the diagnosis of HIV-1 is made in infancy, the protocol has been amended to require that all subjects beginning this study receive ART prior to, or at the time of, first study vaccine/placebo.

2.0 STUDY OBJECTIVES

2.1 Primary

2.11 To evaluate the safety of any dose of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.

2.12 To evaluate the immunogenicity of a 3-dose regimen of RotaTeq™ in HIV-1 infected and uninfected children born to HIV-1 infected mothers, as measured by serum anti-rotavirus IgA ELISA and serum neutralizing antibody [SNA] responses to serotypes G1, G2, G3, G4, and P1A[8].

2.2 Secondary

2.21 To evaluate the fecal shedding of RotaTeq™ strains after each dose of RotaTeq™ given to HIV-1 infected and uninfected children born to HIV-1 infected mothers.

2.22 To evaluate the relationship of anti-rotavirus serologic immune responses to CD4 cell count and/or CD4%, plasma RNA or DNA, and antiretroviral therapy (ART) after a 3-dose regimen of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.

2.23 To evaluate the safety of any dose of RotaTeq™ given to HIV-1 uninfected children born to HIV-1 infected mothers.
2.24 To compare the incidence of HIV-1 infection at the last study visit between those receiving rotavirus vaccine and placebo among the infants who were not HIV-1 infected at enrollment

2.3 Exploratory Objectives

2.31 To evaluate the relationship between virus shedding and rotavirus-specific SNA antibodies, copro-antibodies, and CMI against rotavirus vaccine serotypes in recipients of the rotavirus vaccine.

2.32 To evaluate IgA and IgG copro-antibodies and CMI responses against rotavirus serotypes contained in the vaccine in HIV-1 infected versus uninfected infants born to HIV-1 infected mothers.

2.33 To compare in HIV-1 infected recipients of rotavirus vaccine or placebo the CD4% at the last study visit and the change in CD4% from the first study visit to the last study visit.

2.34 To assess how microbial translocation changes in response to vaccination with RotaTeq™ relative to placebo in HIV-1 infected and HIV-1 uninfected infants.

2.35 To evaluate the relationship of mucosal and cell-mediated immune responses to CD4 cell count and/or CD4%, plasma HIV RNA or DNA, and ART after a 3-dose regimen of RotaTeq™ given to HIV-1 infected children born to HIV-1 infected mothers.

3.0 STUDY DESIGN

This is a Phase II, randomized, double-blind study of the safety and immunogenicity of RotaTeq™ in children born to HIV-1 infected mothers. The study will be conducted at selected international IMPAACT sites, based on their capabilities and the nature and size of their clinic populations. HIV-1 infected pregnant women will be contacted after delivery to seek permission to enroll their newborn child into the vaccine study. This study is not designed to measure efficacy but will evaluate immunologic responses to RotaTeq™ as bridging studies to compare with similar data from efficacy trials of the vaccine that have been conducted previously.

A screening visit for the infant at ≥2 weeks to <15 weeks of life will be used to obtain consent: to determine the presence of HIV-1 DNA (or RNA) in the blood of the infant; and to determine the lymphocyte subsets (including CD4 count and CD4%) of the infant. Screening must be completed so that the first dose of vaccine
can be administered when the subject is ≥4 to <15 weeks of age. Three hundred and twenty (320) infants will be enrolled into four strata: 160 HIV-1 uninfected (Stratum 1) and 160 HIV-1 infected infants (Stratum 2a: CD4 ≥ 20%; Stratum 2b: 15% ≤ CD4 < 20%; and Stratum 2c: CD4 < 15%).

ALL HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ART) before, or at the time of, administration of the 1st dose of study vaccine/placebo. NOTE: It is not acceptable for subjects to take a prescription home with them to start ART therapy on the day of vaccination.

Within each stratum infants will be randomized to two arms: Arm 1 will receive RotaTeq™ and Arm 2 will receive placebo. Table 1 illustrates the study design. Appendix I – Schedule of Evaluations (SOE) contains the study visit details.

<table>
<thead>
<tr>
<th>Stratum</th>
<th>CD4%</th>
<th>Number</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV-1 Uninfected</td>
<td>N=160</td>
<td>80 Vaccine 80 Placebo</td>
</tr>
<tr>
<td>2a</td>
<td>HIV-1 Infected</td>
<td>CD4≥20%</td>
<td>N=80</td>
</tr>
<tr>
<td>2b</td>
<td>HIV-1 Infected</td>
<td>15%≤CD4&lt;20%</td>
<td>N=60</td>
</tr>
<tr>
<td>2c</td>
<td>HIV-1 Infected</td>
<td>CD4&lt;15%</td>
<td>N=20</td>
</tr>
</tbody>
</table>

Accrual will initially open in Stratum 1 and Stratum 2a. After the 20th HIV-1 infected infant in Stratum 2a has enrolled and received the first treatment dose, accrual to Strata 1 and 2a will be temporarily closed until an interim safety analysis for adverse events has been completed by the Study Monitoring Committee (SMC) as described in Section 8.52. If the SMC determines that the adverse event profile permits continuation of the study, accrual will open in all four strata.

After the 20th HIV-1-infected infant has enrolled into Strata 2b or 2c (combined) and received the first treatment dose, accrual to Strata 2b and 2c will be temporarily closed until the completion of a second interim safety analysis of the adverse event profile of these subjects by the SMC. If the SMC determines that the adverse event profile is acceptable in these strata, accrual will re-open. If the SMC indicates that no additional subjects with CD4 < 20% should receive the rotavirus vaccine, then enrollment of all remaining HIV-1 infected subjects will be restricted to those with CD4 ≥ 20% in Stratum 2a.
In addition to the two early safety analyses by the SMC, the study team will review all ≥ Grade 2 adverse events (passively reported laboratory results, signs and symptoms) on regular conference calls (initially weekly, and as the study matures, possibly less frequently, with agreement of the Study Chairs and DAIDS Medical Officer). If at any time the Core Team determines:

1) More than 20% of subjects (or more than four if less than 20 have been enrolled) in any stratum have experienced ≥ grade 3 possibly/probably/definitely vaccine-related adverse events; or

2) That the number and quality of possibly/probably/definitely vaccine-related life-threatening events exceed that expected for the study population at the site where the study is undertaken - the study will be suspended pending a review by the SMC.

3.1 Treatment Regimen(s)

Subjects in both groups will receive three doses (2.0 mL each) of either a live attenuated rotavirus vaccine (RotaTeq™) or placebo. The first dose will be administered at age ≥4 to <15 weeks and subsequent doses will be given at intervals of no less than 4 weeks, but may extend to 10 weeks. The third and final dose must be administered by 32 weeks of age.

The immunologic evaluation of the first and last serum samples will include antibody responses to: (i) serum anti-rotavirus IgA and (ii) SNAs to G1, G2, G3, G4, and P1A (8).

Blood will be drawn just prior to the first dose of vaccine (Day 0) and at two additional visits (at day 21 after the first dose and at day 14 after the third dose), as indicated in Appendix I. Blood samples obtained at screening and at day 14 after the third dose (or Day 42 if not obtained at Day 14) will be tested for lymphocyte subsets (including CD4 count and CD4%). Either HIV-1 DNA PCR or HIV-1 RNA PCR will be collected at screening. HIV-1 RNA (infected) or HIV-1 DNA (uninfected) will also be determined on blood drawn just prior to the first dose of vaccine/placebo (Entry). A drop of blood will be obtained on filter paper from subjects in stratum 1 at the time of the second dose and 21 days later. These specimens will be available for determination of HIV RNA / DNA in the blood of subjects found by testing at the end of the trial to have developed HIV-1 infection during the trial.

Stool samples will be collected to determine the presence of vaccine-strain virus in the stool and to determine the presence of copro-antibodies.
Additional testing for other potential pathogens may be conducted. See Sections 6.2, 8.22 and 8.23 for further details.

Due to a subject’s age at study completion, and the absence of safety data in subjects receiving vaccination at over 32 weeks of age, placebo recipients will not be able to receive active vaccine at study end.

Subjects will be unblinded after follow-up is complete on all enrolled subjects and the clinical and laboratory databases required for the primary and secondary objectives have been reviewed and finalized for analysis. Blinding for processing of laboratory tests required for exploratory objectives will be maintained as necessary. Once this date has been determined by the Protocol Team, unblinding lists for each site will be distributed as outlined in the IMPAACT Unblinding SOP (SDM-4001-01). [This document can be accessed by going to the IMPAACT website (http://www.impaactgroup.org); the user name is impaact, the password is cure. Under “Member Area,” select SOPs and Guidelines, and under Statistical Data Management section, choose SDM-4001-01.]

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria for Step 1

4.11 A child age ≥ 2 weeks to < 15 weeks at time of screening.

4.12 Subjects must be between the ages of ≥ 4 to < 15 weeks to receive first dose.

4.13 A child born to an HIV-1 infected mother whose HIV-1 diagnosis was determined by two different tests performed on the same or separate maternal samples obtained before or during pregnancy or during the postpartum period. Acceptable tests are (antibodies in serum or saliva, HIV RNA or HIV DNA, or HIV antigen in the blood).

4.14 The presence or absence of HIV RNA or HIV DNA in the blood of the infant has been determined. When using quantitative HIV RNA tests, the viral load should be ≥ 5,000 copies/mL for the sample to be considered positive. Any positive test must be confirmed by repeat testing, which must be obtained prior to randomization to study arm.

4.15 The CD4% is documented at screening.
4.16 Parent or legal guardian agrees to give written informed consent and is willing to comply with study requirements.

4.17 Parents/guardians of each subject must state their willingness to have the subject follow the country-specific childhood Expanded Programme on Immunization (“EPI”) schedule for concomitant childhood vaccines recommended during the study period.

4.18 **ALL HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ART) before, or at the time of, administration of the 1st dose of study vaccine/placebo.** NOTE: It is not acceptable for subjects to take a prescription home with them to start ARV therapy on the day of vaccination.

4.2 **Inclusion Criteria for Steps 2 and 3**

4.21 Successful administration of first vaccine (for Step 2) and second vaccine (for Step 3).

4.22 **Subjects must be <32 weeks of age at the time of the 3rd vaccine/placebo dose**

4.3 **Exclusion Criteria for Steps 1, 2 and 3**

4.31 Concurrent participation in any study of an investigational drug or vaccine, except for studies for prevention of perinatal HIV-1 transmission.

4.32 Known allergy to any component of the study vaccine.

4.33 Active gastrointestinal illness or fever. Fever is defined as ≥38.5º C in accordance with WHO guidelines for administration of childhood vaccines.

4.34 Subjects cannot be enrolled from any site at which rotavirus vaccine is available and is being administered.

4.35 **Any condition, which would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.**

4.36 Any other condition, situation, or clinically significant finding
(other than HIV infection) that, in the investigator’s opinion, would interfere with study participation, or interpretation.

4.37 Subjects with a known history of SCID or intussusception.

4.4 Exclusion Criteria for Steps 2 and 3

4.41 Any Grade 4 adverse events believed to be possibly/probably/definitely related to vaccine will disqualify subjects from receiving additional doses. Grade 3 adverse events believed to be possibly/probably related to vaccine must be demonstrated to have improved to ≤ Grade 2 prior to receiving the next scheduled dose.

4.5 Concomitant Medication Guidelines

4.51 Disallowed Medications

Investigational medications/vaccines that have not been licensed should not be administered from study entry to 6 weeks after receiving the last dose of RotaTeq™/placebo.

