P1107
(DAIDS Document ID 11883)

Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-1 Infected Subjects who Require Bone Marrow Transplantation for any Indication and Its Observed Effects on HIV-1 Persistence

This file contains the current IMPAACT P1107 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #2, dated 24 November 2014
- Clarification Memorandum #1, dated 28 February 2014
- Protocol Version 1.0, dated 1 August 2013
Clarification Memorandum #2 for:

IMPAACT P1107

Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-1 Infected Subjects who Require Bone Marrow Transplantation for any Indication and Its Observed Effects on HIV-1 Persistence

Version 1.0, dated August 1, 2013

DAIDS ES# 11883

Clarification Memo Date: 24 November 2014

Summary of Clarifications

This Clarification Memorandum clarifies the types of transplants that P1107 participants may receive.

Implementation

Institutional Review Board (IRB) approval of this Clarification Memorandum is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs for their information or, if required by the IRBs, for their approval prior to implementation. The clarification included in this memorandum will be incorporated into the next full protocol amendment.

- For pre-transplant cohort participants, multiple cord transplants and haploidentical transplants are permitted, provided at least one cord blood unit is CCR5Δ32, homozygous or heterozygous.

- For post-transplant cohort participants, multiple cord transplants and haploidentical transplants are permitted, provided at least one cord blood unit is CCR5Δ32, homozygous.
Clarification Memorandum #1 for:

IMPAACT P1107

Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-1 Infected Subjects who Require Bone Marrow Transplantation for any Indication and Its Observed Effects on HIV-1 Persistence

Version 1.0, dated August 1, 2013

DAIDS ES# 11883

Clarification Memo Date: 28 February 2014

Summary of Clarifications

This Clarification Memo (CM) clarifies (1) standard processes according to which study sites may modify the sample informed consent forms appended to the study protocol, (2) the intent of the protocol to permit operational flexibility in conducting the study informed consent process, and (3) the intent of the protocol to optimize efficiency of data collection. This CM also identifies the IMPAACT Operations Center as FHI 360 and provides current contact information for the Clinical Trials Specialist.

Implementation

Institutional Review Board (IRB) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs for their information or, if required by the IRBs, for their approval prior to implementation. The clarifications included in this memorandum will be incorporated into the next full protocol amendment.

1. Standard Policies Permitting Sites to Modify Sample Informed Consent Forms (SICs) per Center for International Blood and Marrow Transplant Research (CIBMTR) Requirements

This CM highlights standard processes for study sites to modify wording provided in the SICs appended to the study protocol. Consistent with sponsor policies permitting modification of wording provided in the SICs for compliance with site institutional and/or IRB requirements, it is permissible for wording preferred by the CIBMTR for use at participating transplant centers to be incorporated into site-specific informed consent forms. For ease of reference at all sites, CIBMTR’s preferred wording for the Release of Medical Information section of the SICs in protocol Appendices IV and V, which addresses CIBMTR data collection in relation to study participation, is provided below (with added text shown in bold and deleted text shown in strikethrough). This wording must be included in site IRB submissions and approved by site IRBs prior to use in the P1107 study. IRB-approved site-specific informed consent forms must be submitted to the DAIDS Protocol Registration Office.
Release of Medical Information

As part of the study, we will ask permission to make copies of your/your child’s transplant medical records through the CIBMTR to be used to complete case report forms. This information will be shared with IMPAACT/ACTG. If you do not agree to share your transplant medical records, you cannot be in this study. The Center for International Blood and Marrow Transplant Research (CIBMTR) is required by the federal government to collect information from transplant centers about the related and unrelated donor transplants performed at their center. Because of this requirement, your transplant physician will send information to the CIBMTR about your transplant at the time of your transplant and at specific time points after the transplant. If you agree to participate in this study, the CIBMTR will send IMPAACT/ACTG the information it has about your disease, transplant, and how you are doing after the transplant. In addition, the researchers at your transplant center may send IMPACCT/ACTG additional information about your disease or transplant that the CIBMTR does not have.

2. Operational Flexibility in Conducting the Informed Consent Process

In protocol Sections 3.5, 4.4, and 4.52, and in the SoEs in Appendices IA, IB, IIA, and IIB, reference is made to the transplant site and/or the IMPAACT/ACTG site obtaining informed consent for study participation. This CM serves to clarify that, while it is generally expected that transplant site staff will conduct the informed consent process with potential participants (and/or their parents/guardians), this responsibility may be fulfilled by either transplant site staff or IMPAACT/ACTG site staff, as agreed upon by the collaborating sites prior to study implementation.

3. Efficiency of Data Collection

In all SoEs (Appendices IA-IIIC), footnote 2 is intended to specify data elements to be recorded on IMPAACT study case report forms (CRFs). As described elsewhere in the protocol, other data elements will be transferred from CIBMTR to the IMPAACT Data Management Center. To avoid duplication of CIBMTR data collection, this CM clarifies footnote 2 to limit CRF data collection to required data elements that will not be transferred from CIBMTR, as follows (added text shown in bold, deleted text shown in strikethrough):

Chart abstractions for data recording on study CRFs should include weight; ARV concomitant medications; hematology (hemoglobin, hematocrit, white cell count, differential, platelets) through Day 100 post-transplant; opportunistic infections post-transplant; vaccinations and immune responses to vaccinations post-transplant; results of standard of care HIV viral load assays performed post-transplant; and results of standard of care biopsy specimen testing performed post-transplant (when applicable, autopsy data will be obtained from CIBMTR, rather than through chart abstraction) chemistry (SGOT, SGPT, bilirubin [total, direct, indirect]) and renal tests (BUN, creatinine), as well as the reason for the transplant and any concurrent illness.

4. Protocol Team Roster

To reflect current protocol team membership, this CM identifies the current Clinical Trials Specialist as follows:

Anne Coletti, M.S.
FHI 360
PO Box 21059
Durham, NC  27703
Phone: (919) 544-7040 x11238
Email: acoletti@fhi360.org
Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-1 Infected Subjects who Require Bone Marrow Transplantation for any Indication and Its Observed Effects on HIV-1 Persistence

A Multicenter, Domestic 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 of Child Health and Human Development (NICHD)

Non-IND study  
DAIDS ES# 11883

The IMPAACT HIV-1 CURE Committee Chair:  Deborah Persaud, MD

Protocol Chair:  Yvonne Bryson, MD
Protocol Vice Chairs:  Theodore Moore, MD  
Deborah Persaud, MD  
Diane Wara, MD

NIAID Medical Officer:  Elizabeth Smith, MD
NICHD Medical Officer:  Rohan Hazra, MD
Clinical Trials Specialist:  Elizabeth Petzold, PhD

Version 1.0  
FINAL  
August 1, 2013
IMPAACT P1107 TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to impaact.teamp1107@fstrf.org. Remember to include the participant’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to impaact.teamp1107@fstrf.org. 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 rcsafetyoffice@tech-res.com or call 1-800-537-9979 or 1-301-897-1709 or fax 1-800-275-7619 or 301-897-1710. For enrollment questions, contact the Data Management Center at 716-834-0900 or by email at sdac.random.desk@fstrf.org.

Protocol Chair

Yvonne Bryson, MD
Professor
Chief, Division of Pediatric Infectious Diseases
David Geffen School of Medicine at UCLA
10833 Le Conte Ave., MDCC 22-442
Los Angeles, CA, 90095-1752
Phone: (310) 825-5235
Email: ybryson@mednet.ucla.edu

Protocol Vice Chairs (continued)

Theodore Moore, MD
Professor
Division of Pediatric Hematology/Oncology
David Geffen School of Medicine at UCLA
200 UCLA Medical Plaza
Los Angeles, CA 90095
Phone: (310) 825-6708
Email: tbmoore@mednet.ucla.net

Diane Wara, MD
Professor
University of California, San Francisco School of Medicine
505 Parnassus Avenue, Moffitt
San Francisco, CA 94143
Phone: (415) 476-2865
Email: WaraD@peds.ucsf.edu

Protocol Vice Chairs

Deborah Persaud, MD
Associate Professor of Pediatrics
Division of Infectious Diseases
John Hopkins University School of Medicine
David M. Rubinstein Child Health Building
200 N. Wolfe Street, Room 3151
Baltimore, Maryland 21287
Phone: (443) 287-3733
Email: dpers@jhmi.edu
NIAID Medical Officer

Elizabeth Smith, MD
Pediatric Medicine Branch
NIH, NIAID, DAIDS, TRP
Room 5105
6700-B Rockledge Drive, MSC 7624
Bethesda, MD 20892-7624
Phone: (301) 402-3226
E-mail: mesmith@niaid.nih.gov

NICHD Medical Officer

Rohan Hazra, MD
Maternal and Pediatric Infectious Disease Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institutes of Health
6100 Executive Blvd., Room 4B11
Bethesda, MD 20892-7510
Phone: (301) 435-6868
Email: hazrar@mail.nih.gov

Clinical Trials Specialist

Elizabeth Petzold, PhD
IMPAACT Operations
Social & Scientific Systems
1009 Slater Road, Suite 120
Durham, NC 27703
Phone: (919) 287-4314
Email: epetzold@s-3.com

Protocol Statistician

Meredith Warshaw, MSS, MA
Center for Biostatistics in AIDS Research
Harvard School of Public Health
651 Huntington Avenue, FXB-547
Boston, MA 02115
Phone: (617) 432-2481
Email: mwarshaw@sdac.harvard.edu

Protocol Data Manager

Adriane Hernandez, MA
Data Manager
Frontier Science & Technology Research Foundation
4033 Maple Road
Amherst, NY 14226-1056
Phone: (716) 834-0900 x7495
E-mail: hernandez.adriane@fstrf.org

Protocol Virologists

Deborah Persaud, MD
Associate Professor of Pediatrics
Division of Infectious Diseases
John Hopkins University School of Medicine
David M. Rubinstein Child Health Building
200 N. Wolfe Street, Room 3151
Baltimore, Maryland 21287
Phone: (443) 287-3733
Email: dpers@jhmi.edu

John Mellors, MD
Professor, Department of Medicine
Chief, Division of Infectious Diseases
Director, HIV/AIDS Program,
University of Pittsburg Medical Center
818 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261
Phone: (412) 624-8512
E-mail: mellors@dom.pitt.edu

Protocol Immunologist

Savita Pahwa, MD
Professor of Microbiology and Immunology,
Director, Miami CFAR
Room 712,
Bachelor Children’s Research Institute
University of Miami Health System
Phone: (305) 243-7732
Email: spahwa@med.miami.edu
Protocol Pharmacologist

Raman Venkataramanan, PhD, FCP
Professor of Pharmaceutical Sciences and
Pathology Director of TDM Lab,
UPMC
718 Salk Hall, School of Pharmacy
3501 Terrace Street
University of Pittsburgh,
Pittsburgh, PA 15261
Phone: (412) 648-8547
E-mail: rv@pitt.edu

Investigators

Coleen Cunningham, MD
Professor
Chief, Division of Pediatric Infectious Diseases
Duke University Medical Center,
Erwin Road
P.O. Box 3499
Durham, NC 27710
Phone: (919) 668-4851
Email: coleen.cunningham@duke.edu

Ronald Mitsuyasu, MD
Professor of Medicine
David Geffen School of Medicine at UCLA
Director, UCLA CARE Center
9911 W. Pico Blvd, Suite 980
Los Angeles, CA 90035
Phone: (310) 557-1893
Email: rmitsuya@mednet.ucla.edu

Lawrence Petz, MD
Medical Director
StemCyte International Cord Blood Center
1589 W. Industrial Park Street
Covina, CA 91722
Phone: (626) 646-2502
Email: lpetz@stemcyte.com

Laboratory Technologist

Patricia Anthony, BS, CLS
University of Southern California
Maternal-Child Virology Research Lab
1801 East Marengo Street, GLB 1G8
Los Angeles, CA 90033
Phone: (323) 226-4161
E-mail: patricia.anthony@usc.edu

Field Representative

Carol Vincent, PhD, CRNP
Children’s Hospital of Philadelphia
3535 Market Street, Suite 1371
Philadelphia, PA 19104-4318
Phone: (215) 590-2262
Email: vincentc@email.chop.edu

Laboratory Data Coordinator

Anthony Bloom
Laboratory Data Coordinator
Frontier Science and Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone (716) 834-0900 x7431
Email: bloom@fstrf.org

Westat Clinical Research Associate

Rita Patel, MS
Clinical Research Associate
Westat
1441 W. Montgomery Ave., WB292
Rockville, MD 20850
Phone: (240) 453-2693
Email: ritapatel@westat.com
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IV DAIDS Sample Informed Consent Template – Consent Form for Pre-Transplant Cohort

V DAIDS Sample Informed Consent Template – Consent Form for Post-Transplant Cohort
### List of Commonly Used Abbreviations and Definitions

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>Ab</td>
<td>Antibody</td>
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<tr>
<td>ACTG</td>
<td>Adult Clinical Trials Group</td>
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<td>ACTN</td>
<td>AIDS Clinical Trials Network</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<tr>
<td>ALL</td>
<td>Acute Lymphoblastic Leukemia</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic Lateral Sclerosis</td>
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<tr>
<td>AML</td>
<td>Acute Myeloid Leukemia</td>
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<tr>
<td>ARV</td>
<td>Antiretrovirals</td>
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<tr>
<td>BMT</td>
<td>Bone Marrow Transplant</td>
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<tr>
<td>CAP</td>
<td>College of American Pathologists</td>
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<tr>
<td>CBU</td>
<td>Cord Blood Unit</td>
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<td>CCR5</td>
<td>C-C chemokine receptor 5</td>
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<tr>
<td>CIBMTR</td>
<td>Center for International Blood and Marrow Transplant Research</td>
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<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendment</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>CXCR4</td>
<td>C-X-C chemokine receptor 4</td>
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<td>DAIDS</td>
<td>Division of AIDS</td>
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<td>DAERS</td>
<td>DAIDS Adverse Event Reporting System</td>
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<td>DMC</td>
<td>Data Management Center</td>
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<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>dUCB</td>
<td>double umbilical cord blood</td>
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<td>EAE</td>
<td>Expedited Adverse Event</td>
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<td>EBMT</td>
<td>European Group for Blood and Marrow Transplantation</td>
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<td>EBV</td>
<td>Epstein - Barr virus</td>
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<td>EIA</td>
<td>Enzyme Immunoassay</td>
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<td>ELISA</td>
<td>Enzyme Linked Immunosorbent Assay</td>
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<td>Enzyme Linked Immunosorbent Spot</td>
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<td>Foundation for Accreditation of Cellular Therapy</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FSTRF</td>
<td>Frontier Sciences Technology &amp; Research Foundation</td>
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<td>GVHD</td>
<td>Graft vs. Host Disease</td>
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<td>HAART</td>
<td>Highly Active Antiretroviral Treatment</td>
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<tr>
<td>HCT</td>
<td>Hematopoietic Cell Transplantation</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology and End Results</td>
</tr>
<tr>
<td>SOE</td>
<td>Schedule of Evaluations</td>
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<tr>
<td>TCF</td>
<td>fludarabine</td>
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<td>TRM</td>
<td>Transplant Related Morbidity</td>
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<tr>
<td>UCB</td>
<td>Umbilical Cord Blood</td>
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<tr>
<td>UCBT</td>
<td>Umbilical Cord Blood Transplant</td>
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<tr>
<td>UCLA</td>
<td>University of California at Los Angeles</td>
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<td>WB</td>
<td>Western Blot</td>
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SCHEMA

Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-1 Infected Subjects Who Require Bone Marrow Transplantation for any Indication and Its Observed Effect on HIV-1 Persistence

**DESIGN:** Observational, multi-center study

**POPULATION**

Cohort identified prior to transplant “Pre-transplant cohort”: HIV-1 infected participants ≥12 months of age, who require a hematopoietic stem cell transplant (HSCT) for whom a suitable match heterozygous or homozygous CCR5Δ32 cord blood is identified. There is no upper age limit.

Cohort identified after receiving a transplant “Post-transplant cohort”: HIV-1 infected participant’s ≥12 months of age, who have already received homozygous CCR5Δ32 cord blood per standard of care within 2 years. There is no upper age limit.

**SAMPLE SIZE:** Up to 25 participants to obtain:

Pre-transplant cohort:
(a) Up to 10 evaluable participants receiving CCR5Δ32 homozygous cells;
(b) Up to 10 evaluable participants receiving CCR5Δ32 heterozygous cells

Post-transplant cohort:
(c) Up to 5 evaluable participants homozygous CCR5Δ32 cord blood recipients

**STRATIFICATION:** There is no stratification as part of this study

**REGIMEN:** There is no study drug as part of this study

**STUDY DURATION:** Subjects will be followed for up to five years post-transplant

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\(^1\) Participants who are followed for less than 100 days will be considered unevaluable.
OBJECTIVES:

Primary Objectives:

1. To describe the safety of transplantation of CCR5Δ32 cord blood stem cells in HIV-1 infected participants who require a hematopoietic stem cell transplant for malignancy, hematopoietic disease or other underlying disease and for whom matched hematopoietic stem cells are available.

2. To describe the engraftment of hematopoietic cells, as measured by chimerism for CCR5Δ32 cells, and immune recovery at 100 days and 52 weeks post-transplant.

3. To describe the incidence and severity of graft vs. host disease in all cohorts.

4. To assess the effect of CCR5Δ32 cord blood stem cell transplant on the quantity of HIV-1 DNA in peripheral blood over the time course of the transplant and the potential to achieve non-detectable proviral DNA.

Secondary Objectives:

1. To describe CCR5Δ32 cord blood stem cell engraftment and its effect on biomarkers of HIV-1 infection, including plasma viral load and replication-competent reservoirs, as well as in gut and other sites (if tissue samples are available).

2. To describe immune reconstitution after transplantation with CCR5Δ32 cord blood stem cells.

3. To describe the changes in HIV-1 induced inflammatory effects (systemic inflammation and immune activation) and HIV-1 specific immune responses (antibody and T cell responses) pre- and post- CCR5Δ32 cord blood stem cell transplantation in all cohorts.

4. To describe in participants who stop antiretrovirals, to determine rates of functional or sterilizing cure of HIV-1 (see Section 7.2 for definitions).
1.0 INTRODUCTION

P1107 is a unique and new type of protocol from the International Maternal, Pediatric and Adolescent AIDS Clinical Trials (IMPAACT) Network and the AIDS Clinical Trials Group (ACTG). The protocol will enroll HIV-1 infected participants who receive a homozygous or heterozygous, CCR5Δ32, allogeneic, hematopoietic stem cell transplantation (HSCT) for treatment of an underlying disease other than HIV-1. When an individual with HIV-1 infection is identified who requires stem cell transplantation, cord blood from a unique bank of CCR5Δ32 deleted units (StemCyte, Inc.) will be made available. If the patient’s primary healthcare team selects a CCR5Δ32 unit for transplant, the patient is eligible for this observational protocol. Additionally, if a patient has already received a homozygous CCR5Δ32 transplant, they are eligible for the protocol. This protocol will be a joint IMPAACT (or ACTG) site and transplant site collaboration. A transplant site with a subject as described above, will partner with an IMPAACT or ACTG site to create a virtual study site. The IMPAACT (or ACTG) site PI will be responsible for working with their partner transplant site to facilitate and verify all IRB submissions for both sites, informed consent procedures, form submissions for the IMPAACT network, data entry into the IMPAACT network database, regular communications with the transplant site, and certification of specific records from the transplant subject’s medical records, for a shadow file as well as the maintenance of the shadow file at the IMPAACT (or ACTG) site.

This protocol requires extensive collaboration and coordination between the Network sites (ACTG and IMPAACT) and the transplant centers. In order to avoid duplicate data collection, whenever possible, data will be retrieved from the transplant program data collection and will be downloaded from the central transplant coordinating center (CIBMTR) and sent in a paper format directly to the FSTRF Data Management Center for abstraction of relevant study related data. Forms containing HIV-1-related treatment and laboratory data will be completed through chart abstraction by the IMPAACT/ACTG staff. Adverse events and safety monitoring will be monitored and collected as part of standard of care by the transplant centers and not by the IMPAACT /ACTG site. The P1107 team will only obtain summary data relevant to the protocol objectives from the CIBMTR forms as previously agreed in a Memorandum of Understanding (MOU) between the IMPAACT and CIBMTR network leadership groups. Blood sample collection for the P1107 laboratory studies will coincide with clinical care samples and visits pre-and post-transplantation, whenever possible.

1.1 Background

HIV-1 and the CCR5Δ32 mutation

The HIV scientific community is now intensely focused on treatment strategies aimed at clearing HIV-1 infected cells from infected individuals to achieve a cure. Individuals homozygous for the CCR5Δ32 mutation of the HIV-1 co-receptor are naturally resistant to HIV-1 infection; therefore, reconstitution of the immune
system with hematopoietic stem cells carrying the CCR5Δ32 mutation should confer resistance to infection with R5 HIV-1 variants. In a single case report, stem cells from a CCR5Δ32 homozygous donor were used to transplant an HIV-1 infected man (‘The Berlin Patient’) after he developed acute myeloid leukemia (AML) requiring two bone marrow transplants [1]. Five years after the final (CCR5Δ32 deleted) transplant, the participant remains off antiretroviral therapy and replication-competent HIV-1 cannot be recovered [2]. This unique and well-documented case of clearance of HIV-1 infection following bone marrow transplantation with CCR5Δ32 homozygous cell provided proof-of-concept that long-lived HIV-1 infected cells can be cleared sufficiently from an infected individual to allow for HIV-1 free survival in the absence of antiretroviral treatment [2]. The combination of no viral rebound in the absence of antiretroviral therapy and lack of recoverable replication-competent virus represents the working definition of “cure” for HIV-1 [3].

Umbilical Cord Blood Transplantation
The first allogeneic hematopoietic stem cell transplantation (HSCT) was performed in 1968 [4]. Bone marrow transplant (BMT) has since evolved as a viable therapeutic modality for malignant and non-malignant diseases. One barrier for the use of this treatment is that only 25% of potential recipients have a suitable human leukocyte antigen (HLA)-matched donor. This problem can be overcome, at least in part, through use of umbilical cord blood (UCB). UCB transplants may be successfully performed with partial HLA matches. The first umbilical cord blood transplant (UCBT) was performed in a patient with Fanconi anemia in 1988 from an HLA-haplodynamic sibling [5]. Since then, over 25,000 umbilical cord blood transplants (UCBT) have been performed in adults and children. Cord blood can be used as a stem cell product for transplant for any diagnosis for which bone marrow can be used.

The primary drawback of umbilical cord blood transplants, when compared to bone marrow transplant, is a longer time to engraftment: the mean time to absolute neutrophil count (ANC) >500 cells/mL is 23 days (compared to 18 days) and to platelet transfusion independence is greater than 50 days (compared to 29 days). However, there are numerous advantages to umbilical cord blood transplants, including:

1) UCB is easy to obtain with no risk to the donor.
2) Once obtained, UCB are cryopreserved and stored in a standardized manner, resulting in units available for shipment when needed. Therefore, transplants do not require identification and scheduling of a bone marrow donor.
3) The cord blood units are tested for infectious agents prior to storage and selection.
4) Cell-dose limitations for use in adults can be overcome by reduced intensity conditioning regimens and the implementation of double-cord transplants (where two umbilical cord blood units are transfused).

5) Transplantation can be performed successfully with 4/6 or greater HLA matched units.

While CBT were more routinely performed in children than adults because of cell number limitations, the plasticity of cord blood has allowed for the use of double-cord transplants (dUCB), in which two UCB units are infused, even though only a single unit engrafts. As a result of double UCBs, there are now extensive adult umbilical cord blood transplantations [6].

An advantage to umbilical cord blood transplantation is that, lymphoid cells in cord blood are immune naïve leading to less graft vs. host disease (GVHD) [7]. This feature allows for the use of more significantly mismatched units thereby making it easier to identify a compatible cord blood unit compared with bone marrow transplant. This feature allows for success of 4/6 HLA-matched umbilical cord blood transplants. It has been estimated that of the over 500,000 cord blood units already in storage, 95% include a 4/6 HLA matched unit for individuals who require a hematopoietic stem cell transplantation [8].

In addition, the risk of transmission of other infections such as CMV or EBV is lower with cord blood transplantation. Overall, the one-year survival following unrelated cord blood stem cell transplantation is approximately 70%, with children showing even longer survival [7]. A recent report of cord blood stem cell transplantation in both malignant and non-malignant conditions shows that there are several factors critical to enhancing success. These include having an HLA match that is equal to or greater than 4 of 6 alleles and the dose of cells infused. An HLA 4 to 6/6 matched umbilical cord blood compared to grafts from HLA 8/8 matched and mismatched unrelated donors in the treatment of adults with acute leukemia after myeloablative conditioning show good results in multiple studies [7,9-13].

Complications of Cord Blood Transplantation
Any type of stem cell transplantation, including cord blood, is a complicated and potentially risky procedure. Therefore, this protocol is only open to individuals who require transplantation as part of the standard of care for a disease other than HIV-1. The more common complications of transplantation include side effects from induction chemotherapy, profound immune suppression while waiting for engraftment, and graft vs. host disease. It is expected that post transplantation the patient will experience a period of neutropenia (mean of 23 days), and require transfusions for platelets and perhaps blood products until their bone marrow recovers. To prevent infections, patients receive immunoprophylaxis for common transplant infections such as herpes simplex virus, cytomegalovirus and Pneumocystis jirovecii pneumonia according to the standard of care for
hematopoietic stem cell transplantation recipients. If fever or other signs of infection develop, patients are treated with broad spectrum antibiotics, antifungals, and/or antivirals. Graft vs. host disease may occur in up to 50% of patients, though rates are lower with cord blood transplants. Management of these and other transplant related complications will be by the transplant team caring for the patient.

Expected Time to Engraftment
In general, the mean time of engraftment of the donor cells is approximately 90 to 100 days post-transplant and this can be monitored by measuring the percent chimerism of donor cells. It takes additional time (up to one year) for other cells in the body such as the gut, lymph nodes, lung and central nervous system to be replaced by donor cells. The major transplant related morbidity or mortality usually occurs in the first 100 days post-transplant. The major criterion for success of the transplant is defined as event free survival (no recurrence of cancer or initial disease or major morbidity) at one year.

Double Umbilical Cord Hematopoietic Cell Transplantation in Adults
In a recently published, multi-center, retrospective analysis of the efficacy of two umbilical cord blood units (n=140) compared to peripheral blood progenitor cells showed that the risk of transplant-related and overall mortality was similar between the two groups. Relapse rates were not different; however, acute graft versus host disease appeared to be slightly more common while chronic graft versus host disease was slightly less common in the double umbilical cord blood vs. the peripheral blood progenitor cell recipients, after taking the degree of HLA matching into consideration [14]. Furthermore, a relatively low rate of transplant-related mortality was observed after a double umbilical cord blood with fully ablative regimens in a recent analysis of the European Group for Blood and Marrow Transplantation (EBMT) [15]. Similar outcomes were observed in a multi-center phase II trial in the United States that tested fully ablative total body irradiation, cyclophosphamide, fludarabine (TCF) conditioning regimen with double umbilical cord bloods in adults with leukemia and lymphoma [16]. Together these data support the safety and feasibility of double umbilical cord blood transplantation with fully ablative therapy in adults who lack a suitable unrelated volunteer donor for hematologic malignancies.

Stem Cell Transplant for Treatment of Malignancy in HIV-1-Infected Individuals
Important questions related to transplant in HIV-1-infected individuals include whether there are enough HIV-1-infected children and adults who require transplant for treatment of an underlying disease to perform this study and, if so, is there data supporting transplantation in individuals with HIV-1 infection. The answer to both questions is yes. With the improved life expectancy of HIV-1 infected persons treated with highly active antiretroviral therapy (HAART), the rate of malignancies has increased; in particular, that of B-cell Non-Hodgkin’s lymphoma, which may be treated with autologous or allogeneic stem cell
transplantation. In addition, the Surveillance, Epidemiology and End Results (SEER) data demonstrate a significantly higher incidence of several cancers that are treated with allogeneic hematopoietic cell transplantation in HIV-infected individuals compared to similar aged individuals without HIV-1, including Hodgkin lymphoma and leukemia [17]. In a review of the CIBMTR registry data, 23 participants with HIV-1 infection were identified as having undergone allogeneic transplant [18]. Nine of the 23 (39%) underwent allogeneic hematopoietic cell transplantation after 1996, in the HAART era. At a median follow-up of 59 months, six of the 23 participants were alive. Four of the nine participants transplanted after 1996 were alive whereas only 2 of 14 pre-1996 participants were alive. The data suggest that allogeneic hematopoietic cell transplantation is feasible for selected HIV-1-positive participants.

A complicating factor in the management of HIV-1 infection in individuals who require hematopoietic cell transplantation is the ability to continue HAART in setting of hematopoietic cell transplantation due to their inability to take the medications, as well as drug-drug interactions. This can be managed with reduced intensity allogeneic hematopoietic cell transplantation. Reduced-intensity conditioning aims to suppress the participant's immune system sufficiently so that it will accept the donor stem cells and is especially helpful for older adults or less clinically fit participants who may be poor candidates for myeloablative conditioning regimens. There is growing interest in using reduced intensity conditioning (RIC) prior to potentially curative allogeneic hematopoietic stem cell transplantation transplant. Reduced-intensity allogeneic HCT for participants with HIV-1 has expanded with the recent publication of the Ohio State University experience [19]. In this report, three subjects (ages 39-55 years) with HIV-1 underwent allogeneic hematopoietic cell transplantation. The underlying malignancies included acute myeloid lymphoma, Burkett lymphoma and plasmablastic lymphoma. Conditioning consisted of fludarabine and busulfan with or without antithymocyte globulin (1 subject without). Graft versus host disease prophylaxis included tacrolimus and mini-dose methotrexate. Subjects continued HAART throughout the transplant course without interruption. One subject developed acute graft versus host disease. At the time of the study publication, all subjects were alive, free of the malignant disease and off immunosuppressive therapy 368 to 802 days post-transplant [20].