4.52 Concomitant Medications and Vaccinations

Concomitant administration (same day dosing) of study vaccine / placebo and routine EPI vaccines (including OPV) should be standard procedure in this study. However, if non-concomitant administration of these vaccines is necessary, it is strongly recommended that dosing of the study vaccine/placebo and OPV be separated by at least 14 days (preferably 28 days) and that study vaccine/placebo preferably be given first followed by OPV at least 14 days later. Concomitant medications and/or vaccinations from birth and throughout the study should be documented on the appropriate case report form (CRF). Routine vaccinations approved at the site for this age group are acceptable.

4.6 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other
applicable regulatory entity (RE). 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 informed consent forms (ICFs) WILL NOT be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. 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 approval(s) 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.

4.7 Maternal Data Collection

During subjects’ weekly office visits, clinicians will also collect on appropriate case report forms, information regarding maternal CD4 counts (including CD4%, if available), ARV treatment regimens, and intercurrent diarrheal illnesses.

4.8 Co-enrollment

Co-enrollment is allowed for perinatal prevention trials and treatment studies utilizing licensed antiretroviral or anti-infective drugs, and any non-
treatment studies. Co-enrollment requires approval of the Chair(s) of the other studies.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

5.11 Regimens

**Step 1:**
Eligible subjects will be randomized to either receive the live attenuated rotavirus vaccine (RotaTeq™) OR the matching Placebo for RotaTeq™.

**Step 2:**
Subjects that successfully complete step 1 may proceed to step 2 and receive a second dose. This dose can be given between 4 weeks and 10 weeks after the previous dose, as indicated in the schedule of evaluations.

**Step 3:**
Subjects that successfully complete step 2 may proceed to step 3 and receive a third dose. This dose must be given as indicated in the schedule of evaluations. It must be administered by 32 weeks of age. Because the country-specific EPI schedule will be followed, other approved routine pediatric immunizations (such as OPV, BCG, DTwP, Hib, and HepB) should be administered if indicated on the same day as RotaTeq™/placebo.

5.12 Inspection of Pouch

When opening the pouch and preparing to administer the dose, inspect the pouch and the dosing tube for signs of product residue and/or leaking product. This residue would present itself as a clear liquid or a white crusty material. Pay special attention to the corners of the seal opposite the dispensing tip. (Reference the below magnified image of dosing tube seal end with leaking product circled.) Additionally, the presence of product residue may make the dosing tube sticky and/or difficult to remove from the pouch.

If any signs of residue and/or leaking product are identified, do not administer the subject dose. Please return the dosing tube
with the pouch to your Pharmacist of Record who must quarantine the product and then notify the DAIDS Protocol Pharmacist.

If no signs of residue and/or leaking product are identified, continue with administration as directed. (See Protocol section 5.13 on Administration). It is recommended that good general hand washing practices be observed during inspection and administration of the product.

5.13 Administration

The RotaTeq™ or matching placebo consists of 2 mL of ready-to-use liquid doses administered orally. There are no restrictions on the infant’s consumption of food or liquid, including breast milk, either before or after the oral dose of vaccine. The study product must not be mixed with any other vaccines or solutions, and must not be reconstituted or diluted.

Instructions for Use:

a) Tear open the pouch and remove the dosing tube.
b) Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.

c) Open the dosing tube in 2 easy motions:
   i. Puncture the dispensing tip by screwing cap clockwise until it becomes tight.

   ii. Remove the cap by turning it counterclockwise.

d) Administer dose by gently squeezing liquid into infant’s mouth toward the inner cheek until dosing tube is empty. (A residual drop may remain in the tip of the tube.)

e) If for any reason an incomplete dose is administered (e.g., infant spits or regurgitates the vaccine), a replacement dose is NOT recommended, since such dosing was not studied in the clinical trials. The infant should continue to receive any remaining doses in the recommended series.

5.2 Drug Formulation

RotaTeq™ 2 mL for oral use, is a ready-to-use solution of live re-assortant rotaviruses, containing G1, G2, G3, G4 and P1A which contains a minimum
of $2.0 - 2.8 \times 10^6$ infectious units (IU) per individual re-assortant dose, depending on the serotype, and not greater than $116 \times 10^6$ IUs per aggregate dose.

Both RotaTeq™ and the placebo contain sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.

In the manufacturing process for RotaTeq™, a porcine-derived material is used, DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq™ PCV-1 and PCV-2 are not known to cause disease in humans.

Each dose of RotaTeq™ or matching Placebo is supplied in a container consisting of a squeezable plastic, latex-free dosing tube with a twist-off cap, allowing for direct oral administration only (no injection). The placebo was created by Merck & Co., Inc. in the image of the active product.

RotaTeq™ or matching Placebo must be stored and transported refrigerated at 2-8°C (36-46°F). Study vaccines should be administered as soon as possible after being removed from refrigeration and must be protected from light. Discard the empty tube and cap in approved biological waste containers according to local regulations and institutional policies. The product must be used before the expiration date.

5.3 Drug Supply, Distribution and Pharmacy

The live attenuated rotavirus vaccine (RotaTeq™) and the matching placebo for RotaTeq™ will be provided by Merck & Co., Inc.

Antiretroviral therapy will NOT be provided as part of the study medications. These medications will be provided via local access programs or through standard of care.

Study vaccine will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT pharmacist can obtain the study agents for the protocol by following the instructions in the manual “Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks” in the section entitled Study Product Control.

The NIAID CRPMC will not provide antiretrovirals as part of this study. The IMPAACT pharmacist is required to maintain complete records of all study vaccine received from the NIAID CRPMC and subsequently dispensed. All unused study vaccine must be returned to the NIAID
CRPMC after the study is completed or terminated, or managed as directed by the NIAID procedures on handling unused study products. The procedures to be followed are given in the manual, “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks” in the section entitled Study Product Control. The non-US pharmacists should contact the Pharmaceutical Affairs Branch (PAB) protocol pharmacist for further instructions before returning any study product.

6.0 SUBJECT MANAGEMENT

Questions concerning clinical management of study subjects and all communication regarding adverse experiences should be addressed to the core P1072 Protocol Team (Chairs, Medical Officers, Statisticians, Data Manager, CTS) at actg.p1072cmc@fstrf.org; remember to include the subject’s PID. All other protocol-related communication should be addressed to the full P1072 Protocol Team at actgteamp1072@fstrf.org.

6.1 Toxicity Management

Subjects will be followed for adverse events, including intussusception and acquisition of new HIV-1 infection during the interval between doses and for at least 6 weeks after the third dose. It is anticipated that vaccine-associated adverse events (AEs) will occur frequently, but that these will be minor and side effects will rarely necessitate interruption of the immunization schedule. Toxicities will be graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December, 2004, Clarification August 2009, which is available on the RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance).

Management of AE’s will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest edition of the Harriet Lane Handbook and/or Nelson’s Textbook of Pediatrics for normal ranges/values and should document this for monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution.

In order to optimize reporting of AE’s, missed clinic visits will result in attempts to contact the caretaker of the subject (by telephone or in person) and a home visit will ensue if possible.
6.2 Study Management Plan

Office visits will be conducted after each treatment dose as outlined in the Schedule of Evaluations (Appendix I). If a subject is unable to travel to the clinic for a scheduled appointment, the study clinician may visit the subject at home to conduct the appropriate treatment and/or evaluation. If the next treatment dose is administered before the 42 day visit is scheduled, this 42 day visit will be omitted, and the evaluations scheduled for that visit will be done just before the next dose is administered. A standardized case report form will be completed by study personnel at each visit to elicit adverse events. The relationship of an adverse event to the treatment administered will be determined independently by the site investigator and the Core Team. caretakers will be instructed to inform the site if they suspect a serious adverse event. All suspected serious adverse events will be seen at the study site within 48 hours of reporting such an event. Fecal samples for evaluation of vaccine-virus shedding and evaluation of the presence of copro-antibodies will be collected from all subjects at many of the protocol visits according the Schedule of Evaluations (Appendix I). Additional testing for other potential pathogens will be conducted. Blood samples will also be collected for virology; immunology and other special tests (see Appendix I for additional details).

At ALL scheduled/unscheduled study visits (including clinic/office or home visits), a directed history and clinical exam, including an abdominal exam to exclude any signs of intussusception, should be carried out. Sites are also encouraged to follow-up on tests/investigations (e.g. X-rays) that are ordered on a study participant to ensure that the participant was able to complete them.

Infant length and weight and temperature measurements as well as breastfeeding status, maternal ARV treatment and any intercurrent maternal diarrheal illness will be collected at each vaccination visit and will be recorded on standardized case report forms. In addition, all adverse events ≥ grade 1 will be recorded on a standardized case report form.

Any dose should be deferred when the Site Investigator determines that a significant gastroenteritis or other illness or fever (see 4.34 for definition) is present. The dose should be given when the subject no longer has significant symptoms, providing that 4 weeks have elapsed since the prior dose and the subject is not older than 32 weeks.

Any subject who is unable to receive a vaccine dose within the prescribed window (between days 28 and 70 after the previous dose) should get their missing dose as soon as possible. There should be a minimum of 4 weeks...
between doses and the last dose must be administered by the age of 32 weeks. Any subject, who develops intussusception after a dose of RotaTeq™, will not be given any additional doses of the vaccine.

Subjects discontinuing study treatment will not be unblinded to their treatment unless the information is critical for making immediate therapeutic decisions for the subject (e.g. if withholding the treatment information would put the subject at risk of serious adverse events or death). If a subject does need to be unblinded, then the site should notify the Core Team and with their approval, submit a request to the Data Management Center using the Unblinding Request Program on the DMC Web site, as outlined in the IMPAACT Unblinding SOP (SDM-4001-01).

Unplanned Visits for Gastroenteritis (GE)

Fecal samples will be collected from a subject with acute gastroenteritis within 7 days (preferably 3 days) of any episode of gastroenteritis that occurs from the time of the first vaccination until the subject completes the final study visit. These may be obtained during a scheduled or unscheduled clinic visit. If a subject develops symptoms of acute gastroenteritis (e.g., looser than normal stools, diarrhea, and/or vomiting), caretakers may call the sites for further directions or they may bring the patient directly to the clinic. In clinic, a case record form will be completed and a stool sample obtained. Six (6) mL of stool is sufficient for testing. The purpose is to identify those subjects with confirmed rotavirus-positive gastroenteritis in order to eliminate this as a confounding factor for the immunogenicity analyses. Additional testing for other potential pathogens will be conducted.

Severity of rotavirus disease must be graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004, Clarification August 2009, which is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance).

Severe dehydration will be treated with intravenous fluids on admission. Children with moderate dehydration will receive oral rehydration solution and be reassessed after 4 hours in the clinical setting. In case of improvement the child will be send home with caretakers who will receive instruction how to feed and prevent progressive dehydration (preparation of oral rehydration fluid; feeding techniques; continuation of breastfeeding, etc) in the child. Caregivers will be advised to return immediately to clinic if their child’s condition worsens.
All sites have site and country specific clinical protocols for the management of gastroenteritis. Patients with signs and symptoms of gastroenteritis will have a history taken and will be clinically evaluated, focusing on grade of dehydration, bloody diarrhea, abdominal distension or masses, and presence of possible other concomitant diseases.

For this protocol, although normally not routine in children with diarrhea, stool samples will be collected for testing for rotavirus as specified in Section 8.222. Additional specific stool investigations will be ordered according to stool frequency and consistency. Individual symptoms and standard of care at each site will determine the specific investigations, which may include diagnostic tests for *Shigella, Cholera, Salmonella, Campylobacter, Yersinia, ova and parasites* and other potential pathogens. In countries with endemic malaria a routine blood smear for malaria parasites will be taken. An abdominal ultrasound will be performed when intussusception is in the differential diagnosis. Children might be evaluated with further investigations depending on signs and symptoms (e.g., blood culture if high fever, electrolytes, CBC). In the absence of a strong suspicion of a bacterial etiology, and in absence of other bacterial infections, antibiotics are not routinely prescribed. When significant infection is present, paracetamol may be used after exclusion of other causes.

### 6.3 Criteria for Deferral of Second or Third Dose of Vaccine

Any Grade 4 adverse events believed to be possibly/probably/definitely related to vaccine will disqualify subjects from receiving additional doses. Grade 3 adverse events believed to be possibly/probably/definitely related to vaccine must be demonstrated to have improved to ≤ Grade 2 prior to receiving the next scheduled dose.

All exclusion criteria (see 4.3 and 4.4) that apply before administration of the first dose of vaccine must be met prior to administration of each additional dose. The second and third doses must be given within the required windows.

### 6.4 Criteria for Study Treatment Discontinuation

- Possibly/probably/definitely vaccine-related toxicity that requires permanent study drug discontinuation as defined in Section 6.1.
- The investigator determines that further participation would be detrimental to the subject’s health or well-being.
- The caregiver fails to comply with the study requirements so as to cause harm to the subject or seriously interfere with the validity of the study results.
• Subject is diagnosed with intussusception after a dose of RotaTeq™
vaccine.

If the second or third dose is not received, all applicable activities scheduled
for the Early Discontinuation visit should be completed and the subject will
continue to be followed for safety every 6 weeks for 12 weeks if the second
dose is missed and for 6 weeks if the third dose is missed. Safety
monitoring includes all adverse events. These timeframes will facilitate
consistency in the number of follow-up weeks for subjects regardless of the
number of doses received.

6.5 Criteria for Study Discontinuation

• The legal guardian refuses further treatment and/or follow-up
evaluations.
• The investigator determines that further participation would be
detrimental to the subject’s health or well-being.
• The caregiver fails to comply with the study requirements so as to cause
harm to the subject or seriously interfere with the validity of the study
results.
• If a national recommendation for rotavirus vaccine is implemented at a
participating clinical site, subjects on study who are in the placebo group
will receive vaccine as per site implementation if their age permits them
to receive vaccine (there are recommended limitations on upper age and
specified interval).

6.6 Guidelines for Managing Subjects in Countries Where RotaTeq™
Licensure Occurs During the Study

The protocol currently limits the study to sites where rotavirus vaccine
is not licensed. In the situation where RotaTeq™ licensure is obtained
in a specific country while study subjects are participating in the study,
the following guidelines will go into effect:
• No new subjects at that site will be enrolled into P1072.
• In conjunction with DAIDS, the team will provide instructions to
the site(s) regarding how to un-blind on an individual basis,
ONLY the affected subjects who are within the age range where
they could receive the full series of three vaccinations.
• Subjects on study who are in the PLACEBO group will receive
study vaccine as per national (or site) implementation if their age
permits them to receive vaccine (NOTE: there are recommended
limitations on upper age and specified interval). Subjects will
then continue to be followed as per the protocol schedule of evaluations in Appendices IA (HIV-infected) or IB (HIV-uninfected).

- Subjects on study who are in the VACCINE group will complete the vaccine series per national (or site) implementation and will continue to be followed as per the protocol schedule of evaluations in Appendices IA (HIV-infected) or IB (HIV-uninfected).

- Where applicable, unblinding lists for each site will be distributed as outlined in the IMPAACT Unblinding SOP (SDM-4001-01). [This document can be accessed by going to the IMPAACT website (http://www.impaactgroup.org); the user name is impaact, the password is cure. Under “Member Area,” select SOPs and Guidelines, and under Statistical Data Management section, choose SDM-4001-01.]

- Every effort should be maintained by site personnel to keep study team members blinded to treatment assignment and prevent dissemination of information for these subjects.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAIDS Adverse Experience Reporting System (DAERS) internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/
For questions about EAE reporting, please contact the RSC (DAIDSRS CSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

- The study agents for which expedited reporting is required are RotaTeq™ vaccine and Placebo for RotaTeq™ vaccine.

- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are all cancers and vaccine overdoses. An overdose is defined as receiving more than one dose of vaccine/placebo in a 12 day period.

7.3 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.

- After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

The primary objectives of this randomized study are to assess the safety of RotaTeq™ in HIV-1 infected infants in the developing world and to estimate immunogenicity in HIV-1 infected and HIV-1 exposed but uninfected infants. Secondary objectives include the safety of RotaTeq™ in HIV-1 uninfected infants and fecal shedding of vaccine virus in HIV-1 infected and uninfected infants born to HIV-1 infected mothers, some of
whom may become HIV-1 infected through breast milk. Safety and immunogenicity will be summarized separately in these infants, although these summaries will have limited precision.

Because exposure to rotavirus may vary geographically and over time, accrual of the HIV-1 infected and HIV-1 uninfected infants will be regulated to ensure similar accrual rates at each site and over time. The study team will monitor practices with respect to treatment of HIV-1 infected infants with antiretrovirals and standard of care for their mothers during pregnancy and after delivery at each participating site. Use of these drugs will complicate assessment of vaccine-relationship for the primary safety endpoint and may affect immunogenicity in both populations. All analyses will be done unadjusted. Additional analyses will adjust for site, antiretroviral use in the infants and their mothers, and breastfeeding.

Study treatment consists of three doses of vaccine. To regulate the timing and eligibility for each dose, the study will have 3 steps, with each step corresponding to each vaccine dose.

8.2 Outcome Measures

8.21 Primary Endpoints:
8.211 Safety as assessed by:
   All ≥ Grade 3 laboratory values (hematologic and chemistry), all ≥ Grade 3 signs or symptoms (adverse events) not present before the administration of the first vaccination and occurring until the subject goes off study, as specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004, Clarification August 2009). Relationship to the vaccinations administered in this study will be assessed by the site and subsequently reviewed by the Core Team.
   • Hospitalizations
   • Deaths
   • Occurrence of new clinically significant diagnoses
   • Growth (height and weight)
8.212 Immunogenicity of RotaTeq™ as measured by

- Serum anti-rotavirus IgA ELISA
- SNA responses to type-specific outer surface proteins of the vaccine virus (G1, G2, G3, G4 and P1A [8]).

A positive response is defined as a ≥3-fold rise over pre-vaccine levels at least 14 days after the third vaccination. Assays will be conducted at Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio, U.S.A.

8.22 Secondary Endpoints and Outcomes:

8.221 Fecal shedding of RotaTeq™ strains at entry and on days 7, 14, 21 and 42 days after the first dose, and at days 7 and 21 after the next two doses. The presence of vaccine-virus strains in the stools will be assessed by the following assays: Enzyme ImmunoAssay (EIA) rotavirus antigen detection, testing for infectious virus (e.g. Florescent Focus Assay (FFA)), RT-PCR specific for specific for rotavirus gene 6, which codes for the VP6 protein. In addition, the identity of the vaccine-virus strain in any rotavirus positive-stool sample will be determined by an RT-PCR assay specific for VP7 genotyping. Additional molecular characterization of rotavirus strains and testing of specimens for other potential pathogens may be conducted. The assays to detect the presence of rotavirus in routine stool samples will be conducted at Cincinnati Children’s Hospital Medical Center (CCHMC), Cincinnati, Ohio, U.S.A., and/or at Pharmaceutical Product Development (PPD), Vaccine and Biologics Labs.

8.222 The presence of rotavirus in stool samples resulting from acute gastroenteritis will be assessed by the following assays: EIA, testing for infectious virus and RT-PCR (specific for rotavirus genome 6, coding for the VP6 protein). Any of the samples which are rotavirus-positive will have their VP7 and the VP4 genotypes determined by RT-PCR. Additional molecular characterization of rotavirus strains and testing of specimens for other potential pathogens may be conducted. The assays to detect the presence of rotavirus in any acute gastroenteritis stool sample will be conducted at CCHMC, Cincinnati, Ohio, U.S.A., and/or at PPD, Vaccine and Biologics Labs.

8.223 CD4 count and CD4 % at entry and the last determination at the end of the study.
8.224 HIV RNA or DNA in blood at entry and at the last determination at the end of the study.

8.225 Safety as defined in 8.21 for HIV-1 uninfected subjects.

8.226 Acquisition of HIV-1 infection by subjects classified at screening or entry as HIV-1 uninfected.

8.23 Exploratory outcomes:

8.231 Anti-rotavirus IgA and IgG copro-antibodies against rotavirus serotypes contained in the vaccine prior to vaccination and at day 21 after each dose of vaccine.

8.232 Microbial translocation measures: LPS, sCD-14, LBP and EndoCAb measured at entry, day 21 after the first dose of vaccine and day 14 after the third dose of vaccine.

8.3 Randomization and Stratification

Subjects will be enrolled into four strata: 160 HIV-1 uninfected (Stratum 1) and 160 HIV-1 infected infants (Stratum 2a: CD4% ≥ 20%; 2b: 15% ≤ CD4% < 20%; and 2c: CD4% < 15%). Within each stratum, subjects will be randomized in equal proportions to two arms with subjects in Arm 1 receiving the RotaTeq™ vaccine and subjects in Arm 2 receiving placebo vaccine. Randomization will be balanced within site with no accrual limits by site.

Because exposure to rotavirus may vary geographically and over time, sites will be asked to enroll HIV-1 infected and HIV-1 uninfected infants at similar rates. This will be monitored daily by the randomization desk at the Data Management Center. If at any particular site the total number of HIV-1 infected and HIV-1 uninfected infants differs by more than 2, the randomization system will automatically send an email to the site notifying them and the Protocol Team. The site will be expected to respond to the Protocol Team with a course of action to reduce the difference.

8.4 Sample Size and Accrual

The study will enroll 160 HIV-1 infected and 160 HIV-1 uninfected infants, with half in each stratum receiving active vaccine and half receiving placebo. The primary safety analysis endpoint is any new ≥ Grade 3 adverse events (serious AEs), including both laboratory and clinical events,
occurring after the first, second or third vaccination in the HIV-1 infected strata. When there is a difference in assessment of relationship of an AE to study treatment between the site PI and the Core Team, the most related assessment will be used for analysis of adverse events. Given the small sample size, the study is only powered to detect relatively large differences in adverse event rates between the placebo and vaccine arms. Table 2 shows the differences in adverse event rates that would be detectable with at least 80% power and a Type I error rate of 5%. With the proposed sample size of 80 subjects in each Arm, differences in adverse event rates between the vaccine and placebo arms of more than 24% will be detectable with at least 80% power. If adverse event rates in the placebo arm are lower than 40%, the study is powered to detect somewhat smaller differences (e.g. 21% if the placebo rate is <15%). These estimates also apply to the secondary safety analysis in the HIV-1 uninfected strata.

Table 2: Detectable differences in adverse event rates between Arms 1 and 2 with various baseline adverse event rates in Arm 2 (placebo)*

<table>
<thead>
<tr>
<th>Arm 2 Adverse Event Rate (%) (placebo)</th>
<th>Detectable difference in Adverse event rate with ≥80% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>25</td>
<td>23%</td>
</tr>
<tr>
<td>40</td>
<td>24%</td>
</tr>
</tbody>
</table>

* Sample size calculations done using difference of two proportions in strata.

It is possible that vaccine recipients in the HIV-1 uninfected cohort may be at either increased or decreased risk of becoming HIV-1 infected through breast milk transmission relative to those on placebo. With the proposed sample size, the study would be well powered (>85%) to detect a large (three-fold) difference in HIV acquisition if the proportion of subjects becoming HIV-1 infected during follow-up on placebo was 10%, but less well powered to detect the same difference if the HIV-1 acquisition rate was 5%.

The endpoint for immunogenicity estimation is the proportion of subjects with a three-fold increase over pre-vaccination levels in serum anti-rotavirus IgA ELISA. Assuming 90% of the subjects in the study are evaluable for the immunogenicity analysis (n=72) and the true response rate is about 90%, the response rate will be estimable to within ± 7% with 95% confidence. If the true response rate is 80%, the precision will be lower (± 9%).