High-dose chemotherapy with autologous hematopoietic cell transplantation has been extended to participants with AIDS-related non-Hodgkin’s lymphoma (NHL) and Hodgkin lymphoma and results appear to be comparable to those achieved in participants without HIV-1 infection. Across multiple trials, the probability of survival after high-dose conditioning followed by autologous hematopoietic cell transplantation for participants with AIDS-related NHL ranges between 39% and 85% [21].
The incidence of malignancy or other disorders requiring hematopoietic stem cell transplantation in HIV-1 infected children is low, but it does occur. In a recent survey (May 2011) of 19 domestic IMPAACT sites, the sites reported 24 HIV-1 infected children or adolescents with a malignancy in the last 10 years. The diagnoses include acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), lymphoma and Burkett’s lymphoma. Ages range from one year to 20 years, with the majority in the 8 to 10 year old age group.

A recent study of two HIV-1 infected individuals, one a perinatally-infected young adult, each with a malignancy, who received reduced intensity allogeneic hematopoietic cell transplantation (not CCR5 deleted) and continued on HAART report no detectable HIV-1 proviral DNA, single copy HIV-1 plasma RNA or replication-competent CD4 T cell reservoirs detected post-transplant. These patients were originally CCR5delta32 heterozygous but now are wild type with complete engraftment of donor cells; however, they are still receiving HAART and therefore are not considered cured of the infection [22]. Furthermore, studies of tissue reservoirs have not been performed. These data suggest that the replacement of the recipient’s cells with donor hematopoietic cell transplantation (even with potentially susceptible cells) under treatment with HAART may have a significant effect on persistence of HIV-1 in patient reservoirs.

As noted previously, double cord transplants are used in adults to enhance engraftment and myeloid and platelet reconstitution and increase the cell dose although by 100 days, only one of cords predominates and fully engrafts [23]. In an HIV-infected individual, it is possible that a CCR5 delta 32 homozygous cord unit will have a selective advantage over the non-deleted unit since it is innately resistant to HIV-1 infection.

Together, these results indicate that although uncommon, there are HIV-1 infected adults and children who will require stem cell transplantation for treatment of a malignancy who could potentially benefit from the establishment and availability of a cord blood unit donor bank and who would be available for enrollment into this protocol.

Use of CCR5Δ32 Cord Blood

Investigators at UCLA have completed further work to confirm the feasibility of cord blood transplantation with CCR5Δ32 cells. First, investigators determined if engrafted cells from an HIV-1 uninfected individual who received a CCR5Δ32 transplant were resistant to HIV-1 challenge in vitro. In this preliminary study, peripheral blood mononuclear cells (PBMCs) isolated post-transplant from an HIV-1 negative individual who received a CCR5Δ32 transplant for treatment of cancer were resistant to challenge with both R5 and CXC-R4 viruses. Cells from an individual who received a unit that was not CCR5Δ32 were not resistant [24]. This study and the “Berlin patient” demonstrate that CCR5Δ32 units are capable of engrafting in HIV-1 uninfected and HIV-1 infected individuals; further, that the
engrafted cells are resistant to HIV-1 infection. In other studies, investigators have shown that the HIV-1 co-receptor tropism may revert from X4 to R5 under the pressure of HAART [25] and replication competent virus recovered from CD4 T-cell reservoirs in children are R5 [25,26]. Both of these studies support the potential efficacy of an approach that only modifies the CCR5 receptor, without changing the alternate HIV-1 co-receptor, CXC-R4.

Additional concerns are whether sufficient CCR5Δ32 units can be identified in the U.S. and whether the HIV-1 infected patients, who are primarily racial and ethnic minorities, will have matches among the identified units. The Cord Blood Registry based at StemCyte Inc. (California) has genotyped approximately 10,000 cord blood units for the CCR5 Δ32 mutation and have identified 150 units as CCR5Δ32 homozygous. The CCR5Δ32 allele is present at a high rate in Caucasian populations of European descent among whom approximately 1% are homozygous (Δ32/Δ32) and 15-20% are heterozygous (CCR5Δ32/CCR5); however, the mutation is rare in other racial/ethnic groups. In an earlier study, investigators at UCLA, City of Hope, and StemCyte initially identified 48 and 754 units as homozygotic and heterozygotic, respectively, and compared the HLA types of those units to those of 44 randomly selected HIV-1-infected children from Los Angeles composed of 65% racial and ethnic minorities. A 4/6HLA matched unit was identified for 7/44 (15.9%) participants and a 3/6 match unit was identified for 20/44 (45.4%) [27]. Thus, even when HLA typing was available for only 48 CBU, matches were available for at least 15% of the HIV-1-infected children who are primarily racial and ethnic minorities.

Strategy
The proposed study is a collaborative study between IMPAACT, ACTG, David Geffen School of Medicine at UCLA, City of Hope National Medical Center, and StemCyte Inc. Cord Blood Bank as well as other cord blood banks who wish to have CBU screened for the CCR5Δ32 mutation. This study will enroll HIV-1 infected individuals’ ≥12 months of age who receive homozygous or heterozygous CCR5Δ32 cord blood stem cells. The study will only be conducted in individuals who require a hematopoietic stem cell transplant as part of standard of care for treatment of a disease other than HIV-1. Once a potentially eligible subject is identified, the primary healthcare team will review all available transplant options and available units. CCR5Δ32 cord blood units will be made available as part of the standard cord blood matching process and the on-site clinicians will determine which cord blood unit is the best match for an individual participant. If the unit selected is CCR5Δ32, then the participant will be offered enrollment into this study. If the individual does not have a suitable homozygous CCR5Δ32 matched unit, a heterozygous CCR5Δ32 unit may be considered. The decision on the choice of cord blood unit for transplant will be that of the transplant physicians and the participant.
The factors that may be considered in selecting the optimal unit of stem cells to transplant are many and include the risk of graft rejection with mismatched units, the availability of units with sufficient cells, and the potential benefit on HIV-1 disease with transplantation with homozygotic or heterozygotic CCR5Δ32 mutated cord blood units. The added benefit from a delta 32 stem cell transplant is uncertain. The decision regarding the choice of a cord unit should be made independent of the study by the patient, family (if minor) and treating physician.

The study will explore whether CCR5Δ32 transplantation results in “Sterilizing Cure” of HIV-1 [3] as was observed in the Berlin participant or “Functional Cure” as might be accomplished with other less drastic treatment approaches (see section 7.221). These definitions share the common feature of being able to discontinue antiretroviral drugs in the individual without the person experiencing rebound viremia above the limit of detection of clinical assays while at the same time maintaining immune health with respect to CD4+ T cells numbers and function, and levels of immune activation and inflammation. The definitions differ in regards to detection of HIV-1 within the body. Potential Sterilizing Cure would have occurred if, when antiretroviral therapy is discontinued, rebound viremia does not occur within five years of study follow-up, and replication-competent virus is no longer detectable, with the caveat that infected cells may be present but have fallen below the limit of detection of current methods. Because this is an emerging area of HIV-1 therapeutics, these working definitions are likely to evolve as the scientific field learns more about HIV-1 cure.

Biopsy

When patients on study undergo biopsy for clinical indications, residual tissue specimens will be saved for virologic and immunologic studies as part of this protocol. In the past decade, there has been an essential paradigm shift focusing on mucosal tissue/secreted fluids in HIV-1 pathogenesis, transmission and latency studies. This has resulted in clarification of the important role played by compartmental viral burden and the number of higher-risk target cells within the various tissue compartments compared to blood/plasma/PBMCs. This is especially true in the gastrointestinal tract with its extensive, gut-associated, lymphoid tissue (GALT) where 60-80% of the body’s total immune system resides, compared with only ~2% in blood. Importantly, each of these compartments reflects different phenotypes of each immune cell type. For example, gut lymphocytes are nearly all ‘activated’ and memory whereas blood lymphocytes are predominately ‘resting’ and naïve. GALT is both a source of potential target cells for HIV-1 spread as well as a latent reservoir which must be depleted in eradication efforts; therefore, quantifying HIV-1 in gut mucosal compartments will provide important data to guide future cure efforts.

To investigate the hypothesis that transplantation with CCR5-Δ-32deleted cord-blood derivatives will result in HIV-1 vulnerable target T-cell replacement and,
eventually, whole body eradication of HIV-1 virus, tissue-focused efforts will utilize sensitive and reproducible PCR techniques to quantify HIV-1 RNA (qRT-PCR) and DNA (q-PCR) and CCR5 gene expression (qPCR) performed on residual biopsy samples when biopsy is performed for clinical reasons.

1.2 Research Strategy and Status of Project

Efforts to enhance the donor pool of Cord-Blood Derived Hematopoietic Cells with CCR5Δ32 mutation:

StemCyte has identified 171 homozygous deleted CBU as of March 2013. StemCyte is collaborating with other cord blood banks to identify additional units with a goal of identifying 300 homozygous CCR5Δ32 deletion units. To date, Duke University, Saint Louis University and MD Anderson have agreed to assist in identifying CBU from Caucasian individuals for screening. Together, they plan to create a database for a special inventory of CBU for priority use for HIV-1 infected individuals who also need a transplant. It is expected that the feasibility of finding a match of 4/6 or greater in a cord blood bank with 300 units is approximately 60 to 70% for those of Caucasian mix race.

1.3 Timeline

Clinical IMPAACT/ACTG network sites involved in the care of HIV-1 infected patients that have the capacity to perform stem cell transplantation will be made aware of the availability of cord blood units and of the protocol. If the cord blood unit chosen for a patient by the transplant team is CCR5Δ32 homozygous or heterozygous then the patient will be eligible for this observational study. If the CCR5 status of the unit is unknown, the protocol team will arrange for testing to determine whether the unit is CCR5Δ32 homozygous or heterozygous. After patient consent and enrollment, blood will be drawn at the same time as standard care lab tests, whenever possible, so that baseline virological and immunological studies can be performed, including viral load testing, and viral co-receptor usage (cell tropism). The P1107 team anticipates that 1 to 2 HIV-1 infected patients will be identified during the first year. If patients do not have an appropriate match with a cord blood unit homozygous for CCR5Δ32, they can also consider a match with a cord blood unit heterozygous for CCR5Δ32. Patients will be followed at their site or referred to the most appropriate transplant unit for care. Patients will be followed for control of HIV-1 infection in their blood and HIV-1 reservoirs, immune-reconstitution, and other safety and effectiveness markers as outlined below.

Within the first two to three years that this protocol is open to enrollment, the team expects to accrue at least 4 evaluable patients. A patient will be considered evaluable for the primary study outcomes if he/she has received a CCR5Δ32 cord blood unit transplant and been observed for at least 100 days post-transplant. This
The proposed project is not intended or designed to support statistical inference, but to provide initial observations of the approach in HIV-1 infected individuals who require transplantation for other underlying conditions using HIV-1 naturally resistant donor cells. This is a proof of concept novel approach to potentially cure or control two fatal diseases and is intended to recapitulate the initial observation in the Berlin patient.

Up to ten patients receiving CCR5Δ32 homozygous units may be enrolled in the study, as well as up to 10 adults/adolescents/children who receive a heterozygous CCR5Δ32 unit may be enrolled. In addition, up to 5 subjects who have already received a homozygous transplant within the prior 2 years will be studied.

The team anticipates that umbilical cord blood transplantation with CCR5Δ32 cells may lead to continued suppression of HIV-1 infection without the necessity of antiretroviral (ARV) therapy. The choice of discontinuing ARVs will not be dictated by the protocol; however, if the patient and his/her clinical care providers opt to interrupt ARVs, this will be of extreme interest to the protocol team. Upon discontinuation of ARV for 14 or more consecutive days once the patient is greater than 100 days post-transplant, a modified follow-up schedule of evaluations will begin, which will assess virologic control and immune health off ARVs, and potential for cure. The team anticipates that over 8 to 12 months post-transplant viral reservoirs may diminish as the donor monocytic and lymphocytic lineage CCR5Δ32 homozygous cells engraft. This strategy will provide proof of concept for future advances in stem cell and gene therapy promoting HIV-1 resistant cells as immunotherapy for HIV-1.

The primary role of the IMPAACT/ACTG Networks and the AIDS Malignancy Consortium will be to provide the contextual framework for intensive virologic and immunologic studies following identification of eligible candidates for transplant and to provide a mechanism to document the tolerability of CCR5Δ32 stem cells transplantation in HIV-1-infected persons and its effect on HIV-1 persistence in a comprehensive manner. It is expected that the transplant procedure itself will be carried out and supported by mechanisms that are standard of care, including third party insurance. The IMPAACT / ACTG Networks are the logical networks to use as a mechanism to identify and recruit eligible patients for evaluation for a match with potential cord bank specimens and to assist in patient referral to transplant centers that are most appropriate and feasible for the patient and family. The actual site of the transplant will include sites that have a well-recognized transplant unit with experience in cord blood stem cell transplantation in pediatric and adult patients (as enrolled in the CIBMTR program), as well as available expertise in HIV-1 care.

NOTE: The participant does not need to physically relocate to the collaborating International Maternal, Pediatric and Adolescents AIDS Clinical Trials (IMPAACT) site and/or AIDS Clinical Trials Group (ACTG) for enrollment;
however, the IMPAACT or ACTG site will assist the transplant site as much as possible with completing the enrollment, study visit reminders and data abstraction.

Post-transplant cohort. A cohort of five subjects, who are identified after having received CCR5Δ32 cord blood within 2 years, will also undergo studies and procedures as outlined above for the pre-transplant cohort (see section 4.6 below).

1.4 Rationale

The goal of this proposal is to determine the efficacy and tolerability of hematopoietic transplantation using CCR5Δ32 stem cells for the immune reconstitution of HIV-1 infected participants who have a hematopoietic malignancy or other underlying disorder requiring an allogeneic transplant. This study will inform potential future studies, evaluating this approach in participants who are failing all therapy with HIV-1.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To describe the safety of transplantation of CCR5Δ32 cord blood stem cells in HIV-1 infected participants who require a hematopoietic stem cell transplant for malignancy, hematopoietic disease or other underlying disease and for whom matched hematopoietic stem cells are available.

2.12 To describe the engraftment of hematopoietic cells, as measured by post-transplant chimerism for CCR5Δ32 cells, and immune recovery at 100 days and 52 weeks post-transplant.

2.13 To describe the incidence and severity of graft vs. host disease in all cohorts.

2.14 To assess the effect of CCR5Δ32 cord blood stem cell transplant on the quantity of HIV-1 DNA in peripheral blood over the time course of the transplant and the potential to achieve non-detectable proviral DNA.

2.2 Secondary Objectives

2.21 To describe CCR5Δ32 cord blood stem cell engraftment and its effect on biomarkers of HIV-1 infection, including plasma viral load and replication-competent reservoirs, as well as in gut and other sites (if tissue samples are available).
2.22 To describe immune reconstitution after transplantation with CCR5Δ32 cord blood stem cells.

2.23 To describe the changes in HIV-1 induced inflammatory effects (systemic inflammation and immune activation) and HIV-1 specific immune responses (antibody and T cell responses) pre- and post- CCR5Δ32 cord blood stem cell transplantation in all cohorts.

2.24 To describe in participants who stop antiretrovirals, rates of functional or sterilizing cure of HIV-1 (see Section 7.22 for definitions).

3.0 STUDY DESIGN

P1107 will evaluate the feasibility and success of transplantation of CCR5Δ32 cord blood stem cells in HIV-1 infected participants’ aged ≥ 12 months, who require a stem cell transplant for underlying disease, including those who are identified for enrollment into the study for up to 2 years after they have received the transplant (post-transplant cohort; see Section 4.6).

Selection of the optimal unit for transplant, pre-conditioning, and patient management before, during, and after transplantation will all be determined by the treating clinicians at the transplant center. This research protocol does not dictate patient management or adverse event reporting as these are accomplished as part of the standard of care for transplant centers.

This study will utilize available data from the transplant center database collection system. Transplant staff will provide certified copies of source documents to allow the IMPAACT/ACTG staff to complete the IMPAACT case report forms. Thus, forms with information on HIV-1-related treatment and laboratory tests will be completed through chart abstraction by the IMPAACT/ACTG staff to answer the objectives of the study. The CIBMTR forms will be sent directly to the FSTRF DMC. The DMC will perform the abstraction based on team/protocol requirements. Queries from the DMC will be sent to the IMPAACT/ACTG site and may require the IMPAACT/ACTG site PI to initiate discussion with the transplant site.

Whenever possible, this study will utilize results from SOC blood draws, use split samples from specimens already being collected, and collection of available data with those planned at the transplant center, to answer the objectives of the study.

Figure 1 illustrates the flow of the pre-transplant cohort study design from IRB submission to CRF completion.
Figure 2 illustrates an overview of the geographic distribution of the IMPAACT/ACTG sites and the CIBMTR transplant sites.

IRB Approval of the Protocol, or other Protocol Management Documents

For each site (IMPAACT / ACTG and transplant centers) there will need to be documented IRB approvals in place. Whether sites do this as one submission or separate submissions, or a combination, depends on whether the sites are co-located at the same institution, or whether they use the same IRB, or not. The IMPAACT/ACTG PI will be responsible for verifying and/or certifying all IRB approvals for the protocol and any other regulatory or study management documents. Certification for any records, including the SIC, in order to create a shadow file at the IMPAACT or ACTG site is explained in the MOPS for this study.

Blood Draws

Participants will have evaluations prior to HSCT at entry and pre-conditioning. After HSCT, evaluations will take place at 100 days, Week 26, Week 52 (1 year) and then every 6 months until 5 years, as part of this research study. Whenever possible, clinic visits and blood draws for this study will be completed at the same time as post-transplant clinic visits and blood draws. IMPAACT/ACTG specimen tracking forms will be used to monitor the movement of study blood samples and biopsy/autopsy samples, from the transplant center, to one of two central labs for processing, and then to specific laboratories for testing (see Manual of Procedures [MOP]). NIH guidelines on allowable blood volumes to be drawn will be followed for all blood draws.

Biopsies

If a biopsy is performed as part of clinical care for the transplant, the study team requests a piece of the biopsy for HIV-1 studies. Biopsy tissue may include, but is not limited to, muscle, brain, liver, lung, and GI tract. IMPAACT/ACTG tracking forms will be used for biopsies sent to the laboratory for studies (see MOP for biopsy details).

Autopsy

If a participant dies and undergoes an autopsy, the study team requests tissue to determine presence of CCR5delta32 in various organs and to evaluate viral reservoirs. IMPAACT/ACTG tracking forms will be used for tracking autopsy specimens sent to performing labs for studies (see MOP for autopsy details).
Figure 1. P1107 Study Design – Pre-transplant Cohort

IMPAACT/ACTG site IRB submission

Transplant center IRB submission

PRO Approval
IMPAACT/ACTG site – main site on IOR form
Transplant center – sub-site on IOR form

Identify subject

Screen StemCyte CCR5delta32 stem cell bank for HLA match

Screen other stem cell banks for HLA match

HLA matching units found

Aliquots of matching units sent to StemCyte for CCR5delta32 screening

IMPAACT/ACTG site informed on signed study consent form

IMPAACT/ACTG site completes FSTRF enrollment

Subject signs consent form at transplant center

Study visits completed at transplant center / IMPAACT/ACTG site

CCR5delta32 matching unit found

Transplant team and subject decide which unit to use in transplant

CCR5delta32 unit chosen; ELIGIBLE for study

IMPAACT/ACTG site completes IMPAACT specific CRFs

CRFs sent to FSTRF

Transplant center completes CIBMTR CRFs

CCR5delta32 unit not chosen - NOT eligible for study
Figure 2. Distribution of the IMPAACT, ACTG and CIBMTR transplant centers. Please refer to MOP for detailed line listing of sites.
Blue markers – CIBMTR transplant sites; Green pins – IMPAACT sites; Red pins – ACTG sites
4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.11 Confirmation of HIV-1 Infection

Tests Performed at < 2 years of age

An infant will be considered to be infected with HIV if TWO separate peripheral blood specimens from different days are drawn and each specimen is positive by at least one of the following assays:

- HIV DNA PCR,
- Plasma HIV RNA (quantitative or qualitative),
- HIV total nucleic acid tests

At least one of the above tests must be done in a CLIA or CAP-certified laboratory. If the mother or infant is receiving antiretroviral drugs, then an HIV DNA assay may be more sensitive.

Tests Performed at > 2 years of age

Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. For studies conducted under an IND, all test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GLCP and approved by the IMPAACT central laboratory.

- Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in subject’s charts. Source documentation [patient’s medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.] must be available if requested.
- Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites)

Acceptable Tests

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

If Sample #1 is positive, then collect and test Sample #2.

Sample #2 may be tested using any of the following:
- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

4.12 Age ≥12 months. There is no upper age limit.

4.13 Willing to provide written, informed consent or, if < 18 years, parent/guardian able to provide written/informed consent

Pre-transplant Cohort Only

4.14 An underlying disease appropriate for HSCT, as determined by the transplant team as part of standard of care.

4.15 Availability of an appropriately matched (as determined by the transplant center) CCR5Δ32 cord blood unit (homozygous or heterozygous) and intention to proceed with transplantation. NOTE: Double cord transplants are allowed. If a double cord is used, at least one cord blood unit should be CCR5Δ32 (homozygous or heterozygous).

Post-transplant Cohort Only

4.16 Having already received a CCR5Δ32 homozygous cord blood or bone marrow transplant within the last two years.
4.2 **Exclusion Criteria**

4.21 Having already received, or planning to receive, more than one CCR5Δ32 homozygous cord blood or bone marrow transplant

4.3 **Concomitant Medication Guidelines**

There are numerous potentially serious drug interactions between drugs normally used in transplantation and those used to treat HIV-1 infection. A partial list of the known interactions is provided in the Manual of Procedures (MOP); however, none of these medications are prohibited but all should be managed by providers experienced in the use of these drugs and familiar with clinical and laboratory monitoring for toxicities.

Please also see section on antiretroviral medications in section 5.4 of this protocol.

4.4 **Enrollment Procedures**

Please refer to Figure 1 for the study design of the pre-transplant cohort from IRB submission to CRF completion.

Following IRB approval, the IMPAACT/ACTG principal investigator will be responsible for submitting the 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 and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files. NIAID sites are required to wait for the IMPAACT Operations Center notification of approval before proceeding with enrollment of their first subject.

Upon receiving final IRB and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. The IMPAACT/ACTG site PI is responsible for facilitating and verifying any and all IRB approvals and implementations at a site. IMPAACT/ACTG 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 IMPAACT/ACTG/Transplant site's regulatory files. Regulatory oversight responsibility and verification and facilitation for this trial lie with the IMPAACT/ACTG site PI.

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.

http://rsc.tech-res.com/protocolregistration/

Guidelines for completing protocol registration in the following three scenarios are addressed in the Manual of Procedures (MOP), with additional guidance supplied in the Protocol Registration Manual (http://rsc.tech-res.com/protocolregistration/).

a) Co-located IMPAACT/ACTG sites with the same IRB
b) Co-located IMPAACT/ACTG sites with different IRBs
c) Separate IMPAACT/ACTG site and transplant center

Participants meeting the study eligibility criteria will be enrolled via the IMPAACT/ACTG site personnel through the Data Management Center (DMC) registration screens. Written informed consent for study participation will be completed by the transplant center or by the IMPAACT/ACTG staff and must be obtained before any study related procedures are performed.

At the time the subject is consented, there will be additional consents to obtain part of any biopsy or autopsy specimens for analysis in the informed consent document (Appendices IV and V). There will be required, routine close communication between the network site and transplant center, so that the network site will be alerted when this consent has been obtained. Oversight of this process is the responsibility of the IMPAACT/ACTG site PI.

4.5 Enrollment in the Pre-Transplant Cohort

NOTE: The P1107 team strongly encourages all IMPAACT/ACTG sites to submit to their local IRB immediately upon availability of the protocol, in order to assure IRB approval BEFORE a patient is identified for enrollment. At the time of IRB submission, IMPAACT/ACTG sites will need to notify their IRB’s of the potential transplant sites with whom they can collaborate and the transplant sites should provide a letter of acknowledgment. At the time of IRB submission at the transplant site, the collaborating ACTG or IMPAACT site should be identified and contacted and they should provide a letter of acknowledgement. A sample letter of acknowledgement can be found in the MOPS.
The transplant center should be affiliated with an IMPAACT or an ACTG site. If they are not affiliated with such a site at their institution, the transplant center should contact the team for guidance (impaact.teamp1107@fstrf.org).

a) The principal investigators/study coordinators of the IMPAACT/ACTG and transplant sites meet to discuss the protocol logistics and responsibilities and agree to collaborate. A letter of acknowledgement should be created for each collaborator.
b) The IMPAACT/ACTG site will ensure that IRB approval is in place at both the transplant center and IMPAACT/ACTG locations, and protocol registration at DAIDS PRO has been completed.
c) Once an HIV-1 infected participant in need of HSCT is identified, the transplant center should proceed through the normal search process for HSC procurement.

4.51 Identification of Cord Blood Unit for Transplantation – Standard of Care

a) The transplant center submits participant sample(s) to StemCyte for identification of an available and closely matched CBU within the CCR5delta32 CBU bank.
b) The transplant center and participant will select the most appropriate stem cell product for transplant using standard of care criteria for selection. If multiple CBUs are identified that have not been screened for the CCR5Δ32 mutation, samples of these CBU can be sent to StemCyte for CCR5Δ32 mutation screening.
c) If the final product selected for transplantation is homozygous or heterozygous for CCR5Δ32, the participant may be approached for participation in P1107.

4.52 Enrollment

a) IMPAACT/ACTG staff work with the transplant site to confirm participants HIV-1 status and other eligibility criteria as part of enrollment. Note that certified copies of the source documents must be present in the shadow file at the IMPAACT/ACTG site. If the original source document is at the transplant site, the site should follow the directions in the MOP for details on obtaining a certified copy.
b) The transplant site explains the study to the participant/family and completes the informed consent process. The transplant site will also take initial responsibility for verifying the inclusion criteria, but the final responsibility for verification will be done by the IMPAACT/ACTG site. The transplant center coordinator has 2 business days to alert the IMPAACT/ACTG site that the consent has been signed and facilitate the provision of this documentation to the
IMPAACT/ACTG site with designation of the location of the appropriate source documents and/or facilitation of access to the source documents for the IMPAACT/ACTG personnel. Correct certification of any copies is ultimately the responsibility of the IMPAACT/ACTG site PI’s. The Network site can then enter the enrollment through the Data Management center (DMC) Subject Enrollment System (SES) at www.fstrf.org.

NOTE: The participant does not need to physically relocate to the IMPAACT and/or ACTG site for enrollment; however, the IMPAACT/ACTG site will assist the transplant site as much as possible with completing the enrollment, study visits and specimen and data collection. Incomplete enrollments or enrollment of ineligible subjects will ultimately be the responsibility of the IMPAACT/ACTG site.

c) Transplant identification number (ID) is assigned by the Center for International Blood & Marrow Transplant Research (CIBMTR)

d) IMPAACT/ACTG patient identification number (PID) is assigned by the IMPAACT /ACTG site, using the PID list provided to the site by FSTRF for participation in IMPAACT or ACTG studies.

e) The IMPAACT/ACTG site maintains the link for transplant ID and FSTRF PID link. As well, this is captured on an IMPAACT CRF. The link between the transplant ID and the participant name will be maintained at the transplant center.

f) Day of transplant is designated as Day 0 for this protocol. (Figure 3.)

g) Enrollment occurs within 30 days prior to the transplant. All preparation/ablation (conditioning) as well as GVHD and infection prophylaxis will be at the discretion of the local transplant providers. HIV-1 treatment will be at the discretion of the local HIV-1 care provider with consultation, if desired, from the IMPAACT/ACTG site.

h) General information about potential drug-drug interactions is provided in the Manual of Procedures (MOP).

4.6 Enrollment in the Post-transplant Cohort

a) HIV-1 infected individuals who have previously undergone a homozygous CCR5Δ32 hematopoietic stem cell or bone marrow transplant may be enrolled in the post-transplant cohort, within two years of the transplant.

b) IRB approval in collaboration with IMPAACT/ACTG site PRO approval must be in place before the patient is approached.

c) The participant will complete the informed consent process and then will be entered into the enrollment system at FSTRF at the IMPAACT/ACTG site.

d) Participants will have an initial visit at the IMPAACT/ACTG Network site where protocol activities will largely follow SOC as an HIV treatment
provider and collect pertinent past medical history information and draw blood.
  o The sites will coordinate study visits with regular transplant follow up visits
  o Data transfer and collection of specimens will be organized through the CIBMTR coordinating center in collaboration with the protocol team, and based on the Schedule of Evaluations.

e) Participants should then follow the schedule of evaluations for the post-transplant cohort (Appendix IB or Appendix IIB, depending on the weight of the participant) at the appropriate time post-transplant. For example, if the participant is at 2 years post-transplant, the participant should start the study with an initial visit and then move to the 2 year (week 104) post-transplant visit and continue follow-up until the end of the study.