Subjects may acquire rotavirus and develop immunity independent of the vaccination. The extent to which this occurs in this study will be reflected in the placebo arm. The additional immunological benefit from the RotaTeq™ vaccine can be measured by the difference in response rates.
between Arm 1 (active vaccine) and Arm 2 (placebo). Table 3 shows the largest benefit the study could reasonably (with 80% power) attribute to the RotaTeq™ vaccine over the background rate. For example, if there was no naturally acquired immunity in the placebo arm and the vaccine was 95% effective, the study has 80% power to show a benefit due to the RotaTeq™ vaccine of 88%. If the difference was smaller, i.e., 20% of subjects in the placebo arm developed natural immunity and the vaccine was only 80% effective, then there would be at least an 80% chance to show a benefit due to the RotaTeq™ vaccine above 43%. These estimates also apply to the assessment of immunogenicity in the HIV-1 uninfected strata.

Table 3: Largest estimate of immunogenicity attributable to RotaTeq™ vaccine*

<table>
<thead>
<tr>
<th>Arm 2 response rate (placebo) %</th>
<th>Arm 1 response rate (RotaTeq™) %</th>
<th>Immunogenicity benefit of RotaTeq™ (Arm 1-2)</th>
<th>Largest detectable benefit of RotaTeq™</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>90</td>
<td>90</td>
<td>90</td>
<td>79</td>
</tr>
<tr>
<td>95</td>
<td>95</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td>60</td>
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<td>90</td>
<td>70</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>95</td>
<td>75</td>
<td>75</td>
<td>61</td>
</tr>
</tbody>
</table>

*Calculations done by simulation of B(n,p1) and B(n,p2) estimating 20th percentile of 1000 95% lower confidence bounds (normal approximation) of difference in two proportions.

Target enrollment is 160 HIV-1 infected and 160 HIV-1 uninfected children. The site survey responses from Uganda, Tanzania, Botswana, Zambia and Zimbabwe indicate that 100 HIV-1 infected newborns would enroll into this study each year. It is anticipated that enrollment to Stratum 2a may be completed before Strata 2b and 2c, and that enrollment to Stratum 2c may lag further. If enrollment to these two strata is not completed within 6 months of the closure of Stratum 2a, the study team may consider closing these strata and re-opening Stratum 2a in order to achieve the target of 160 HIV-1 infected subjects.

8.5 Monitoring

The study will be reviewed by a Study Monitoring Committee (SMC), whose members will be independent of the study (except for the protocol statistician and the non-voting, ex officio protocol medical officers) and have no financial or perceived conflict of interest. The SMC will conduct two early interim safety analyses (see Section 8.52) and yearly reviews thereafter, and will operate according to the procedures determined by the network. Details on the contents of analyses presented to the SMC will be described in a separate analysis plan which will be prepared after the study opens to accrual and before the first interim analysis. Data summaries will
be by treatment group. The Chair of the SMC will have primary responsibility for reporting the Committee’s comments to the IMPAACT Leadership and to the P1072 team.

The Core Team (Study Chair, Co-Chair, NIAID and NICHD medical officers, statistician, data manager, and CTS) will perform blinded reviews of all ≥ Grade 2 adverse events on regular conference calls (initially weekly, and as the study matures, possibly less frequently). Details on the contents of routine monitoring reports will be described in a separate monitoring plan which will be prepared before the study opens to accrual.

A difficulty in monitoring this study is that it is being conducted in a population where the incidence of gastrointestinal disease and other serious illnesses is relatively high. For example, in Zambia, incidence rates of diarrhea are estimated to be about 18 per 100 person-years (PY), unexplained fever is about 6/100 PY and vomiting about 5/100 PY. Subjects in P1072 will be followed for a maximum of 34 weeks after initial dose, so if these rates are similar in the P1072 population, the expected proportion of subjects experiencing diarrhea during study follow-up would be about 6%. It will be important to only trigger unscheduled safety reviews by the SMC if adverse event rates are higher than the expected background rates and to interpret the observed rates during the scheduled interim analyses accordingly. In Merck’s Phase III REST study, conducted in immunocompetent HIV-1 uninfected children, the incidence of elevated temperature and diarrhea was as high as 24%, but those that would have been assigned grades of ≥ 3 according to the Division of AIDS Grading Table would be less than 2%. The Protocol Team anticipates the observed rate of ≥ Grade 3 signs and symptoms in this study population will be less than 20% and that the rate assigned to be possibly/probably related to the vaccine to be lower, or around 10%. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004, Clarification August 2009 must be used and is available on the RSC website at (http://rsc.tech-res.com/safetyandpharmacovigilance).

8.51 Routine Monitoring

Core team calls will be held weekly (with the frequency possibly decreasing as the study matures) to review blinded data. Reviews will include assessment of accrual, loss to follow-up, study conduct (in particular, satisfactory collection and storage of blood samples required to assess the secondary endpoints), incidence of rotavirus disease, and to review all new ≥ grade 2 adverse events (passively reported laboratory results, signs and symptoms and unexpected
diagnoses), reportable EAEs, any cases of intussusception and new HIV infection occurring during the trial. Relationship to vaccination for all new adverse events will be assigned and recorded in the database. It is the responsibility of the Core Team to interpret toxicity data and make any decisions needed to protect subjects from undue risk. If at any time the Core Team determines that there are any vaccine-related endpoints that may compromise subject safety, the study may be suspended pending a thorough investigation by the SMC.

Specifically, the study may be paused for safety if:

- More than 20% of subjects (or more than four subjects if less than 20 subjects have been enrolled) in any stratum have experienced ≥ Grade 3 possibly/probably/definitely vaccine-related events,
- The number and quality of possibly/probably/definitely vaccine-related life-threatening events exceed that expected for the study population at the site where the study is undertaken,

If either of these events occurs, administration of the vaccines and accrual will be temporarily suspended in that stratum and the relevant safety data presented to the SMC. The SMC will make recommendations for continuation or suspension of the vaccine in that stratum and/or the study.

8.52 Interim Analyses (Safety Review by SMC)

The study will be formally reviewed by the SMC in an unblinded manner for safety monitoring purposes.

1. After enrollment and at least 14 days follow-up of 20 HIV-1 infected infants with CD4% ≥20% in Stratum 2a, and
2. After enrollment and at least 14 days follow-up of 20 HIV-1 infected infants with CD4% < 20% in Strata 2b and 2c (combined), and
3. Once a year thereafter.

Since results from assays to measure immunogenicity will be available only after the study closes to follow-up, SMC reviews will be for safety only, and specifically for reviewing any large and unexpected differences between the vaccine and placebo groups within strata.
Table 4: Probability of observing at least one life-threatening event or 2, 3 or 4 ≥ Grade 3 adverse events under potential rates of true toxicity at the first safety review (n=10)

<table>
<thead>
<tr>
<th>Life-threatening ≥ Grade 3</th>
<th>Probability of observing at least one-life-threatening event Or at least 2 ≥ Grade 3 events</th>
<th>Or at least ≥ Grade 3 events</th>
<th>Or at least 4 ≥ Grade 3 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.50</td>
<td>0.95</td>
<td>0.83</td>
</tr>
<tr>
<td>0.00</td>
<td>0.40</td>
<td>0.83</td>
<td>0.62</td>
</tr>
<tr>
<td>0.00</td>
<td>0.30</td>
<td>0.62</td>
<td>0.35</td>
</tr>
<tr>
<td>0.00</td>
<td>0.20</td>
<td>0.32</td>
<td>0.12</td>
</tr>
<tr>
<td>0.00</td>
<td>0.10</td>
<td>0.07</td>
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<tr>
<td>0.00</td>
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<td>0.01</td>
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</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.98</td>
<td>0.97</td>
</tr>
<tr>
<td>0.20</td>
<td>0.20</td>
<td>0.94</td>
<td>0.92</td>
</tr>
<tr>
<td>0.15</td>
<td>0.15</td>
<td>0.85</td>
<td>0.82</td>
</tr>
<tr>
<td>0.10</td>
<td>0.10</td>
<td>0.68</td>
<td>0.66</td>
</tr>
<tr>
<td>0.05</td>
<td>0.05</td>
<td>0.41</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Table 4 shows, for a range of true underlying rates of life-threatening and Grade ≥3 adverse events, the probability of observing at least one life-threatening event or at least 2, 3, or 4 Grade ≥3 adverse events at the first interim analysis in the vaccine group (n=10). For example, the probability of observing at least one life-threatening event or at least two ≥ Grade 3 adverse events would be 32% if the true underlying rate of life-threatening adverse events was 0% and the rate of ≥ Grade 3 adverse events was 20% and is 7% if the rate of ≥ Grade 3 events is ≤ 10% (the anticipated rate of possibly/probably/definitely vaccine-related events). These probabilities increase as the underlying true rates of adverse events increase.

At the time of the first interim analysis, the precision with which the adverse event rate will be estimated will be poor (the width of a 95% confidence interval will range from 31% to 62%) and there will be low power to detect differences in rates of adverse events between the vaccine and placebo groups (<80% power unless the true difference between the vaccine and placebo groups is greater than 60%). An additional complication is that the underlying rate of adverse events unrelated to vaccination will be relatively high. Rates of ≥ Grade 3 adverse events and life-threatening events will be reported (all and those assessed to be possibly/probably/definitely related to the study vaccine by the Core Team) in each stratum by treatment group, as well as expected background rates at each study site. Taking these issues into account, and after considering the specific types of toxicities and their clinical importance, if the lower limit of a 95% confidence interval for the difference in proportions...
of possibly/probably/definitely vaccine-related ≥ Grade 3 adverse events between the vaccine and placebo groups is >0% in the HIV-1 infected strata (which translates into an observed difference in number of events of at least 5), then the SMC should consider whether the study should continue.

At the second interim analysis there will be similar issues with small sample size in the HIV-1 infected subjects with CD4% <20%. However more precise estimates of rates of adverse events and differences between the vaccine and placebo groups in the HIV-1 infected subjects in Stratum 2a and in the HIV-1 uninfected subjects will be available to put the rates in Strata 2b and 2c in context. Taking these rates into account, and after considering the types of toxicities and their clinical importance, if the lower limit of a 95% confidence interval for the difference in proportions of possibly/probably/definitely vaccine-related ≥ grade 3 adverse events between the vaccine and placebo groups is >0% in the HIV-1 infected subjects with CD4% <20%, then the SMC should consider closing these strata to further accrual.

8.6 Data Analyses

Each outcome will be summarized by treatment group for the HIV-1 infected (by CD4% stratum and overall), HIV-1 uninfected, and subjects becoming HIV-1 infected after the first vaccination via breastfeeding separately. Formal comparisons will be done:

1. Between the vaccine and placebo groups in the HIV-1 infected subjects
2. Between the vaccine and placebo groups in the HIV-1 uninfected subjects

Since comparisons between the HIV-1 infected and HIV-1 uninfected groups are non-randomized, estimates of outcomes will be presented with appropriate confidence intervals.

Unadjusted comparisons will be presented as well as comparisons adjusted for potential confounders such as breastfeeding status, infant antiretroviral use (at entry and initiated during follow-up), maternal ARV use at birth and during infant follow-up, HIV disease status, etc. With the relatively small sample size of this Phase II study, multivariate analyses will have limited power to detect other than large effects on outcomes.
Stratum assignment will be based on HIV and CD4% results at screening. Some subjects may be found to have been incorrectly assigned as a result of HIV-1 tests collected at the entry visit. The stratum assignment of these subjects will be left as assigned in all primary analyses. Sensitivity analyses of primary and secondary objectives will be done a) removing these subjects and b) re-assigning them to the correct stratum. Details of all analyses will be itemized in a separate Analysis Plan which will be finalized after the study opens to accrual and before the first interim analysis.