4.7 Study Management

Study Visits
The transplant center will provide the main contact with the participant and will complete the study visits, with the IMPAACT/ACTG site acting as the facilitating coordinating center for the IMPAACT/ACTG data base and overseeing protocol management within the IMPAACT/ACTG network and for NIH. For subjects who are 100 days or greater post-transplant, if additional study visits are required, such as in the case of stopping ARV for 14 or more consecutive days, the study visits may be conducted at the IMPAACT/ACTG site or with the HIV-1 care provider, if different. Efforts will be made to coordinate visits with the standard transplant visits, whenever possible. In the event that a subject does not live near a transplant or IMPAACT/ACTG site, the study team will work with a local healthcare provider to obtain the necessary specimens and data. In this case, the local HIV-1 healthcare provider will need to obtain IRB approval for the study as well. The IMPAACT/ACTG partner site PI will be responsible for correct verifying and certification of copies of pertinent documents for a shadow file at the IMPAACT/ACTG site.

The transplant team will complete the CIBMTR (Center for International Blood and Marrow Transplant Research) forms and when entered into the CIBMTR system, the forms will be quality checked as per usual practices in the CIBMTR network and will then be printed out and sent to the IMPAACT Data Management Center (FSTRF). The IMPAACT/ACTG site will complete the IMPAACT study specific CRFs. Select transplant source documents will be certified per the MOP at the transplant center and shared with the IMPAACT/ACTG Network site. Obtaining correct certification will be the responsibility of the IMPAACT/ACTG site as will extraction of HIV-1-treatment and laboratory monitoring data from the clinical records or from certified copies by an IMPAACT/ACTG coordinator.
Administration of Vaccines
Another standard of care measure is the recommendations for revaccination at 6 to 24 months, including some live vaccines at ≥24 months. The need for revaccination is based on the recognition that the recovering lymphoid system following CBU transplants is immunologically naïve. Reconstitution of memory B cell pool can only occur following environmental or vaccine-based exposure to common pathogens and in the presence of adequate help from CD4 T cells. Live vaccines are administered only if participants are no longer receiving immunosuppression, show no signs of GVHD, and have evidence of functional immunity as determined by increase in antigen-specific antibodies following vaccination or infection [28,29]. The P1107 team anticipates that transplant centers will follow accepted guidelines for re-vaccination. Participants will be monitored for ability to mount immune responses to vaccines, to ensure that seroprotective titers have been generated and also as a test to determine that immune competence has been established. Testing for immune cell reconstitution (immunophenotyping and quantitative immunoglobulins and seroresponse to vaccines) will be performed in transplant centers, in accordance with the guidelines of the participating sites. Recovery of the immune system may be influenced by adverse effects of GVHD, as well as impact of chronic immunosuppression on a reconstituting immune system.
Logistics of Study Participation

Figure 3. A Timeline of Pre- and 1 Year Post- Hematopoietic Stem Cell Transplantation (HSCT) in the Pre-Transplant Cohort
Stopping Antiretroviral Therapy

If the participant is off ARV for 14 or more consecutive days after 100 days or more post-transplant, the subject should be switched from the original SOE to Appendix I-C or II-C depending on their weight, so that additional blood samples can be collected to determine whether functional or sterilizing cure has occurred. The IMPAACT/ACTG site will track the ARV medications. There will have to be close communication between the network site and transplant center, so that the network site will be alerted when the subject is off ARV for more than 14 days. Status of ARVs will also be recorded on the monthly telephone call case report form. HIV-1 therapy may be reinitiated at any time, based on the decision of the clinical care provider, following which a “Back on ART” visit will occur, as specified in Appendix IC or Appendix IIC. The participant would then return to their original SOE once back on ARVs. Participants may stop/restart ARV therapy for longer than 14 consecutive days multiple times post-Day 100, but every stop event requires re-starting the Appendix IC or Appendix IIC SOE at Day 0. There will be a specific stop/restart ARV form as part of the study specific CRFs to be completed by IMPAACT/ACTG site. The transplant center will need to provide certified copies of the ARV source documents in order for the Network sites to complete the CRFs.

The research visits specified in Appendices IC or IIC may occur either at the IMPAACT/ACTG site or at the bone marrow transplant site with consultation from the IMPAACT/ACTG team. If HIV-1 consultation is provided from a local infectious disease expert, rather than the IMPAACT/ACTG team, then the off ART visits (Appendix IC or IIC) may occur at the local infectious disease expert site with input/coordination from the IMPAACT/ACTG team. It should be noted that if this clinic is not affiliated with the approving institution, they will also need IRB approval. The IMPAACT/ACTG site will take responsibility for communicating with this additional site and facilitating the process to obtain study data.

Specimen Collection

Every effort will be made to have research visits for collection of specimens, coincide with standard of care clinic visits (transplant or HIV-1 management).

Two separate schedule of evaluations (SOEs) are listed for study participants depending on their body weight; Appendix IA, IB and IC (≥50kg) or Appendix IIA, IIB and IIC (<50kg). At each study visit, the patient will be weighed. If the participant is ≥ 50kg, they will have blood volumes drawn per the ≥50kg appendix (Appendix IA or IB, depending on whether they were enrolled pre- or post-transplant). If they are <50kg, they will have blood volumes drawn per the <50kg appendix (Appendix IIA or IIB, depending on whether they were enrolled pre- or post-transplant).
Additional research visits may be necessary if the participant is 100 days or greater post-transplant and ARVs are discontinued for 14 or more consecutive days. Refer to Appendices IC and IIC.

If the IMPAACT/ACTG site is located at a distance from the transplant site, the IMPAACT/ACTG site will coordinate laboratory processing and shipping as needed and, if necessary, site personnel may travel to the transplant site to assist with the completion of the study visits for the identified participant.

Returning Results to the Participant
The virology studies proposed will use ultrasensitive assays that are currently not used for clinical care and, therefore, are not assays that require CLIA-certification. These studies are highly exploratory. Further, the research assays will not be done in real-time; therefore, the results will not be available for the care of individual patients. For these reasons, results will not be shared with the participants directly, but will be shared with the transplant site personnel. A summary of the findings in lay terms will be distributed to the study participants and primary healthcare physicians following the completion of each transplant and the availability of the research results. IMPAACT/ACTG sites will provide these to each transplant site for distribution to participants.

Data Management
a) The FSTRF IMPAACT database is located at Frontier Science and Technology Research Foundation (FSTRF) in Buffalo, NY and the CIBMTR databases are located in Milwaukee, WI and Minneapolis, MN.
b) Transplant data (CIBMTR forms for a research subject) will be completed by the transplant site staff and will be sent electronically to the CIBMTR, whereupon they will be assessed for quality control.
c) Once the data has been assessed for quality control by entry into the CIBMTR data entry system, the transplant site will print out the specific pre-identified forms and send them to the IMPAACT data management center. The timing of collection and transfer of data will meet the standard CIBMTR guidelines.
d) IMPAACT/ACTG sites are responsible for completing the IMPAACT CRFs; the IMPAACT DMC will query the IMPAACT/ACTG sites for QA/QC on the IMPAACT CRFs and data entered by standard procedure.
e) IMPAACT/ACTG sites will need to obtain certified copies of the source documents from the transplant sites and the HIV-1 care provider, in order to support the IMPAACT CRFs. Refer to the MOP for details.
5.0 PARTICIPANT MANAGEMENT

5.1 Toxicity Management

P1107 will follow the participant pre- and post- HSCT for the pre-transplant cohort and only post-HSCT for the post-transplant cohort. Management of toxicity while on study is the responsibility of the treating physician at the transplant site and should follow standard of care practice at the transplant site.

5.11 Reporting

Serious Adverse Event Reporting is not being done as part of this protocol since no treatment or intervention will be given as part of the study. Adverse events will be identified, graded and reported by the transplant clinical sites as part of the transplant standard of care.

5.2 Biopsy Specimens

If a biopsy is performed as part of clinical care, the study team would like to receive a part of the biopsy for HIV-1 studies. Biopsy tissue may include, but is not limited to, muscle, brain, liver, lung, and GI tract. The team will need to be notified as soon as possible by the transplant site regarding an upcoming biopsy. The protocol will use IMPAACT/ACTG tracking forms to monitor shipping and logging in biopsy specimens to the performing laboratory (see MOP).

5.3 Autopsy Specimens

If a participant dies and undergoes autopsy, the study team would like to receive part of any specimens collected as part of the autopsy for HIV-1 studies. The IMPAACT / ACTG Network site will need to be notified as soon as possible by the transplant site regarding an autopsy. The team should also be notified. The desired autopsy samples to be obtained for P1107 are described in the MOP. The protocol will use IMPAACT/ACTG tracking forms to monitor shipping and logging in any autopsy specimens obtained and sent to the performing laboratory site.

5.4 Criteria for ARV Treatment Discontinuation

This protocol will not involve making decisions about ARV treatment discontinuation. Treatment decisions are the responsibility of the clinical health care providers.
Continuation of ARV before, during, and after the transplant is desirable; however, the presence of ARV requires additional considerations. First, the development of resistance to ARV is facilitated by intermittent adherence to ARV. Thus, if a participant is only able to intermittently take ARV due to nausea, vomiting or mucositis, then complete discontinuation of all ARV until oral medications can be tolerated is better than intermittent dosing. Further, because of the variable half-life of the ARVs, if all are stopped at the same time, those with a long half-life remain in the system resulting in functional monotherapy for a period of time until all drugs are cleared. Therefore, when stopping medication, particularly the non-nucleoside reverse transcriptase inhibitors (NNRTI), it is best to continue the reverse transcriptase inhibitors for 1 week following discontinuation of the NNRTI. Finally, and most importantly, there are numerous drug interactions with the ARVs, especially the protease inhibitors (PI), with ritonavir being the most difficult agent to manage. Please refer to the Manual of Procedures (MOP) for general information about the known and/or more common drug interactions. The transplant clinicians are encouraged to review the participant’s specific regimen and the potential drug interactions as soon as a transplant is contemplated.

Any participant on a high dose ritonavir regimen should be changed to an alternate regimen prior to transplant. However, even low dose ritonavir at levels used to boost the other PI will lead to significant drug interactions. Therefore, whenever possible, clinicians should consider changing participants to an alternate regimen as far as possible before the transplant. A raltegravir-based regimen has the fewest interactions, followed by NNRTI, and then PIs other than ritonavir.

The protocol does not manage antiretrovirals but advises that there be an HIV-1 specialist on-site assisting in the management of the participant’s ARV and that the participant stay on appropriate antiretrovirals if possible throughout the post-transplant period and minimally until donor engraftment is complete and the immune system has recovered for at least one year.

The sites will be asked to work with the transplant center to assure that the subject has an appropriate HIV-1 consult either by the IMPAACT/ACTG Network the protocol team or the transplant infectious disease consult team. If/when the HIV-1 consultant, along with the participant and the transplant team, decide to discontinue antiretroviral therapy, the participant will be followed as is described in section 4.7 and Appendix IC or IIC. The IMPAACT/ACTG Network site should be notified immediately if ARV therapy is discontinued. The study team should also be notified.
5.5 Criteria for Study Discontinuation

Participants must be discontinued from the study if:

5.51 The participant or parents or legal guardian refuses further participation in the study.
5.52 The participant cannot attend study visits.
5.53 The investigator determines further participation would be detrimental to the participant’s health or well-being.
5.54 Failure to proceed to transplant with homozygous or heterozygous CCR5Δ32 CBU.
5.55 The site investigator, NIAID, IMPAACT, the Office for Human Research Protection (OHRP), or the site Institutional Review Board (IRB) discontinues the study.
5.56 The subject has a second transplant.

6.0 EXPEDITED ADVERSE EVENT REPORTING

6.1 Adverse Event Reporting to DAIDS

EAE reporting to DAIDS is not being done as part of this study.

6.2 Death and Autopsy

When a site is aware of a participant’s death or a pending death, the team should be emailed as soon as possible (impaaact.teamp1107@fstrf.org). Priority should be given to obtaining an autopsy. The desired autopsy samples to be obtained for P1107 are described in the MOP.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

This observational, open label, multi-center study will evaluate the success of transplantation using CCR5Δ32 cord blood stem cells in HIV-1 infected participants’ aged ≥ 12 months, who require a stem cell transplant for reasons other than their HIV-1 status.

Up to 25 evaluable participants will be enrolled, as follows:
Pre-transplant cohorts: Up to 10 evaluable participants receiving CCR5Δ32 homozygous CBU; and up to 10 evaluable participants receiving CCR5Δ32 heterozygous CBU.

Post-transplant cohort: Up to 5 evaluable participants, who have received homozygous CCR5Δ32 cord blood. Even though these participants had already received the transplantation prior to study entry, they will be allowed to enroll, as they will still provide valuable information.

Participants who are followed <100 days will be considered unevaluable and will be replaced (the primary outcome cannot be determined without survival/disease status data at the 100 day evaluation.) Note: Participants who die before 100 days will be considered evaluable and will be counted as failures in the analyses. There will be no limits on the number of participants from IMPAACT vs. ACTG sites.

The major responsibility of the IMPAACT and ACTG sites will be in the screening of potential candidates following identification at sites, collection of data for IMPAACT CRFs and completion of specified follow-up visits for laboratory studies. The performance of the transplant and acute management of the participant, including hospitalization and follow up for the primary disease requiring HSCT, will be the responsibility of the participating transplant team and will be performed using standard clinical care protocols. Given these factors and the limited sample size, the statistical analyses will be descriptive.

7.2 Outcome Measures

7.21 Primary Outcome Measures

7.211 Survival at 100 days, Week 26, Week 52 and then every 6 months until 5 years after transplantation.

7.212 Event free survival at 100 days, Week 26, Week 52 and then every 6 months until 5 years after transplantation, defined as survival where the cancer does not recur, the graft takes and there are no life-threatening events.

7.213 Graft versus host disease.

7.214 Severity of graft versus host disease (see MOP).

7.215 Time to hematopoietic cell and immune recovery.

7.216 Chimerism (≥ 98% of blood cells bearing CCR5Δ32).

7.217 HIV-1 proviral DNA levels in peripheral blood.
Secondary Outcome Measures

7.221 Achievement of a state of ‘Functional Cure’ or “Sterilizing Cure”. Working definitions (Any changes to the network definitions that occur will be communicated by clarification memo):

**Functional Cure:** For the purpose of clinical trials, following the discontinuation of all HIV-1 related treatment interventions, including HAART, a participant will be considered to have achieved an HIV-1 functional cure if for at least 5 years they: maintain an undetectable plasma viral load, using standard clinical assays, have achieved full CD4+ lymphocyte recovery with normal levels of T cell activation and proliferation, and normal levels of immunoglobulins with no disease progression. It is anticipated that participants who have achieved a functional cure will continue to have detectable HIV-1 in peripheral blood cells and/or tissues.

**Sterilizing Cure:** As above but no detectable replication-competent virus in peripheral blood and minimal (near limits of detection) HIV-1 DNA in peripheral blood and or tissues.

7.222 Plasma viral load <50 copies/ml

7.223 Existence of replication competent HIV-1 reservoirs in peripheral blood, gut and other tissue compartments

7.224 HIV-1 induced effects including systemic inflammation, immune activation. Outcome measures will consist of plasma cytokines (IL-1, IL-6 and TNF-a) and cellular markers HLA-DR and CD38 on CD4 and CD8 T cells.

7.225 Gut immune reconstitution: Outcome measures for the gut immune status will consist of tissue immunohistochemistry to analyze CD4 T cells when feasible, and for plasma markers of gut microbial translocation namely lipopolysaccharide (LPS) and soluble CD14 (sCD14) a marker of monocyte activation attributed to LPS effects.

7.226 HIV-1 specific humoral and cellular immune responses as measured by HIV-1 Ab levels in plasma and ELISPOT for IFN-γ (as part of assessment of cure).

Randomization and Stratification

There will be no randomization and no stratification.
7.4 Sample Size and Accrual

No formal sample size calculations have been performed for this study. In the team's opinion, a sample size of 10 in each of the two pre-transplant cohorts would provide sufficient information to assess the safety of transplantation of CCR5Δ32 cord blood stem cells in this population, as well as be a feasible number to enroll in a reasonable amount of time.

The post-transplant cohort is included because it is possible that while some sites are in the process of getting ready to participate in this study, some of their patients will undergo transplantation. The study team wants to be able to credit these sites for their work and use the data from these participants. It is not expected that many participants will be in this situation. Hence, an N of 5 was chosen as the size of the post-transplant cohort.

Up to 25 HIV-1 infected participants’ ≥12 months of age will be enrolled as follows.

Pre-transplant cohorts: Up to 10 evaluable participants receiving CCR5Δ32 homozygous CBU; and up to 10 evaluable participants receiving CCR5Δ32 heterozygous cells.

Post-transplant cohort: Up to 5 evaluable participants, who have received homozygous CCR5Δ32 cord blood prior to enrollment in the study.

7.5 Monitoring

7.51 Safety Monitoring

Since no treatment or intervention will be given as part of the study, no formal safety monitoring by IMPAACT / ACTG will take place. Adverse events will be identified, graded and reported by the clinical sites as part of the transplant standard of care.

7.52 Routine Monitoring

The protocol team will have regular conference calls to ensure that its members are aware of ongoing issues concerning the conduct of the study and will review reports about the status of the study on a quarterly basis. These will include reports on accrual, baseline characteristics, data and sample collection timeliness and completeness,
The accrual timeframe is expected to be 3-4 years. Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. Initially, the protocol team will monitor site registration monthly to ensure that an adequate number of sites have registered to complete the protocol. In addition, the team will monitor feasibility quarterly, first based on site protocol activation and then on accrual.

A full protocol monitoring plan with more specific details on monitoring of accrual, loss to follow-up, samples and data collection will be prepared before the study opens to accrual.

7.6 Analyses

Due to the limited sample size, the statistical analyses will be descriptive. No formal comparison will be made between the cohorts. For post-transplant cohort participants, some early time points may be missing.

7.6.1 Primary Analyses

The rate of mortality at 100 days, Week 26, Week 52 and every 6 months until 5 years post transplantation will be presented, for each of the three enrollment groups, with these proportions bounded by an exact 90% confidence interval using Kaplan-Meier estimates to account for censoring.

For each participant, hematopoietic cell and immune recovery will be assessed. Descriptive analyses will consist of frequency distributions of these outcomes at 100 days and 52 weeks post-transplant, broken down by cohort.

The rates of post-transplant chimerism for CCR5Δ32 in peripheral blood will be presented, for each of the three enrollment groups. Descriptive analyses will consist of frequency distributions of these outcomes at 100 days and 52 weeks post-transplant, broken down by cohort.

The rate of graft versus host disease post-transplantation at 100 days and 1 year will be presented, for each of the three enrollment groups, with these proportions bounded by an exact 90% confidence interval.
7.62 Secondary Analyses

Changes from pre to post transplant for all the measures described in Section 8.0 will be presented descriptively, but formal analyses will not be possible due to the small sample size.

For individuals who elect to interrupt HAART after transplantation, the rate of development of a state of “Functional Cure” or “Sterilizing Cure” will be presented at 100 days, Week 26, Week 52 and monthly until 5 years post transplantation, for each of the three enrollment groups, with these proportions bounded by an exact 90% confidence interval using Kaplan-Meier estimates to account for censoring.

8.0 LABORATORY ASSAYS

8.1 Virological Assays

8.11 Biomarkers of HIV-1 infection following Cord Blood Transplantation

Standard testing used to confirm HIV-1 infection include: HIV-1 antibody testing and viral load measures using assays that can quantify free virus to <20 or <50 copies/mL of plasma. In order to measure very low levels of HIV-1, special research assays are required that may include: quantitative HIV-1 proviral DNA in peripheral blood mononuclear cells (PBMC) or tissue; ultrasensitive HIV-1 RNA assays that can detect as few as a single copy/mL of HIV-1 RNA in plasma; 2 LTR HIV-1 circles; and measures of replication competent virus in PBMC.

Using the repository PBMC samples the P1107 team will assess lymphocyte lineage chimerism in order to determine if engrafted CCR5Δ32 T cells have a selective advantage over other lymphoid cells in those patients with split chimerism. If sufficient cells are available the team will check chimerism for CCR5Δ32 in purified CD4 T cells relative to HLA chimerism in these cells. The same will be done for CD8 T cells.

Nearly all HIV-1 infected individuals with clinically undetectable viral loads continue to have measurable viremia using these specialized assays at a median level of 1 to 3 copies of HIV-1 RNA/mL of plasma [30]. This low level of virus has the potential to be eradicated if transplantation with CCR5Δ32 homozygous cord blood units is successful. In addition, molecular assays that detect 2-HIV-1 LTR circles, which are formed in recently infected cells but where infection is aborted, are used to decipher ongoing cycles of HIV-1 replication in participants with clinically
undetectable viral loads [31]. Furthermore, since most of the proviral DNA detected in peripheral blood mononuclear cells are defective, and therefore not capable of producing infectious virus, enhanced virus coculture assays that involve processing of large volumes of whole blood to enrich for the resting memory CD4+ T cells, are needed to assess the persistence of replication-competent HIV-1 genomes [32]. Using this assay, one can comment on the persistence of replication-competent proviruses and their infected cell frequencies per million resting CD4+ T cells, also known as IUPM. These assays will be used in this protocol to assess the impact of transplantation on latent and replication competent HIV-1.

8.12 **Analysis of HIV-1 tropism pre-and post-transplantation with CCR5Δ32/32 cord blood cells.**

Two distinct phenotypes of HIV-1 exist based on the co-receptor used for entry into target cells (CXCR4 and CCR5) [33]. While, HIV-1-variants that utilize the CCR5 co-receptor are the preferential variants transmitted and/ or amplified during primary infection [34], HIV-1-infected individuals also harbor low-levels of CXCR4 variants, as these are shown to emerge under drug selective pressure with CCR5-antagonists, and also during advanced stages of disease. At present, commercially available assays (Trofile™ - Monogram’s Co-receptor Tropism Assay, Monogram Biosciences) are used to determine co-receptor usage of replicating virus in plasma or in proviral DNA in participants with low or undetectable plasma viral load levels. An alternative method to quantify CXCR4 and CCR5 viruses is a genetic approach based on sequencing of the V3 region of HIV-1 env and looking for signature amino acid changes in the V3 loop of gp120 that are predictive of the virus phenotype. More recently, ultra-deep pyrosequencing approaches have been applied which allows for in-depth analysis and quantitation of HIV-1 quasi-species through time. Knowledge of the proportion of CXCR4 and CCR5 variants present within the individual prior to transplantation is important for assessing the virologic outcomes of this study.

8.13 **Anticipated time course of HIV-1 biomarkers following transplantation with CCR5Δ32/32 homozygous cord blood cells.**

It is anticipated that transplantation of cord blood cells that are CCR5Δ32/32 homozygous will result in engraftment of donor cells that are resistant to HIV-1 infection and detectable in PBMC by a mean of 90 days post-transplant, followed by gradual engraftment in tissues such as the gut and lung over the next 6 months. Prior to transplantation, the study team anticipates that study participants receiving effective antiretroviral therapy will test negative for HIV-1 RNA standard clinical assays but for
low levels of viral expression to continue (1 to 19 copies HIV-1 RNA/mL) when an ultrasensitive single-copy assay is used [30]. In addition, the study participant is expected to have detectable HIV-1 DNA in PBMC at levels between 100 to 1000 copies per million PBMC. If feasible, analysis for replication competent virus with enhanced co-cultures will be performed and are expected to yield replication-competent viral isolates (at an infected cell frequency of 0.5 to 1 per million resting CD4+ T cells [35-37]) and viral isolates recovered should represent an archive of the infection over the time course of the infection [38]. As the donor cells engraft in an individual with 100% engraftment, the P1107 team expects HIV-1 proviral DNA to be non-detectable. For individuals with mixed chimerism, HIV-1 proviral DNA will still be detectable but likely at lower than baseline levels likely due to dilutional effect with uninfected donor cells. Over the time course post-transplantation, if the transplant is successful and the HIV-1 resistant cells have a survival advantage, the proviral burden will likely decline. In contrast, in individuals in whom the transplant has failed, the proviral burden will remain unchanged or increase due to clonal expansion of cells. Similarly, with engraftment of the donor cells, replication-competent virus should no longer be possible at the limits of detection of the assay from large blood volumes. The P1107 team will interpret the results of the virological assays according to the current working definitions of functional HIV-1 cure or sterilizing cure (see Section 7.22) with the understanding that this is a proof of concept protocol and a partial functional cure (i.e. transient loss of HIV-1 DNA or prolonged suppression of plasma viremia off antivirals, or significant decrease in HIV-1 provirus with or without complete recovery of CD4+ T cells will be considered meaningful results, as this effect has not been shown with any other HIV-1 targeted interventions.

8.14 Anticipated time course for co-receptor usage following transplantation with CCR5Δ32/32 homozygous cord blood cells.

The tropism of the participants’ virus population at entry and at subsequent time points post-transplantation will be assessed on plasma virus in those with viral load ≥ 1000 copies/mL or on proviral DNA if viremia is below this level using the commercially available Trofile™ assay provided by Monogram Biosciences. In an exploratory study, in-vitro studies of susceptibility of engrafted PBMC to autologous and laboratory strains will be performed when donor engraftment has been demonstrated. Furthermore, a sequence-based approach with ultra-deep pyro sequencing will be used to examine whether quantitative shifts in co-receptor usage is occurring post-transplantation which will provide evidence for cryptic virus replication and viral escape under target cell selection.
8.2 Immune Correlative Studies

8.21 Immunologic Reconstitution following Cord Blood Transplantation

All participants will be evaluated for immune recovery as per standard of care for cord blood transplantation. Re-establishment of immunocompetence after CBU transplants takes several months, and some participants continue to demonstrate deficits in cell mediated and humoral immunity for several years after the transplant. Standard of care for monitoring CBU transplants includes assessment of recovery of neutrophils, monocytes, NK-cells, platelets, red cells, and B and T lymphocytes, usually in that order. Neutrophil recovery usually occurs by 4 weeks with umbilical cord blood grafts. NK cells are the first lymphocyte subset to recover and full NK cell recovery is typically achieved within 1 to 2 months following HSCT.

In general, recovery of T and B lymphocytes is more delayed and is dependent upon regeneration from lymphoid progenitors in bone marrow, recapitulating ontogeny of regeneration of a naïve immune system, similar to newborns [39,40]. CD8 T cells recover first, followed by B cells and ultimately CD4 T cells recover. In children given CBU transplant, recovery of lymphocyte number and function is comparable to BMT. Adult CBU recipients have poor thymopoiesis as compared to children, and thus have a longer period of T lymphopenia and impaired functional recovery [41]. Recovery of immune system in CBU transplants with CCR5Δ32 cells will be evaluated as per standard of care for CBU transplants.

8.22 HIV-1 specific and associated immune responses in participants receiving CBU transplant

An important aspect of the CCR5Δ32 transplants is the potential influence of the transplant on HIV-1 disease status, owing to the inherent resistance of CCR5Δ32 cells to HIV-1 infection. Thus the goal of the special immunologic studies will be to evaluate the impact of the transplant on the direct and indirect effects of HIV-1 on the immune system, with the expectation that these effects will decrease or become undetectable following eradication of HIV-1.

HIV specific immune responses:
In the chronic HIV-1 infected state, the immune system is highly dysregulated. Chronic antigenic stimulation can drive HIV-1 specific immune responses that may not be protective, but are indicative of ongoing antigenic stimulation. Included in these responses are serologic
48 responses with HIV-1 envelope binding IgG Ab. It is expected that all study participants will be positive for HIV-1 Ab prior to transplant and if a state of complete or partial eradication of HIV-1 occurs, there will be a decrease in antigenic burden and a gradual loss of such Ab. The P1107 team will determine HIV-1 Ab post-transplant at regular intervals to see if it will disappear. If Ab re-appears after initial decline, this may indicate re-emergence of the virus in some compartment in the body.

Cellular immune responses are also generated in HIV-1 infected persons, and ex-vivo assessment of these responses will be performed to evaluate immunologic memory to HIV-1 antigens. A state of polyfunctional T cell responses [42,43] with induction of 2 to 5 cytokines following antigen stimulation ex-vivo in cultured cells is considered to indicate “good” immune responses, whereas a single cytokine such as IFN-γ is indicative of a weak immune response. These cellular immune responses will be determined to assess pre and post transplantation to determine if in vivo immune stimulation by HIV-1 has been eliminated and to evaluate persistence of immunologic memory to HIV-1 antigens. The P1107 team hypothesizes that all immunologic responses to HIV-1 will eventually wane after a successful CBU transplant with HIV-1 resistant CCR5Δ32 cells.

**HIV-1 associated generalized immune defects:**
Chronic HIV-1 infection is also associated with excessive immune activation and inflammation [44,45]. Underlying immunoregulatory mechanisms driving immune activation are not fully understood and there is evidence of residual persistent immune activation in most participants who have achieved undetectable levels of plasma viremia despite potent HAART. Besides the direct effects of HIV-1 in causing immune activation, a major contributing mechanism is microbial translocation (MT) in the gut due to the damage inflicted by HIV-1 early in the course of infection [46-48]. It is not yet understood if treatment with HAART is sufficient to heal the gut completely, and if so, how long it takes for the gut to heal. The P1107 team hypothesizes that the CBU transplant will restore immunoregulatory mechanisms and also lead to healing of the gut, restoration of mucosal immunity and elimination of microbial translocation and of other factors contributing to immune activation. Thus, it is important to establish the baseline values of inflammatory cytokines and cellular immune activation and use these assays to assess the extent of virologic control.

Individuals with HIV-1 infection also manifest abnormalities in the distribution of their maturation subsets of T and B cells with skewing in favor of effector T cells and loss of memory B cells [49-52]. These markers will be evaluated following HSCT. The P1107 team expects
gradual normalization of the distribution of peripheral blood T and B cell maturation subsets following a successful CBU transplant with HIV-1 resistant CCR5Δ32 cells.