8.61 Primary objective: to evaluate the safety of any dose of RotaTeq™ given to HIV-1 infected children

All subjects who receive at least one study vaccination and have follow-up will be included in the safety analysis. Primary analyses will use all safety outcomes including all ≥ Grade 3 hematology and chemistry laboratory results, all ≥ Grade 3 signs or symptoms (adverse events) not present before the administration of the first vaccination and occurring up to 42 days after the first, second or third vaccination. Secondary analyses will include: a) all events while subjects are on study, including any events occurring more than 42 days after each vaccination; and b) only those events deemed to be related to the vaccinations as determined by Core Team review. In these analyses, when there is a difference in the site principal investigator (PI) and the Core Team’s assessment of relationship to vaccine, the most-related assessment will be used. Separate tables will also be generated for adverse events of special interest, including elevated temperature (e.g., rectal temperature ≥ 38.1°C [≥100.5°F]), vomiting, diarrhea, and irritability) occurring within 7 days of each vaccination, occurring at any time after the first vaccination, and for those events deemed to be related to the vaccinations as determined by Core Team review. Acquisition of HIV during the trial will also be summarized (see section 8.633).

Numbers, proportions and 95% confidence intervals of subjects experiencing at least one new ≥ Grade 3 adverse event within 42 days of each vaccination will be summarized. Differences in proportions, as outlined in 8.6, will be estimated and compared using exact methods. Time to first new ≥ Grade 3 adverse event will be illustrated in each group using Kaplan-Meier curves. Comparisons will be done overall and then by important covariates including breastfeeding status and antiretroviral use at entry and initiated during follow-up.
Survival and the occurrence of new clinically significant diagnoses will be estimated and compared using Kaplan-Meier curves and log rank tests. Number of hospitalizations will be summarized and compared using Wilcoxon rank sum tests. Growth at each study visit will be summarized at each study visit and changes from baseline compared between strata.

8.62 Primary objective: To evaluate the immunogenicity of a 3-dose regimen of RotaTeq™ in HIV-1 infected and uninfected children born to HIV-1 infected mothers as measured by serum anti-rotavirus IgA and serum neutralizing antibody (SNA) responses to serotypes G1, G2, G3, G4 and P1A [8].

A positive response is defined as a ≥3-fold rise over pre-vaccine levels at least 14 days after the third vaccination. Summary statistics including 95% confidence intervals will be provided for the proportion of subjects with a three-fold increase over pre-vaccination levels for each outcome. Risk differences for the comparisons of interest will be estimated with 95% confidence intervals. Summaries of geometric mean titer (GMT) pre- and post-vaccine will be presented with confidence intervals. Correlations of changes in titer levels (on the log_{10} scale) from pre to post-vaccine will be calculated between IgA ELISA responses. This analysis will include subjects who receive the three scheduled doses and adhere to guidelines for the administration of the vaccines. Analyses will be done overall and adjusted for important covariates such as breastfeeding status and antiretroviral use (at entry and initiated during study follow-up).

8.63 Secondary objectives

8.631 To evaluate the fecal shedding of virus strains contained in the rotavirus vaccine after each dose of RotaTeq™. Proportions of subjects with vaccine strains in fecal samples will be summarized and compared on days 7, 14, 21 and 42 days after the first dose, and at days 7 and 21 after the next two doses. Stool samples from both the vaccine and placebo arms will be evaluated by the laboratory in batches during the study. However, the stool test results will not be available in an unblinded manner (i.e. with regard to treatment arm) until after the study has ended. Only subjects receiving active vaccination with RotaTeq™ will be included in the final analysis of vaccine virus shedding.
8.632 To evaluate the relationship of anti-rotavirus serologic immune responses to CD4 cell count and/or CD4%, plasma HIV RNA or DNA and antiretroviral therapy. HIV-1 infected subjects will be classified as responders (≥3-fold rise in IgA ELISA and SNA responses to each serotype separately) or non-responders as described above. Logistic regression will be used to assess the relationship of response with each covariate separately and in multivariate models. This analysis will include subjects who received the three scheduled doses and adhered to guidelines for the administration of the vaccines.

The following secondary objective will be analyzed using all HIV-1 uninfected patients who receive at least one vaccination:

8.633 To determine the safety of any dose of RotaTeq™ given to HIV-1 uninfected children. This analysis will be as described in the primary objective using data from the HIV-1 uninfected children and separately for those who become HIV-1 infected during the course of the study.

8.634 To compare in HIV-1 uninfected recipients of rotavirus vaccine or placebo, the acquisition of HIV infection by the last study visit. Proportions of subjects classified as HIV-1 uninfected at study entry and HIV-1 infected by their off study visit will be summarized by treatment arm. The timing of HIV infection in previously uninfected infants will be facilitated using the filter paper blood spots collected just prior to and 21 days after the second vaccine dose. These will be tested for the presence of HIV RNA only in subjects who were not HIV-1 infected as determined by blood samples tested at enrollment and were found to be HIV-1 infected as determined by blood samples obtained at the end of the study. This analysis will be descriptive only as it is anticipated that very few events will occur.

8.64 Exploratory objectives

8.641 To evaluate the relationship between virus shedding and rotavirus-specific SNA antibodies, copro-antibodies and CMI against rotavirus vaccine serotypes in recipients of rotavirus vaccine. The presence of vaccine-related rotavirus in fecal shedding will be determined as in 8.622 and logistic regression used to assess the relationship of the covariates with its presence in univariate and multivariate models.
Models will be fit separately by HIV group with treatment arm and with all subjects controlling for HIV infection status, treatment and interactions between HIV infection status and treatment. This analysis will be done in subjects who receive vaccine doses at each time point.

8.642 To evaluate IgA and IgG copro-antibodies and CMI responses against rotavirus serotypes contained in the vaccine in HIV-1 infected versus uninfected infants. Scatter plots of antibody response versus CMI responses will be used for exploratory analyses with non-parametric correlations calculated separately by HIV group. Linear regression models on appropriately transformed outcomes will be used to test for differences by HIV group. This analysis will be done in subjects who receive vaccine doses at each time point.

8.643 To compare in HIV-1 infected recipients of rotavirus vaccine or placebo the CD4% at the last study visit and the change in CD4% at the last study visit relative to the first study visit. Changes from baseline to the last study visit in CD4% will be summarized and compared by treatment arm using Wilcoxon rank sum tests.

8.644 To evaluate LPS, sCD-14, LBP and EndoCAb levels over time between HIV-1 infected and HIV-1 uninfected subjects either receiving RotaTeq™ vaccine or placebo, levels and changes from baseline will be summarized at each measured time point for each outcome. Depending on the profiles of response, repeated measures analysis using either parametric models or generalized estimating equations will be used to compare profiles by HIV and vaccination status.

8.645 To evaluate the relationship of mucosal and CMI responses to CD4 cell counts and/or CD4%, plasma HIV RNA or HIV DNA and ART, regression models (either linear or logistic, depending on the distribution of mucosal and CMI responses) will be used to assess the relationship with each covariate separately and in multivariate models.

Data analyses activities will be prioritized to address the primary and secondary objectives of the study, and will be done independently of any analyses of the exploratory objectives.
9.0 HUMAN SUBJECTS

9.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendix II), and any subsequent modifications must be reviewed and approved by the IRB and/or IRB/Ethics Committee (EC) responsible for oversight of the study. Written informed consent must be obtained from the parents or legal guardians of subjects who cannot consent for themselves. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent or legal guardian.

Each site which receives US Health and Human Services (HHS) 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 subjects and determines when a study subject 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 national, local and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the US FDA, by the pharmaceutical sponsor (Merck &Co., Inc.), and by the NIH, IRB/EC, and Office for Human Research Protections (OHRP) or sponsor’s designee.

9.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT Network, NIAID, NIH, OHRP, Merck & Co., Inc., FDA, the site IRB/EC, or other host country governmental regulatory agencies as part of their duties to ensure that research subjects are protected.
10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT and Merck & Co., Inc. policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 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 Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx
12.0 REFERENCES


(10) Vesikari T, Matson D, Van Damme P et al. Incidence of intussusception with the pentavalent (human-bovine) reassortant rotavirus vaccine (RRV) is similar to placebo. 23rd Annual Meeting of the European Society for Paediatric Infectious Diseases, Valencia, Spain . 5-18-2005.


(36) Melvin AJ, Mohan KM. Response to immunization with measles, tetanus, and Haemophilus influenzae type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with highly active antiretroviral therapy. Pediatrics 2003; 111(6 Pt 1):e641-e644.


(49) McNeal MM, VanCott JL, Choi AH et al. CD4 T cells are the only lymphocytes needed to protect mice against rotavirus shedding after intranasal immunization with a chimeric VP6 protein and the adjuvant LT(R192G). J Virol 2002; 76(2):560-568.


# APPENDIX IA - Schedule of Evaluations for HIV-1 Infected Infants

## EVALUATIONS

<table>
<thead>
<tr>
<th>Informed Consent</th>
<th>Entry 16 (Day 0)</th>
<th>DOSE #1</th>
<th>DOSE #2</th>
<th>DOSE #3</th>
<th>Unplanned visit for gastroenteritis</th>
<th>Early Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Vaccination 3</td>
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<td>X</td>
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<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Virology

<table>
<thead>
<tr>
<th>RNA PCR for HIV in blood</th>
<th>X17</th>
<th>X8 1mL</th>
<th>X11 1mL</th>
<th>X12 1mL</th>
<th>X 1mL</th>
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<tbody>
<tr>
<td>DNA PCR for HIV in blood</td>
<td>X</td>
<td>1mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried Blood Spot</td>
<td>X15</td>
<td>1mL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Immunology/Other Special Tests

<table>
<thead>
<tr>
<th>Lymphocyte subsets (CD4 counts and CD4%)</th>
<th>X 1mL</th>
<th>X11 1mL</th>
<th>X12 1mL</th>
<th>X 1mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-rotavirus antibody 6</td>
<td>X 2mL</td>
<td>X 2 mL</td>
<td>X12 2 mL</td>
<td>X 2mL</td>
</tr>
<tr>
<td>PBMC for rotavirus CMI and plasma for measuring bacterial translocation7</td>
<td>X 4mL</td>
<td>X 4mL</td>
<td>X 4mL</td>
<td>X 4mL</td>
</tr>
</tbody>
</table>

### TOTAL BLOOD VOLUME (mL)

<table>
<thead>
<tr>
<th>Entry 16 (Day 0)</th>
<th>Day 7*</th>
<th>Day 14*</th>
<th>Day 21*</th>
<th>Day 42*</th>
<th>Day 0</th>
<th>Day 7*</th>
<th>Day 14*</th>
<th>Day 21*</th>
<th>Day 42*</th>
<th>Day 0</th>
<th>Day 7*</th>
<th>Day 14*</th>
<th>Day 21*</th>
<th>Day 42*</th>
<th>Day 0</th>
<th>Day 7*</th>
<th>Day 14*</th>
<th>Day 21*</th>
<th>Day 42*</th>
<th>Day 0</th>
<th>Day 7*</th>
<th>Day 14*</th>
<th>Day 21*</th>
<th>Day 42*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mL</td>
<td>8mL</td>
<td>4mL</td>
<td>6-8 mL</td>
<td>4-8 mL</td>
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</tr>
</tbody>
</table>

*Window for day 7, 14, or 21 visits is ± 3 days;  **Window for day 42 visits is ±5 days
Footnotes:

1. Screening: Must be within the 30 days prior to enrollment. Consent can be obtained prior to expected date of delivery as well as at any time prior to screening. Subjects must be between the ages of ≥2 to <15 weeks to be screened.