8.3 Scientific Studies to be Performed on Biopsies

To investigate the hypothesis that transplantation with CCR5Δ32 deleted cord-blood derivatives will result in HIV-1 vulnerable target T-cell replacement and, eventually, whole body eradication of HIV-1 virus, tissue-focused efforts would utilize sensitive and reproducible PCR techniques to quantify HIV-1 RNA (qRT-PCR) and DNA (q-PCR) and CCR5 gene expression (qPCR). Biopsies obtained during flexible sigmoidoscopy have been shown to provide high recovery of nucleic acids in a manner that accurately reflects viral tissue burden \textit{in vivo}.

Given the clinical safety requirements in this particular protocol, the number of biopsies obtained can be reduced compared to the number of biopsies usually obtained: results from one biopsy have been shown to be representative of up to three biopsies all obtained concurrently at the same level with low intra-patient/inter-biopsy variability and minimal inter-assay variability. Having a separate biopsy sample for various immunohistochemical quantification techniques is essential, especially if phenotypic characterization of replaced cells and/or HIV-1-containing target cells remains an aim. In clinical settings, a formalin-fixed, paraffin-embedded tissue samples is usually obtained for patient management; extra sections for this samples can be acquired for research staining (See MOP for details).

9.0 HUMAN PARTICIPANTS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

9.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (Appendices IV and V), and any subsequent modifications must be reviewed and approved by the IRB responsible for oversight of the study. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. 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 participant (or parent or legal guardian).
Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Participants (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB, local, state and national guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant 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 participant or the participant’s parent or legal guardian, except as necessary for monitoring by IMPAACT, the Office for Human Research Protections (OHRP), the NIH and the local Institutional Review Board (IRB).

9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, the IRB and the OHRP, as part of their duties to ensure that research participants are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by IMPAACT prior to submission.

11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV-1 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 transported in compliance with Federal Regulations and 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

Reference List


8. Bone Marrow Donors Worldwide. 8-1-2012.


**APPENDIX I-A**  
**SCHEDULE OF EVALUATIONS - Participants ≥ 50kg**  
**Pre-transplant Cohort**

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<th>Week 26</th>
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<th>Week 78</th>
<th>Week 104</th>
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NOTES:

- If a subject on Appendix I-A stops taking ARVs post Day 100 for longer than 14 consecutive days, they should switch to Appendix I-C since they will have more frequent blood draws for a short time. If they subsequently then re-start ARVs, they should complete the 'Back on ART' visit in Appendix I-C and then switch back to where they left off in their original SOE at their current post-transplant time point (Appendix I-A).

Footnotes

1. Entry visit should include documentation of HIV-1 infection, HIV-1 diagnosis.
2. Chart abstractions should include weight, ARV concomitant medications, hematology (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin [total, direct, indirect]) and renal tests (BUN, creatinine), as well as the reason for the transplant and any concurrent illness.
3. All chimerism assays except for CCR5Δ32 will be done as part of standard of care by the bone marrow team as part of the transplant.
4. Special immunology tests include the following: Immune activation markers, HIV-1 specific cytokine response by flow, HIV specific cytokine responses by Elispot, T cell maturation subsets, B cell maturation subsets.
5. Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot, in vitro susceptibility testing of donor cells to HIV-1 infection (day 100 and week 52 only).
6. Gut biopsies will only be performed as part of standard of care. If the subject provides consent, a specimen should be collected for research purposes. Gut pathology: HIV-1 RNA/DNA isolation and quantitation and CCR5 expression by PCR. Please contact the team for further guidance.
7. Day 0 (HSCT) is the day of transplant. There is no participant study visit on this date.
8. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
9. Special immunology/virology tests to be performed at this time point include the following: Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot and immune activation markers.

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods)
## APPENDIX I-B

### SCHEDULE OF EVALUATIONS - Participants ≥ 50kg

**Post-transplant Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Entry into study</th>
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<th>Day 100</th>
<th>Week 26</th>
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<th>Week 78</th>
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<tr>
<td><strong>TOTAL BLOOD VOLUMES (mL)</strong></td>
<td>83.5mL</td>
<td>43.5mL</td>
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<td>0mL</td>
<td>53.5mL</td>
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</tbody>
</table>
NOTE: If a subject on Appendix I-B stops taking ARVs post Day 100 for longer than 14 consecutive days, they should switch to Appendix I-C since they will have more frequent blood draws for a short time. If they subsequently then re-start ARVs, they should complete the ‘Back on ARV’ visit in Appendix I-C and then switch back to their original SOE (Appendix I-B).

Footnotes

1. Entry visit should include documentation of HIV-1 infection, HIV-1 diagnosis.
2. Chart abstractions should include weight, ARV concomitant medications, (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin (total, direct, indirect) and renal tests (BUN, creatinine), as well as the reason for the transplant and any concurrent illness.
3. All chimerism assays except for CCR5Δ32 will be done as standard of care by the bone marrow team as part of the transplant. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
4. Special immunology tests include the following: Immune activation markers, HIV-1 specific cytokine response by flow, HIV specific cytokine responses by Elispot, T cell maturation subsets, B cell maturation subsets.
5. Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot, in vitro susceptibility testing of donor cells to HIV-1 infection (day 100 and week 52 only).
6. Gut biopsies will only be performed as part of standard of care. If the subject provides consent, a specimen should be collected for research purposes. Gut pathology: HIV-1 RNA/DNA isolation and quantitation and CCR5 expression by PCR. Please contact the team for further guidance.
7. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
8. Special immunology/virology tests to be performed at this time point include the following: Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot and immune activation markers.

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods)
## APPENDIX I-C

### SCHEDULE OF EVALUATIONS - Participants ≥ 50kg

Participants who stop antiretrovirals after Day 100

<table>
<thead>
<tr>
<th>Visit Windows</th>
<th>Week 0 post-ART</th>
<th>Monthly</th>
<th>Week 4 post-ART</th>
<th>Week 12 post-ART</th>
<th>Week 26 post-ART</th>
<th>Every 26 weeks</th>
<th>Every 52 weeks</th>
<th>PRN as done for standard of care</th>
<th>Back on ART visit ¹</th>
<th>Early D/C</th>
<th>Death</th>
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<td>Resting CD4+T cell latent reservoir</td>
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<tr>
<td>Chimerism - CCR5Δ32</td>
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<td>3.5mL</td>
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<td>HIV-1 tropism</td>
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<td>Biopsy specimens</td>
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<tr>
<td>TOTAL BLOOD VOLUMES mL)</td>
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<td>30 mL</td>
<td>30 mL</td>
<td>86 mL</td>
<td>36mL</td>
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<td>0mL</td>
<td>59.5 mL</td>
<td>59.5 mL</td>
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</tbody>
</table>
NOTE: A participant is considered off ART if they have discontinued ART for longer than 14 consecutive days post Day 100. A participant may stop and then re-start ART more than once during the post-transplant period; each stop event post Day 100 requires re-starting the Appendix I-C SOE at Week 0.

Footnotes

1. If the participant or physicians choose to re-start ART, a ‘Back on ART’ visit is necessary. Once this visit has been completed, the subject should follow the original SOE (Appendix I-A or Appendix I-B) until the end of the study, starting where they left off.

2. Chart abstractions should include weight, ARV concomitant medications, hematology (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin (total, direct, indirect) and renal tests (BUN, creatinine)

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods)At 26 weeks visit if insufficient blood is obtained priority is blood to send to Miami for special virology and then the resting cell assay.
## APPENDIX II-A

### SCHEDULE OF EVALUATIONS - Participants < 50kg

**Pre-transplant Cohort**

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<th>Entry</th>
<th>Pre-conditioning</th>
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<th>Monthly</th>
<th>Day 100</th>
<th>Week 26</th>
<th>Week 52</th>
<th>Week 78</th>
<th>Week 104</th>
<th>Week 130</th>
<th>Week 156</th>
<th>Week 182</th>
<th>Week 208</th>
<th>Week 234</th>
<th>Week 260</th>
<th>PRN as done for standard of care</th>
<th>Early D/C</th>
<th>Death</th>
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<tr>
<td>Visit Windows</td>
<td>-</td>
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<td>-</td>
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<td>Telephone call with transplant center</td>
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<td>Resting CD4+T cell latent reservoir</td>
<td>40mL</td>
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<tr>
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<td>3.5 mL</td>
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<tr>
<td>HIV-1 tropism</td>
<td>6mL</td>
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<td>Virology assays (^5)</td>
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<tr>
<td><strong>TOTAL BLOOD VOLUMES (mL)</strong></td>
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<td>31 mL</td>
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<td>31 mL</td>
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<td>25mL</td>
<td>0mL</td>
<td>43.5 mL</td>
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NOTES:

- Per NIH guidelines, the volume of blood will not exceed the recommended amounts based on weight and age in the younger children.
- For participants less than 50kg, blood draw guidelines are as follows: no more than 5ml/kg of blood to be drawn at any one time; a maximum of 9.5ml/kg of blood drawn over an 8 week period.
- If a subject on Appendix II-A stops taking ARVs post Day 100 for longer than 14 consecutive days, they should switch to Appendix II-C since they will have more frequent blood draws for a short time. If they subsequently then re-start ARVs, they should complete the ‘Back on ART’ visit in Appendix II-C and then switch back to their original SOE (Appendix II-A).

Footnotes

1. Entry visit should include documentation of HIV-1 infection, HIV-1 diagnosis.
2. Chart abstractions should include weight, ARV concomitant medications, (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin (total, direct, indirect) and renal tests (BUN, creatinine), as well as the reason for the transplant and any concurrent illness.
3. All chimerism assays except for CCR5Δ32 will be done as standard of care by the bone marrow team as part of the transplant.
4. Special immunology tests include the following: Immune activation markers, HIV-1 specific cytokine response by flow, IV specific cytokine responses by Elispot, T cell maturation subsets, B cell maturation subsets.
5. Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot, in vitro susceptibility testing of donor cells to HIV-1 infection (day 100 and week 52 only).
6. Gut biopsies will only be performed as part of standard of care. If the subject provides consent, a specimen should be collected for research purposes. Gut pathology: HIV-1 RNA/DNA isolation and quantitation and CCR5 expression by PCR. Please contact the team for further guidance.
7. Day 0 (HSCT) is the day of transplant. There is no participant visit on this date.
8. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
9. Special immunology/virology tests to be performed at this time point include the following: Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot and immune activation markers.

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods)
### APPENDIX II-B

**SCHEDULE OF EVALUATIONS - Participants < 50kg**

**Post-transplant Cohort**

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<th>Visit Windows</th>
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<th>±2wk</th>
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<tr>
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<td>Resting CD4+T cell latent reservoir</td>
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<td>HIV-1 tropism</td>
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<td>Special virology</td>
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<td><strong>TOTAL BLOOD VOLUMES (ML)</strong></td>
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<td>33.5mL</td>
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<td>28.5mL</td>
<td>40mL</td>
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NOTES:

- Per NIH guidelines, the volume of blood will not exceed the recommended amounts based on weight and age in the younger children.
- For participants less than 50kg, blood draw guidelines are as follows: no more than 5ml/kg of blood to be drawn at any one time; a maximum of 9.5ml/kg of blood drawn over an 8 week period.
- If a subject on Appendix II-B stops taking ARVs post Day 100 for longer than 14 consecutive days, they should switch to Appendix II-C since they will have more frequent blood draws for a short time. If they subsequently then re-start ARVs, they should complete the ‘Back on ART’ visit in Appendix II-C and then switch back to their original SOE (Appendix II-B).

Footnotes

1. Entry visit should include documentation of HIV-1 infection, HIV-1 diagnosis.
2. Chart abstractions should include weight, ARV concomitant medications, (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin (total, direct, indirect) and renal tests (BUN, creatinine), as well as the reason for the transplant and any concurrent illness.
3. All chimerism assays except for CCR5Δ32 will be done as standard of care by the bone marrow team as part of the transplant. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
4. Special immunology tests include the following: Immune activation markers, HIV-1 specific cytokine response by flow, IV specific cytokine responses by Elispot, T cell maturation subsets, B cell maturation subsets.
5. Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot, in vitro susceptibility testing of donor cells to HIV-1 infection (day 100 and week 52 only).
6. Gut biopsies will only be performed as part of standard of care. If the subject provides consent, a specimen should be collected for research purposes. Gut pathology: HIV-1 RNA/DNA isolation and quantitation and CCR5 expression by PCR. Please contact the team for further guidance.
7. The chimerism assay should only be repeated if the Day 100 chimerism was <95%.
8. Special immunology/virology tests to be performed at this time point include the following: Special virology tests include: HIV-1 DNA quantification, un-integrated DNA detection, plasma viral load (single copy assay), HIV-1 sequencing (Deep sequencing: envelope tropism), Western blot and immune activation markers

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods)
# APPENDIX II-C

## SCHEDULE OF EVALUATIONS – Participants <50kg

### Participants who stop antiretrovirals after Day 100

<table>
<thead>
<tr>
<th></th>
<th>Week 0 post-ART</th>
<th>Monthly</th>
<th>Week 4 post-ART</th>
<th>Week 12 post-ART</th>
<th>Week 26 post-ART</th>
<th>Every 26 weeks</th>
<th>Every 52 weeks</th>
<th>PRN as done for standard of care</th>
<th>Back on ART visit¹</th>
<th>Early D/C</th>
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<tr>
<td><strong>Visit Windows</strong></td>
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<td>-</td>
<td>±4wk</td>
<td>±4wk</td>
<td>±8wk</td>
<td>±8wk</td>
<td>±8wk</td>
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<td>Resting CD4+T cell latent reservoir</td>
<td>40 mL</td>
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<td>40 mL</td>
<td>40 mL</td>
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<tr>
<td>Chimerism - CCR5Δ32</td>
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<tr>
<td>Biopsy specimens</td>
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<tr>
<td><strong>TOTAL BLOOD VOLUMES (mL)</strong></td>
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<td>25 mL</td>
<td>25 mL</td>
<td>71 mL</td>
<td>31mL</td>
<td>71mL</td>
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<td>49.5 mL</td>
<td>49.5 mL</td>
<td>0 mL</td>
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</table>
NOTES:

- Per NIH guidelines, the volume of blood will not exceed the recommended amounts based on weight and age in the younger children.
- A participant is considered off ART if they have discontinued ART for longer than 14 consecutive days post Day 100. A participant may stop and then re-start ART more than once during the post-transplant period; each stop event requires re-starting the Appendix II-C SOE at Week 0.
- For participants less than 50kg, blood draw guidelines are as follows: no more than 5ml/kg of blood to be drawn at any one time; a maximum of 9.5ml/kg of blood drawn over an 8 week period.

Footnotes

1. If the participant or physicians choose to re-start ART, a ‘Back on ART’ visit is necessary. Once this visit has been completed, the subject should follow the original SOE until the end of the study, starting where they left off.
2. Chart abstractions should include weight, ARV concomitant medications, hematology (hemoglobin, hematocrit, white cell count, differential, platelets), chemistry (SGOT, SGPT, bilirubin (total, direct, indirect) and renal tests (BUN, creatinine)

For insufficient blood draws, priorities are as follows: Standard of care tests, EDTA tubes (P1107 study bloods) At 26 weeks if insufficient blood draw priority is to send special virology to Miami first and then resting cell assay
APPENDIX III
PLANNED LABORATORY TESTING

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Assay</th>
<th>Investigator / Lab</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>Microbial translocation / inflammation</td>
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<td></td>
<td>Ultrasensitive viral load</td>
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<td>Cryopreserved PBMCs</td>
<td>CCR5 Chimerism</td>
<td>StemCyte</td>
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<tr>
<td></td>
<td>Proviral burden / 2-LTR circles</td>
<td>Persaud</td>
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<tr>
<td></td>
<td>Deep sequencing of envelope region - Diversity of proviral pool</td>
<td>Persaud</td>
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<tr>
<td></td>
<td>Resting CD4+ T cell replication competent</td>
<td>Persaud</td>
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<td></td>
<td>In vitro susceptibility of host cells to autologous and laboratory strains of HIV-1</td>
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<td>Immune activation markers</td>
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<td>HIV-1 specific IFN-g responses by Elispot</td>
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<td></td>
<td>T cell and B cell maturation markers</td>
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<td>PBMCs (if viral load &gt;1,000 copies/mL)</td>
<td>Trofile co-receptor tropism assay (Trofile DNA)</td>
<td>Monogram Biosciences</td>
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<td>Biopsy/autopsy specimens</td>
<td>HIV-1 RNA/DNA isolation and quantitation and CCR5 expression by PCR</td>
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<tr>
<td>Whole blood</td>
<td>Western blot</td>
<td>Jackson</td>
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</tbody>
</table>

NOTE: Laboratory addresses can be found in the LPC
INTRODUCTION
You/your child are being asked to take part in this research study because you/your child have the Human Immunodeficiency Virus (HIV-1), which is the virus that causes AIDS and because you/your child have a disease that requires a cord blood transplant for the standard of care treatment decided by you and your doctors. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you/your child want 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/your child agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep. Your consent must be obtained before starting any study procedures.

WHY IS THIS STUDY BEING DONE?
This study is being done to see what happens to the HIV virus when an HIV infected person receives a transplant with known CCR5Δ32 cells. We want to know if the HIV virus is suppressed (reduced) or removed from the body or if it stays in the body after the transplant. This study will also check how the cord blood cells grow in the body after transplant and whether there is any reaction of the body against the cells (graft versus host reaction) and the overall safety of the transplant in a participant who has HIV infection.

You/your child are scheduled to receive cord blood unit(s) identified as containing natural CCR5Δ32 cells. These cells are more difficult to infect with HIV because the virus cannot get into the cells. In the past, one HIV infected patient who received this
type of transplant (with CCR5Δ32 cells) no longer has any evidence of HIV. However, this result may not occur in your case. A small number of people naturally have these cells in their body and are more resistant to infection or to the development of disease with HIV.

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

If you/your child decide to enroll in this study, you/your child will continue to see your/your child’s transplant doctor on a regular basis. The study visits will occur as part of your/your child’s transplant appointments. You/your child will have 2 study visits before the transplant and 11 visits after the transplant at 100 days (3 months), 26 weeks (6 months), 52 weeks (12 months) and then one every 6 months, until 5 years after the transplant, while you/your child are taking HIV (antiretroviral) medication. If you or your physician(s) choose to stop your/your child’s antiretroviral therapy after you/your child are 100 days or greater post-transplant, you/your child will have an additional five visits for one year and then will be seen every 26 weeks to determine whether you/your child have any remaining HIV in your bloodstream. You/your child will also be asked to come in for a final visit if you decide to leave the study early.

Your/your child’s HIV medications are not provided as part of this study. When you/your child come for these visits, we will ask your doctor to share information about your health and the results of any other examinations and tests that are being done as part of your healthcare. In addition, we will collect extra blood samples, about 1-6 tablespoons (20-86mL), if possible. We will do special tests on these samples to see if there are changes in your/your child’s HIV and your immune system after you receive the transplant. From these tests we will look to see:

- Whether the HIV virus in your blood before and after transplant is the kind that should not infect the CCR5Δ32 cells
- Special research tests to look at the cells in your blood that help fight infection (immunology) and also some special tests to look at the HIV virus in your blood (virology)

**Release of Medical Information**

As part of the study, we will ask permission to make copies of your/your child’s transplant medical records through the CIBMTR to be used to complete case report forms. This information will be shared with IMPAACT/ACTG. If you do not agree to share your transplant medical records, you cannot be in this study.

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

I agree to allow my transplant medical records be shared with IMPAACT/ACTG for use in this study.

__________ Yes  __________ No  __________ Date
Blood Samples
Some of your/your child’s blood samples will be shipped to special laboratories for specialized tests.

Storage of Blood Samples
Some of you/your child’s blood will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-1 related research.

Your/your child’s samples will be stored at a special testing laboratory. Only approved researchers will have access to them. People who work at the laboratory will also have access to your/your child’s samples to keep track of them. These people won’t have information that directly identifies you/your child. Your/your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your regular doctor with the results of studies done using your stored 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/your child’s medical care. If the researchers decide that the result of a certain study provides important information for your/your child’s medical care, your 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.

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

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, HIV-1 related research studies.

__________ Yes  __________ No  __________ Date

Biopsies
Biopsy is the medical removal of some tissue or cells so that it can be examined by a pathologist to assess the presence or extent of disease. If you/your child receive a biopsy as part of your clinical care, the study team would like to obtain a sample of the biopsy to do special tests on. If you decide not to share your biopsy specimens, you can still participate in this study.

Please read the following statement carefully and then mark your initials in the appropriate space provided.
I agree to allow my biopsy samples to be collected for use in this research study and for future IMPAACT-approved, HIV-1 related research.

__________ Yes   ___________ No   ___________ Date

**Autopsy Samples**
Autopsy is a surgical procedure that consists of a thorough examination of a body to determine the cause and manner of death and to evaluate any disease or injury that may be present. If you/your child undergo an autopsy, the study team would like to collect some tissue specimens as part of the autopsy. If you decide not to share your autopsy specimens, you can still participate in this study.

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

I agree to allow my autopsy samples to be collected for use in this research study and for future IMPAACT-approved, HIV-1 related research.

__________ Yes   ___________ No   ___________ Date

**OTHER INFORMATION**
The information collected in this study may be used for other IMPAACT approved HIV-1 related research.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
Up to 25 infants, children, adolescents and adults will take part in this study. Up to 20 participants will be enrolled in the pre-transplant cohort.

**HOW LONG WILL I BE IN THIS STUDY?**
You/your child are enrolling in the study, and so will be in the study for approximately 5 years.

**WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?**
The study doctor may need to take you/your child off the study early, without your permission, if:

- You/your child are not able to attend the study visits as required by the study
- The study is cancelled by the National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), IMPAACT, or the site’s Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research participants.
WHAT ARE THE RISKS OF THE STUDY?
Blood samples will be obtained as part of your/your child’s routine healthcare. Blood draws are the only procedure being done as part of this study.

Blood Drawing Risks:
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur when a needle enters the body.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
You/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV-1 and require a cord blood transplant.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
Whether or not you/your child decide to join this study, you/your child be able to continue to receive standard of care treatment from your transplant team and other doctors and standard care for HIV from your doctor.

WHAT ABOUT CONFIDENTIALITY?
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you/your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

People who may review your/your child’s records include the Office of Human Research Protections (OHRP), the site IRB (insert name of site IRB), the National Institutes of Health, study staff, study monitors supporting the study, and their designees.

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

WHAT ARE THE COSTS TO ME?
There are no costs to you/your child for study visits or study procedures. All research related costs will be covered by the study.
WILL I RECEIVE ANY PAYMENT?
All study samples will be collected as part of standard of care blood draws or biopsy, and as such, no additional time is expected to be incurred because of this study. Therefore, you/your child will not receive any payment for participating in the study.

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

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You/your child may choose not to take part or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

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 rights as a research participant, 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 Mother (print)                            Mother’s Signature and Date  

_________________________                             ____________________________________  
Participant’s Father (print)                            Father’s Signature and Date  

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

_________________________                             ____________________________________  
Study Staff Conducting Consent Discussion (print)       Study Staff Signature and Date
APPENDIX V

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

Cord Blood Transplantation with CCR5Δ32 Donor Cells in HIV-Infected Subjects who Require Bone Marrow Transplantation for any Indication and its Observed Effects on HIV-1 Persistence
P1107, Version 1.0, dated 08/01/2013

SHORT TITLE FOR THE STUDY: Cord Blood Transplantation in HIV-1 Infected Patients

CONSENT FOR POST-TRANSPLANT COHORT

INTRODUCTION
You/your child are being asked to take part in this research study because you/your child have the Human Immunodeficiency Virus (HIV-1), which is the virus that causes AIDS and because you/your child have a disease that required a cord blood transplant within the last 2 years for the standard of care treatment decided by you and your doctors. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you/your child decide if you want 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 take part in this study, you will be asked to sign this consent form. You will get a copy to keep. Your consent must be obtained before starting any study procedures.

WHY IS THIS STUDY BEING DONE?
This study is being done to see what happens to the HIV virus when an HIV infected person receives a transplant with known CCR5Δ32 cells. We want to know if the HIV virus is suppressed (reduced) or removed from the body or if it stays in the body after the transplant. This study will also check how the cord blood cells grow in the body after transplant and whether there is any reaction of the body against the cells (graft versus host reaction) and the overall safety of the transplant in a participant who has HIV infection.

You/your child are scheduled to receive cord blood unit(s) identified as containing natural CCR5Δ32 cells. These cells are more difficult to infect with HIV because the virus cannot get into the cells. In the past, one HIV infected patient who received this type of transplant (with CCR5Δ32 cells) no longer has any evidence of HIV. However,
this result may not occur in your case. A small number of people naturally have these cells in their body and are more resistant to infection or to the development of disease with HIV.

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

If you/your child decide to enroll in this study, you will continue to see your transplant doctor on a regular basis. The study visits will occur as part of your/your child’s transplant appointments. You will have an entry visit and then visits at 100 days (3 months), 26 weeks (6 months), 52 weeks (12 months) and every 6 months until 5 years after the transplant (up to 11 visits), while you/your child are taking your HIV (antiretroviral) medications. If you or your physician(s) choose to stop your antiretroviral therapy, you/your child will have an additional five visits for one year and then will be seen every 26 weeks to determine whether you/your child have any remaining HIV in your bloodstream. You/your child will also be asked to come in for a final visit if you decide to leave the study early.

Your/your child’s HIV medications are not provided by this study. When you/your child come for these visits, we will ask your doctor to share information about your health and the results of any other examinations and tests that are being done as part of your healthcare. In addition, we will collect extra blood samples, about 1-6 tablespoons (20-86ml), if possible. We will do special tests on these samples to see if there are changes in your/your child’s HIV and your immune system after you receive the transplant. From these tests we will:

- Look to see whether the HIV virus in your blood before and after transplant is the kind that should not infect the CCR5Δ32 cells
- Perform special research tests to look at the cells in your blood that help fight infection (immunology) and also some special tests to look at the HIV virus in your blood (virology)

**Release of Medical Information**

As part of the study, we will ask permission to make copies of your/your child’s transplant medical records from the CIBMTR to be used to complete the case report forms. This information will be shared with IMPAACT. If you decide not to share your/your child’s transplant medical records with the study, you/your child cannot be in this study.

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

I agree to allow my transplant medical records be shared with IMPAACT for use in this study.

__________ Yes ___________ No ___________ Date
Blood Samples
Some of your blood samples will be shipped to special laboratories for specialized tests.

Storage of Blood Samples
Some of your blood will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-1 related research.

Your/your child’s samples will be stored at a special testing laboratory. Only approved researchers will have access to them. People who work at the laboratory will also have access to your/your child’s samples to keep track of them. These people won’t have information that directly identifies you/your child. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your regular doctor with the results of studies done using your stored 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 medical care. If the researchers decide that the result of a certain study provides important information for your medical care, your 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.

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

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, HIV-1 related research studies.

_________ Yes  __________ No  __________ Date

Biopsies
Biopsy is the medical removal of some tissue or cells so that it can be examined by a pathologist to assess the presence or extent of disease. If you/your child receive a biopsy as part of your clinical care, the study team would like to obtain a sample of the biopsy to do special tests on. If you decide not to share your biopsy specimens with the study, you/your child can still participate in this study.

Please read the following statement carefully and then mark your initials in the appropriate space provided.
I agree to allow my biopsy samples to be collected for use in this research study and for future IMPAACT-approved, HIV-1-related research.

__________ Yes ____________ No ____________ Date

Autopsy Samples
Autopsy is a surgical procedure that consists of a thorough examination of a body to determine the cause and manner of death and to evaluate any disease or injury that may be present. If you/your child undergo an autopsy, the study team would like to collect some tissue specimens as part of the autopsy. If you decide not to share your autopsy specimens with the study, you/your child can still participate in this study.

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

I agree to allow my autopsy samples to be collected for use in this research study and for future IMPAACT-approved, HIV-1 related research.

__________ Yes ____________ No ____________ Date

OTHER INFORMATION
The information collected in this study may be used for other IMPAACT approved HIV-1 related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Up to 25 infants, children, adolescents and adults will take part in this study. Up to 5 participants will be enrolled in the post-transplant cohort.

HOW LONG WILL I BE IN THIS STUDY?
You/your child are enrolling in the study, and so will be in the study for approximately 5 years.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?
The study doctor may need to take you/your child off the study early, without your permission, if:

- You/your child are not able to attend the study visits as required by the study
- The study is cancelled by the National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), IMPAACT, or the site’s Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research participants.
WHAT ARE THE RISKS OF THE STUDY?
Blood samples will be obtained as part of your/your child’s routine healthcare. Blood draws are the only procedure being done as part of the study.

Blood Drawing Risks:
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur when a needle enters the body.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
You/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV-1 and require a cord blood transplant.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
Instead of being in this study you have the choice of not being in this study. Please talk to your doctor about this choice available to you. Your doctor will explain the risks and benefits of this choice.

WHAT ABOUT CONFIDENTIALITY?
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

People who may review your records include the Office of Human Research Protections (OHRP), the site IRB /EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors supporting the study, and their designees.

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

WHAT ARE THE COSTS TO ME?
There are no costs to you/your child for study visits or study procedures. All research related costs will be covered by the study.
WILL I RECEIVE ANY PAYMENT?
All study samples will be collected as part of standard of care blood draws or biopsy, and as such, no additional time is expected to be incurred because of this study. Therefore, you/your child will not receive any payment for participating in the study.

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

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose not to take part or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

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 rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB), Ethics Committee (EC) 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.

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<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<tr>
<td>Participant’s Mother (print)</td>
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<td>Participant’s Father (print)</td>
<td>Father’s Signature and Date</td>
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<td>Participant’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
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<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
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