2. Demographic and medical history (length, height, weight, signs and symptoms ≥ grade 1, diagnoses, ARV history (maternal ARV use during pregnancy, infant ARV use at birth, infant ARV use since birth), other vaccinations since birth, history of breastfeeding since birth). A thermometer will be provided to caretakers, who will be instructed in its use and how to record measurements. A case report form will be provided for use during this visit.

3. Length, weight, temperature, signs and symptoms ≥ grade 1, diagnoses, breastfeeding, ARVs, other non-ARV medications, and vaccinations from birth will be recorded on a case report form. At each study visit, similar information since the previous visit will be captured as well. Maternal CD4 cell count (including CD4% if available), maternal ARV treatment regimen and intercurrent maternal diarrheal illness will also be captured on a case report form at these visits.

4. All post-vaccination visits will include solicitation of adverse events as observed by caretaker and/or clinician including signs and symptoms ≥ grade 1, new clinically significant diagnoses, results of any passively collected laboratory values, and measurement of length and weight. Changes since previous visit in ARVs and other concomitant medications and any other non-study vaccinations should be reported, as well as solicitation of information on breastfeeding status since the previous visit. If a subject is unable to travel to the clinic for a scheduled visit, a study clinician may visit the subject at his/her home. This can be arranged on a case-by-case basis. All suspected serious adverse events will be seen at the study site within 48 hours of reporting such an event. NOTE: At ALL scheduled/unscheduled study visits (including clinic/office or home visits), a directed history and clinical exam, including an abdominal exam to exclude any signs of intussusception, should be carried out. Sites are also encouraged to follow-up on tests/investigations (e.g. X-rays) that are ordered on a study participant to ensure that the participant was able to complete them.

5. Stool specimens: Refer to the LPC. Minimum of 6mL required. Plastic containers (large fecal tubes with scoops) will be provided for collection and storage of stool samples.

6. Serum from these samples will be tested for rotavirus-specific neutralizing antibodies and IgA antibodies measured by ELISA.

7. Heparinized blood from the first 100 HIV-1 infected subjects will be separated into PBMC’s which will be frozen and later evaluated for cell-mediated immune responses to rotavirus antigens and T cell activation. Plasma will be tested for LPS, sCD-14, LBP, and ENDoCAB as measures of translocation of bacterial products from the gastrointestinal tract. Sites will be notified when this stratum has been filled and frozen cells will no longer be needed. See LPC and P1072 MOPs for further information.

8. If only one test result is available to document the subject being HIV-positive (from the screening result or other documented test), the investigator may proceed with enrolling the subject and may use the Entry (Dose #1 Day 0) blood draw to perform an HIV RNA PCR test for confirmation of HIV infection. The site DOES NOT have to repeat the test result before enrollment but blood must be collected prior to administration of the study vaccine.

9. If the second or third dose of vaccine is given before day 42, this visit may be omitted.

10. If the next dose of vaccine is given before day 42, the stool sample will be obtained just prior to administering the second dose of vaccine.

11. If the baby weighs less than 5kg at this visit, the PCR and CD4 blood draws must be omitted – only blood for anti-rotavirus antibody and PBMCs/CMI should be drawn. If the baby weighs more than 5kg at this visit, all blood draws may be drawn.

12. These blood draws will be done only if they were not drawn on the ‘Dose #3 Day 14’ visit.
13. If the second dose of vaccine is missed, there should be a safety follow-up every 6 weeks for 12 weeks. If the third dose of vaccine is missed, there should be a safety follow-up visit at 6 weeks.

14. DNA PCR is the preferred assay for the screening visit. However, if a DNA PCR test is not available, an RNA PCR result is acceptable.

15. A dried blood spot filter paper card with 5 filled blood spots will be obtained from subjects who are HIV-1 positive. This sample will be tested in case there is a discrepancy between the HIV PCR results at screening and entry.

16. ALL HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ARV) before, or at the time of, administration of the 1st dose of study vaccine/placebo. NOTE: It is not acceptable for subjects to take a prescription home with them to start ARV therapy on the day of vaccination.

17. If HIV-1 DNA PCR is unavailable at screening, HIV-1 RNA PCR may also be used.

For insufficient blood draws, priority order is as follows: HIV-1 plasma RNA or DNA and CD4% will measured first (if indicated for that blood draw), followed by testing for anti-rotavirus antibody, and then by assay for rotavirus-specific CMI.
### Appendix IB – Schedule of Evaluations for HIV-1 Uninfected Infants

<table>
<thead>
<tr>
<th>EVALUATIONS</th>
<th>DOSE #1</th>
<th>DOSE #2</th>
<th>DOSE #3</th>
<th>Unplanned visit for gastroenteritis</th>
<th>Early Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office Visit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool Sample</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA PCR for HIV Nucleic Acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried Blood Spot</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets (CD4 counts and CD4%)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-rotavirus antibody</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC for rotavirus CMI; plasma for bacterial translocation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOL(mL)</td>
<td>2mL</td>
<td>7mL</td>
<td>4mL</td>
<td>1mL</td>
<td>4mL</td>
</tr>
</tbody>
</table>

**Notes:**
- *Window for day 7, 14, or 21 visits is ± 3 days;**
- **Window for day 42 visits is ± 5 days**
Footnotes:

1. Screening: Must be within the 30 days prior to enrollment. Consent can be obtained prior to expected date of delivery as well as at any time prior to screening. Subjects must be between the ages of ≥2 to <15 weeks to be screened.

2. Demographic and medical history (length, height, weight, signs and symptoms ≥ grade 1, diagnoses, ARV history (maternal ARV use during pregnancy, infant ARV use at birth, infant ARV use since birth), other vaccinations since birth, history of breastfeeding since birth). A thermometer will be provided to caretakers, who will be instructed in its use and how to record measurements. A case report form will be provided for use during this visit.

3. Length, weight, temperature, signs and symptoms ≥ grade 1, diagnoses, breastfeeding, ARVs, other non-ARV medications, and vaccinations from birth will be recorded on a case report form. At each study visit, similar information since the previous visit will be captured as well. Maternal CD4 cell count (including CD4% if available), maternal ARV treatment regimen and intercurrent maternal diarrheal illness will also be captured on a case report form at these visits.

4. All post-vaccination visits will include solicitation of adverse events as observed by caretaker and/or clinician including signs and symptoms ≥ grade 1, new clinically significant diagnoses, results of any passively collected laboratory values, and measurement of length and weight. Changes since previous visit in ARVs and other concomitant medications and any other non-study vaccinations should be reported, as well as solicitation of information on breastfeeding status since the previous visit. If a subject is unable to travel to the clinic for a scheduled visit, a study clinician may visit the subject at his/her home. This can be arranged on a case-by-case basis. All suspected serious adverse events will be seen at the study site within 48 hours of reporting such an event. NOTE: At ALL scheduled/unscheduled study visits (including clinic/office or home visits), a directed history and clinical exam, including an abdominal exam to exclude any signs of intussusception, should be carried out. Sites are also encouraged to follow-up on tests/investigations (e.g. X-rays) that are ordered on a study participant to ensure that the participant was able to complete them.

5. Stool specimens: Refer to the LPC. Minimum of 6mL required. Plastic containers (large fecal tubes with scoops) will be provided for collection and shipment of stool samples.

6. Serum from these samples will be tested for rotavirus-specific neutralizing antibodies and IgA antibodies measured by ELISA.

7. Heparinized blood from the first 100 HIV-1 uninfected will be separated into PBMC’s which will be frozen and later evaluated for cell-mediated immune responses to rotavirus antigens and T cell activation. Plasma will be tested for LPS, sCD-14, LBP, and ENDoCAB as measures of translocation of bacterial products from the gastrointestinal tract. Sites will be notified when this stratum has been filled and frozen cells will no longer be needed. See LPC.

8. If the second or third dose of vaccine is given before day 42, this visit may be omitted.

9. If the next dose of vaccine is given before day 42, the stool sample will be obtained just prior to administering the second dose of vaccine.

10. If the baby weighs less than 5kg at this visit, the lymphocyte subset blood draw must be omitted – only blood for anti-rotavirus antibody and PBMCs/CMI should be drawn. If the baby weighs more than 5kg at this visit, all blood draws may be drawn.

11. These tests will be done only if not performed on Day 14 after the third dose of vaccine.

12. If the second dose of vaccine is missed, there should be safety follow-up visits every 6 weeks for 12 weeks post Dose #1. If the third dose of vaccine is missed, there should be a safety follow-up visit at 6 weeks post Dose #2.

13. DNA PCR is the preferred assay for the screening visit. However, if a DNA PCR test is not available, an RNA PCR result is acceptable.
14. A dried blood spot filter paper card with 5 filled blood spots will be obtained from subjects who are not HIV-1 infected, at the following time points: Dose #1 Day 0 (Entry), Dose #2 Day 0 and Dose #2 Day 21. These specimens will be labeled and stored as described in the LPC. These samples will be tested for the presence of HIV RNA only if the subject has a positive diagnostic test for HIV at or before the end of the study.

For insufficient blood draws, list priority order: HIV-1 plasma RNA/DNA and CD4% will measured first (if indicated for that blood draw), followed by testing for anti-rotavirus antibody, and then by assay for rotavirus-specific CMI.
## APPENDIX II

**Planned Laboratory Testing on Collected Specimens**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Assay</th>
<th>Testing Lab / Coordinating Lab</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Lymphocyte subsets</td>
<td>All Sites: Local IMPAACT approved lab</td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>HIV-1 RNA PCR or DNA PCR (viral load)</td>
<td>All Sites: Local IMPAACT approved lab</td>
<td></td>
</tr>
<tr>
<td>Dried Blood Spot (DBS)</td>
<td>HIV-1 RNA PCR or DNA PCR (if needed for clarification)</td>
<td>All Sites: Biomedical Research Institute (BRI)</td>
<td>Specimens should be batch shipped quarterly to BRI – final destination UNC, NC</td>
</tr>
<tr>
<td>Serum</td>
<td>Anti-rotavirus antibody</td>
<td>All Sites: Biomedical Research Institute (BRI)</td>
<td>Specimens should be batch shipped quarterly to BRI – final destination PPD</td>
</tr>
<tr>
<td>PBMC</td>
<td>Rotavirus cell-mediated immunity</td>
<td>All Sites: Weinberg Immunology Lab University of Denver, CO</td>
<td>Specimens should be batch shipped quarterly</td>
</tr>
<tr>
<td>Plasma</td>
<td>Bacterial translocation</td>
<td>All Sites: Biomedical Research Institute (BRI)</td>
<td>Specimens should be batch shipped quarterly to BRI – final destination JHU</td>
</tr>
<tr>
<td>Stool</td>
<td>Copro antibodies and testing for vaccine strain virus</td>
<td>All Sites: Biomedical Research Institute (BRI)</td>
<td>Specimens should be batch shipped quarterly to BRI – final destination PPD</td>
</tr>
</tbody>
</table>
APPENDIX III

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

SAMPLE INFORMED CONSENT
For protocol: P1072
Safety and Immunogenicity of a Live, Attenuated, Rotavirus Vaccine (RotaTeq™) in HIV-1 Infected and Uninfected Children Born to HIV-1 Infected Mothers,
Version 3.0, Dated November 10, 2011

SHORT TITLE FOR THE STUDY: Rotavirus Vaccine (RotaTeq™) Study

INTRODUCTION

You are being asked to allow your baby to take part in this research study because when
the mother of a baby is infected with the human immunodeficiency virus (HIV), the baby
may also be infected with HIV. Children who are HIV-1 infected, and are currently
taking anti-HIV medications or are going to start taking anti-HIV medications as
well as those who are HIV-uninfected, are being asked to take part in this study. This
study is sponsored by the National Institutes of Health (NIH) in the United States of
America. The doctor in charge of this study at this site is: (insert name of Principal
Investigator). Before you decide if you want your baby to be a part of this study, we
want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Rotavirus is the leading cause of severe diarrhea in infants and young children throughout
the world. Almost every child in the world is infected with rotavirus by 3 to 5 years of
age. Rotavirus infection in infants can lead to severe vomiting, diarrhea and dehydration.
Research in South Africa and the United States has shown that the symptoms of rotavirus
diarrhea may be worse in HIV-1 infected patients that have other medical problems such
as poor nutrition or other infections, and rotavirus infection may interfere with their
nutrition.

At this time there is no licensed rotavirus vaccine in the countries where this study is
being done. If the vaccine becomes available in your country while your child is
participating in this study, your child will NOT be taken off study, unless you request that your child stop participating. Those children receiving placebo will receive active vaccine if they are eligible. Those children receiving active vaccine will complete the vaccine series. Your child will then be followed on study on the normal schedule described below.

Many infants in Africa who will be getting this vaccine (called RotaTeq™) have HIV-1 infection, and there is not enough information on how HIV-1 infected children will respond to this vaccine. This vaccine may be given to children as young as four weeks of age so that it happens at the same time that other vaccines are given to young infants. RotaTeq™ was developed to protect young children against rotavirus infections. The vaccine used in this study will be provided by Merck & Co., Inc. The vaccine cannot cause rotavirus disease. The vaccine is given as liquid drops in your baby’s mouth. This vaccine was approved on February 3, 2006 by the United States Government group responsible for approving new vaccines, and since then it has been recommended for all infants in the United States. The main purpose of this study is to test how safe the RotaTeq™ vaccine is, when given to HIV-1 infected infants born to HIV-1 infected mothers in the developing world. The vaccine will be studied in both HIV-1 infected infants and non-infected infants so that the two groups can be compared as to how they tolerate the vaccine and how their immune systems respond to the vaccine.

The study will look at the following things:

• To see if there are any important side effects due to the vaccine
• To see if the body’s defense system produces antibodies (substances the body makes in response to an infection or vaccination to help fight off disease) because of the vaccination
• To see if there are any differences in the amount of special immune cells (CD4 T-cells) that fight HIV in the HIV-1 infected children who get the rotavirus vaccine

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

Your baby will have 16 office visits during the estimated 8 months that he/she will be taking part in this study, as indicated on the Subject Visit Schedule on the following page. A more detailed description of what will happen at each visit is outlined below.

Before Starting the Study (“Screening Visit”; this will take approximately 1½ hours)

While you are still pregnant, or in the 15 weeks after your baby is born, you may agree to have your baby participate in this trial. If you agree to allow your baby to participate in this study, between 2 and 15 weeks after your baby is born, he/she will have some basic blood tests done to confirm whether he/she has HIV-1 infection, a physical exam will be conducted, and you will be asked some questions to be sure your child can participate in this study.

• The study staff will ask you some questions about your child’s medical history, including immunizations, and use of any past or present anti-HIV drugs. The staff
may ask for permission to review your child’s medical records. Study staff will also ask if you are breastfeeding your child.

- About ½ teaspoon (2.5 mL) of blood will be taken from your baby for this test to measure the levels of HIV and CD4 cells (cells that fight HIV). You will be given the results of your baby’s HIV/CD4 tests once they become available.

### P1072 SUBJECT VISIT SCHEDULE

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>Screening Visit</th>
<th>Dose 1 (Entry Day 0)</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 42</th>
<th>Dose 2 (Entry Day 0)</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 42</th>
<th>Dose 3 (Entry Day 0)</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office Visit</td>
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<tr>
<td>Stool Sample</td>
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*Screening Visit: The subject must be screened within the 30 days before enrollment. Subjects must be at least 2 weeks of age, but not more than 15 weeks of age to be screened.

**Randomization: This means that you/your child will be placed in a study group by chance, like flipping a coin.

**During the Study**

At the “Enrollment Visit” your child will be assigned to one of the following sections:
- If your infant is not infected with HIV-1, he/she will be in Section 1
- If your infant is infected with HIV-1, he/she will be assigned into Section 2A, Section 2B, or Section 2C depending on the level of CD4 cells in their body.

During the study, your baby will be randomly assigned (placed in a study group by chance, like flipping a coin) to a RotaTeq™ vaccine group or placebo (a substance
identical in appearance to the vaccine, but that is inactive against the rotavirus) group. Each child will have an equal chance of being assigned to the vaccine group or to the placebo group. All placebos were created by Merck & Co., Inc in the image of the active product. This means that the study uses a look-alike vaccine tube for the placebo that resembles RotaTeq™ as much as possible." Neither your child's doctor nor clinic staff, nor you, will know if your child receives the actual RotaTeq™ or the placebo substance while the study is being conducted (i.e., the treatments will be "blinded"). However, after the study ends, this information will be made available and you will be notified which substance (actual RotaTeq™ or placebo) your child received.

During each weekly office visit, the subjects’ mothers will also be asked about their own CD4 counts (including CD4% if available), ARV medications and intercurrent diarrheal illnesses in order to help the investigators learn about how HIV-1 transmission affects HIV-negative infants. Study staff will also ask if you are breastfeeding your child.

At the first visit, study staff will ask you how they can best contact you. If you miss a scheduled clinic visit, study staff will attempt to contact you.

There is a chance that while on this study, your baby may have diarrhea or begin vomiting, although this may have nothing to do with the vaccine, since there are other germs that may cause these conditions. If your child should develop these symptoms, it is very important to telephone your study clinic as soon as possible, or to bring your child to the clinic if you cannot contact them by telephone. Do not give your child any medication unless it is approved by the study doctor or nurse (clinician). After you speak with the study clinician, you may be instructed to bring your child to the clinic, where they will probably take a sample of your child's stool and decide on how to treat the problem.

**First Vaccine:** (This visit will take about 1½ hours.)

On the day that your infant receives his/her first vaccine, a stool specimen will be collected to test for the presence of rotavirus in the stool or if there are any antibodies in your baby’s bowels. **Tests for other germs in the stool may also be done.** In addition, about 1½ teaspoons (7.5 mL) of blood will be taken to measure your baby’s antibodies to the rotavirus. **Additional tests related to the rotavirus vaccine may also be done.** Stool specimens will be collected on days 7, 14, 21, and 42 after the first vaccination, and about one teaspoon (5 mL) of blood will be drawn on day 21 after the first dose of vaccine.

**Second Vaccine:** (This visit will take about 1½ hours.)

Just before the second vaccine, if your baby is not HIV-infected, a drop of his/her blood will be collected for testing at a later date. On days 7 and 21 after your baby receives the second vaccine; a stool specimen will be collected. If your baby receives the second dose less than 42 days after the first dose of vaccine, another stool sample will be collected before your baby is given the third vaccine. These stool specimens will be
tested to see if the vaccine virus is present in your baby’s stool or if there are any antibodies in your baby’s bowels. Tests for other germs in the stool may also be done. In addition, if your baby is not HIV-infected, another drop of your baby’s blood will be collected on a piece of paper at day 21 after the second dose of vaccine for later testing.

**Third Vaccine:** (This visit will take about 1½ hours.)

About 1½ teaspoons of blood (7.5 mL) will be collected on the 14th day after your baby is given the third vaccine to measure your baby’s response to rotavirus. Additional tests related to the rotavirus may also be done. Your child’s blood may also be drawn for HIV testing on days 14 or 42 after the third vaccine. Stool samples will also be collected on days 7 and 21 after the third vaccine. Just like the earlier stool samples, these will be tested to see if the vaccine virus is present in your baby’s stool or if there are any antibodies in the intestinal area. Tests for other germs in the stool may also be done.

If your baby has diarrhea when he or she comes to the clinic, you will be provided results of any tests conducted as part of your study doctor’s routine standard of care.

**Off-Treatment Study Visits (Follow-up Period), and Early Discontinuation Study Visit**

If you no longer want your baby to be in this study, or if he/she no longer can be in this study, you will be asked to bring your child to the clinic one last time for some end of study tests.

**Storage of Blood & Stool Samples**

Some of your baby’s blood and stool may be stored (with usual protectors of identity) at a special laboratory facility and used for future IMPAACT-approved, HIV-related research to understand how a vaccinated child’s blood cells respond to the rotavirus vaccine. Some of your baby’s blood and stool samples may be shipped outside the country (i.e., shipped to the US) where they were collected. Only approved researchers will have access to them. People who work at the facility will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies you/your child. 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 National Institutes of Health (NIH). There is no time limit on how long your baby’s samples will be stored.

The researchers do not plan to contact you or your baby’s regular doctor with the results of studies done using your baby’s stored stool or blood samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your baby’s medical care. If the researchers decide that the result of a certain study provides important information for your baby’s medical care, your baby’s 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 in your address or phone number.

You may decide that you do not want your baby’s samples stored for future research studies. Your baby can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your baby’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

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

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

__________ Yes  __________ No  __________ Date

I (the subject’s mother) agree to allow investigators to ask me about my own CD4 counts (including CD4% if available) and ARV medications.

__________ Yes  __________ No  __________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 320 children will take part in this study; 160 HIV-1 infected and 160 HIV-uninfected.

HOW LONG WILL MY BABY BE IN THIS STUDY?

Your baby will be in this study for about 8 months.

WHY WOULD THE DOCTOR TAKE MY CHILD/BABY OFF THIS STUDY EARLY?

The study doctor may need to take your baby off the study early without your permission if:

- The study is cancelled by the IMPAACT Network, the US Food and Drug Administration (FDA)
- US National Institutes of Health (NIH), the drug company supporting this study, the US Office for Human Research Protections (OHRP), the host country governmental regulatory agencies, or the site’s Institutional Review Board (IRB) or Ethics Committee (EC). An IRB and/or EC are committees that watch over the safety and rights of research subjects.
- A Study Monitoring Committee recommends that the study be stopped early. A Study Monitoring Committee is an outside group of experts that makes sure that the safety of the participating infants is closely evaluated.
- Your baby is not able to attend the study visits as required by the study
During the study:

If your baby must permanently stop taking study vaccine or placebo before his/her study participation is over, the study doctor will discuss other options that may be of benefit to your baby. The study doctor will ask your baby to continue to be part of the study and return for some study visits and procedures.

The study doctor may also need to take your baby off the study vaccine without your permission if:

- Continuing the study vaccine may be harmful to your baby
- Your baby needs a treatment that he/she may not take while on the study
- Your baby is not able to take the study vaccine as required by the study

WHAT ARE THE RISKS OF THE STUDY?

Blood Draw Risks:

Your baby may feel some discomfort when blood is drawn for this study. Other risks may include bleeding, bruising and swelling or a small blood clot may form where the needle enters the skin. There is also a small risk of infection from drawing blood.

Vaccine Risks:

The common side effects that may be expected with RotaTeq™ are: fever, vomiting, irritability, and diarrhea.

In the studies done so far, the side effects of RotaTeq™ have generally been mild. Three studies of over 70,000 infants showed that the vaccine was generally well tolerated.

Other less common side effects have been reported, but none of them have been shown to be caused by the vaccine. The study doctor or staff can discuss these with you. There may be other side effects or risks that are not known at this time. The effect of the vaccination on your child’s HIV infection or chance of acquiring HIV infection are not known; however, we will closely follow all children in the study to become aware as soon as possible if this happens.

When a baby is infected with rotavirus from the environment, the virus is often found in the stool and passed on to others in this manner. A baby that receives the rotavirus vaccine may have the vaccine virus present in the stool for prolonged periods, which is something that we are testing. The vaccine virus in the stool may also be passed on and may possibly cause rotavirus infection in other non-vaccinated family members.
Germs other than rotavirus can also cause vomiting and diarrhea. The study vaccine is directed only against the rotavirus germ and not against the other germs. Your child may have diarrhea caused by rotavirus or one of the other germs.

While your baby is on this study it is very important that you and other family members wash your hands after handling your baby’s diapers to reduce the chance of spreading rotavirus to others.

You must tell your study doctor or nurse before enrolling in any other clinical trials while your child is on this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your baby takes part in this study and gets the vaccine, there may be a direct benefit to him/her, but no guarantee can be made. It is also possible that your baby may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES MY BABY HAVE BESIDES THIS STUDY?

You may choose to not have your infant participate in this study. Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your baby’s personal information confidential. 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 records may be reviewed by the US Food and Drug Administration (FDA), (insert name of site) IRB/EC, US National Institutes of Health (NIH), NIAID, US Office of Human Research Protections (OHRP), study staff, study monitors, the drug company supporting this study (Merck & Co., Inc.) and their designees.

WHAT ARE THE COSTS TO ME?

You will not be expected to pay for any study vaccines, study related visits, or study procedures. Antiretroviral therapy will NOT be provided as part of the study medications. These medications will be provided via local access programs or through standard of care.
WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, he/she will be given immediate treatment for his/her injuries. There is no program for compensation either through this institution or the US National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY BABY’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or leave this study or take your baby out of the study at any time. Your baby will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your baby’s health, welfare or willingness to stay in this study. Let the study staff know if you want the results of the study.

WHAT DO 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 subject, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

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 Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

________________________  ____________________________________
Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date
(As appropriate)

__________________________  ____________________________________
Witness’ Name (print)  Witness’s Signature and Date
(As appropriate)

__________________________  ____________________________________
Father’s Name  Father’s Signature and Date
(If father’s consent is required)  (If father’s consent is required)
WHO Recommendations for Rotavirus Vaccination: Impact on P1072

The WHO Strategic Advisory Group of Experts (SAGE) on immunization met during April 6-8, 2009, and developed recommendations for routine rotavirus immunization. Previously, an expert consultation on rotavirus vaccines had met in November 2007 and concluded that vaccine efficacy data could be extrapolated from one country to other countries with similar rates of under-five child mortality. Initial efficacy trials of rotavirus vaccines Rotarix™ and RotaTeq™ were carried out in Latin America, Europe and US; subsequently additional trials were needed in Africa and Asia. Rotarix™ trials were carried out in Malawi and South Africa and were evaluated by an ad-hoc group of experts in early 2009, in order to provide SAGE with recommendations based on this new evidence. These phase III trials of Rotarix™ in Malawi and South Africa were completed in July 2008. Vaccine was administered in 2 or 3 dose schedules concurrently with other vaccines in the Expanded Programme on Immunization (EPI), including oral polio vaccine (OPV). HIV-1 infected infants and breastfeeding infants were included in the population studied. Based on review of the evidence, SAGE recommended that rotavirus vaccination of infants be included in all national immunization programs. The group strongly recommended the introduction of the vaccine in countries where diarrheal deaths account for >10% of mortality in children under five.

The WHO recommendations are based on very limited information concerning the safety and immunogenicity of rotavirus vaccine in HIV-1 infected children. There are some data on the use of Rotarix™ – a monovalent human rotavirus-derived strain – in HIV-1 infected infants. Steele et al conducted a double-blind, placebo-controlled study of safety, reactogenicity and immunogenicity of Rotarix™ in 100 HIV-1 positive infants in South Africa (1, 8). Similar data are not available for RotaTeq™ – a bovine-based pentavalent vaccine. Thus, even the limited information on safety and immunogenicity for Rotarix™ cannot be assumed to apply to RotaTeq™.

WHO SAGE recommended that data on efficacy and effectiveness be sought for all oral rotavirus vaccines for each of the mortality strata. Bridging data, including immunogenicity data, could be used once appropriate criteria for vaccine evaluation using such data have been established (2). So far, immunogenicity data is not highly correlated with protection from severe disease, although modest correlations have been observed. Further information on correlates of protection is required to accomplish bridging studies using immune responses to vaccine.

Ethical Justification for Use of Placebo Control

It is important to consider the implications of the WHO recommendation that rotavirus vaccination of infants be included in all national immunization programs, particularly in
countries where diarrheal deaths account for greater than 10% of mortality in children below the age of five. This policy has not yet been adopted at the national level by any of the countries in which P1072 will be conducted; however, the existence of the WHO recommendation indicates an increasingly broad consensus that the existing rotavirus vaccines are safe and effective and that their use constitutes an important public health intervention in developing countries where gastrointestinal disease and childhood morbidity and mortality are highest. In general, research subjects in the control arm of a study should receive interventions that have been proven effective and have become the standard of care. In this case, there are questions about whether the level of effectiveness in HIV-1 infected infants is established; there are also questions about whether there could be differential responses in infants who are HIV-1 exposed and breastfeeding. Even in cases where there is a strong argument that effectiveness is established for the specific population under study, the use of placebo as a comparator in clinical research can be ethically acceptable when there are compelling scientific reasons for the use of placebo, and when withholding the standard of care would not result in serious or irreversible harm (3). It is also important that research subjects not be denied access to care that they would otherwise receive because of their involvement in research.

The ethical justification for the placebo controlled design used in P1072 is as follows: First, there are compelling scientific reasons for the placebo control design. There is a need for more data on vaccine responses to different rotavirus genotypes, and for safety and immunogenicity in HIV-1 exposed and HIV-1 infected infants. Placebo controls are the only reliable way to measure adverse events and immunogenicity in these groups, since the background rate of adverse events is high, and because naturally occurring rotavirus infection can complicate analyses of immune response to vaccine in the absence of a placebo control group. Second, the study team will minimize risks to the subjects to ensure that they are not exposed to serious and irreversible harm. Infants in the study, whether recipients of vaccine or placebo, will receive very close follow up and either home-based or hospital care for severe gastroenteritis potentially caused by rotavirus infection. Risk minimization is critical, since severe gastroenteritis has a higher mortality rate in developing countries than in high income countries, in part because of living conditions and access to care. Finally, none of the infants in the study will be denied care that would be otherwise available to them.

Compelling Scientific Reasons for the Use of Placebo

The information available to the WHO does not specify the nature of any interaction between vaccine responses and HIV treatment status. A general statement was based on data from South Africa that indicated that HIV-1 infected infants who were vaccinated with Rotarix™ did not show any evidence of vaccine effects on the course of their HIV disease. However, these data are from small numbers of infants. Further, the information available with the Rotarix™ study does not directly address the potential effects of that (or any) rotavirus vaccine on acquisition of HIV-1 infection by uninfected infants being
nursed by their HIV-1 infected mothers. Information generated in P1072 will provide preliminary data on this point. While the study does not have sufficient statistical power to evaluate differences between vaccine and placebo groups in regard to transmission during breastfeeding, the safety and immunogenicity data generated in this study will help pave the way for future larger studies of vaccination of infants born to HIV-1 infected women. Larger studies would be needed to determine if vaccine efficacy is comparable across groups (HIV-1 exposed uninfected, and HIV-1 infected infants), and to determine if there is any significant effect of the vaccine on transmission of HIV during breastfeeding. These studies might be accomplished before vaccine roll out, or in post-marketing studies after implementation in the relevant countries. This study is an important first step in gathering safety and immunogenicity data in these population subgroups.

The question of different rotavirus subtypes circulating in different countries is also relevant for vaccination policy and rollout. The Rotarix™ vaccine contains antigens from the G1P8 strain, while RotaTeq™ contains antigens from several strains: G1, G3, G4 and GP1A (8). The evidence on cross-protection for different rotavirus strains is conflicting. One meta-analysis shows that the Rotarix™ vaccine does protect well against heterologous virus (4) while another analysis suggested that cross-protection may be limited (5). It may be the case that there are clinical advantages of RotaTeq™ over Rotarix™ in countries where the predominant strains are not G1P8. Epidemiologic studies from sub-Saharan Africa indicate that many strains are circulating, including well known strains as well as novel strains such as those containing G9 serotypes.

P1072 will provide the key immunogenicity and safety data before the WHO recommendations are adopted by countries and funding agencies into their childhood immunization policies and before rotavirus vaccines are available to all infants. The WHO recommendations were made without any concurrent recommendation for determining HIV status in children at the time of vaccination. If significant safety issues emerge, or if future trials show that the vaccine is not effective in HIV-1 infected infants, WHO recommendations might need to be modified to include ascertaining HIV status prior to vaccination. This, in turn, could affect implementation strategies at the national and local levels, since routine testing of infants may not be the norm, and the need to ascertain HIV status may provide additional impetus to provide these integrated services at the time of immunization.

Future research should address the question of efficacy in HIV-1 infected infants once safety is firmly established, as well as the question of possible vaccine-induced increases in transmission of HIV through breastfeeding. Given the possibility of prophylactic antiretroviral treatment of infants to prevent acquisition of HIV from breast milk (6, 7), as well as an evolving evidence base on the effects of maternal HAART on transmission through breastfeeding (7), future implementation of vaccine strategies may need to be evaluated in the context of possible use of these interventions for breastfeeding.
mother/infant pairs. This study will not measure efficacy, since a much larger sample size would be needed, and since safety data ideally should be collected first. Therefore, this study will help inform national policies on vaccination and clinical management of HIV-1 exposed and HIV-1 infected infants.

In summary, the P1072 Team believes that additional information on rotavirus vaccination in HIV-1 exposed and HIV-1 infected infants is currently lacking, and is needed to provide a broader evidence base for the implementation of vaccination programs at the national level in developing countries. P1072 will be completed in time to inform better implementation of the WHO recommendation.

**Ensuring that Subjects Will Not be Denied Access to Care**

Potential subjects at any site will not be enrolled into P1072 if a national recommendation for rotavirus vaccine is implemented at that site. Subjects on study who are in the placebo group will receive vaccine as per site implementation if their age permits them to receive vaccine (there are recommended limitations on upper age and specified interval). The protocol currently limits the study to sites where rotavirus vaccine is not utilized. This information is included in the exclusion criteria and management procedures described in detail in section 6.6 entitled: “Guidelines for Managing Subjects in Countries Where RotaTeq™ Licensure Occurs During the Study”.

The WHO recommendations are unlikely to be immediately implemented in any of the host countries for this study. Licensing and vaccine procurement may take up to two years. Therefore, it is important to note that by participating in P1072 no site will be denying any child access to rotavirus vaccine that would otherwise be available. In fact, by design at least half of the children in P1072 will receive the vaccine on an experimental basis. For recipients of both vaccine and placebo in this study, training for caregivers on managements of gastroenteritis, as well as active follow-up and expert medical care in the clinic, will provide a direct benefit; these benefits will be at least as good as, if not superior to, the local standard of care.

**Minimizing Risks to Subjects**

Per Letter of Amendment #3 (November 9, 2010), all HIV-infected subjects enrolled in P1072 in ALL strata MUST have initiated antiretroviral therapy (ARV) before, or at the time of, administration of the 1st dose of study vaccine/placebo. It is not acceptable for subjects to take a prescription home with them to start ARV therapy on the day of, and following, vaccination.

Enrollment procedures will include assessment of access to clinic by mothers or caregivers, and reasonable provisions for transportation. When possible, telephone contact will be used for active surveillance and to check on missed visits, although
telephone access may not be possible at all sites. Home visits will be specified in the protocol for subjects who miss clinic visits and this element of care will be added to the CRF being developed for clinic visits.

Investigators will train caregivers on appropriate home care of gastroenteritis. A handout sheet will contain the important elements of this information for caregivers who are literate, and oral rehydration packets will be provided.

Additionally, as of October 2011, 96 subjects have enrolled into the P1072 protocol. To date, none of these subjects have experienced any severe gastroenteritis events following vaccination(s).

References