SUMMARY OF CHANGES

A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells

Version 9.0

NCI Protocol #: AMC-097
Local Protocol #: AMC-097

NCI Version Date: 07FEB2022
Protocol Date: 07FEB2022

I. Recommendations from Approval with Recommendations Memorandum for Protocol Version 8.0 (dated 10SEP2021) from R. Little, dated 24SEP2020:

#	Section	Comments
1.	Appendix VII 2.5.4.1	What is being measured by ELISA for Monitoring for immune response to TRIM5α? **PI Response: This procedure was designed to be used if any immune response was being developed against the gene modified cells. We hypothesized that we would initially infer that an immune response toward the cells was occurring if the levels of in vivo gene marking decreased and eventually went to zero over time post-infusion. To date, none of the infused patients have displayed gene marking which would suggest an immune response toward the cells is occurring. Therefore, we have not needed to perform this assay**.
2.	Appendix VII 2.5.4.3, B.	Please expand on as to how the team plan to Monitor of changes in the HIV reservoir and viral diversity in PBMCs? **PI Response: As described in Section 2.5.4.3, B in order to characterize changes in the HIV reservoir and viral diversity blood samples will be collected at baseline, 2 and 10 weeks and then 6, 12- and 24-months post-transplant for HIV reservoir characterization. These studies will include quantitative PCR analysis of PBMC-associated HIV DNA, RNA (including unspliced and multiply spliced forms) and 2-LTR circles. In addition, single genome sequencing of HIV gp120 and HIV pol will be performed to understand sequence evolution following transplantation and detection of minority resistance variants. Single-copy HIV from plasma will also be determined at each of these time points. Samples will be sent to the Timothy Henrich Laboratory at University of California, San Francisco.**

II. Scientific and Substantive Changes:

#	Section	Description of Change
3.	Protocol Schema 2.4 5.1	The ART withdrawal period has been extended from 12 weeks to until at one of the ART resumption criteria are met. This will allow sufficient time for the viral load to spike and then decrease and provided more data for evaluating effects of the transformed cells.
4.	2.4 2.4.2 7.5 App – 1C Appendix-XI Appendix XII Appendix XIII	Monitoring before and during the ART withdrawal period has been updated to include required COVID-19 testing prior to ATI (and as needed) and weekly testing for CD4/CD8 counts, viral load, and clinical assessments (review of medical and medication history, height, weight, BSA, neurological exam, and toxicity assessment) to closely monitor for acute retroviral syndrome and opportunistic infections (OI). Clinical assessments may be performed remotely to minimize the study burden on participants. In addition, several appendices have been added including an ATI disclosure form for participants, ATI risk mitigation counseling forms, and PrEP information sheets for participants. The ATI disclosure form must be reviewed with participants prior to ATI. ATI risk mitigation counseling must be performed prior to-ATI and weekly during ATI, and may be performed remotely. PrEP information sheets should be given to participants as a resource prior to ATI.
5.	2.4.1 2.4.2 App – 1C	ART resumption criteria have been revised to expand on the clinical and viral load safety parameters. The viral load criterion has been revised to require ART to be reinstated if there are persistent increases in HIV viral load over a period of time rather than relying on an extremely high single value. Participants with an initial viral load greater than 400 copies/ml during weekly testing must be retested within 3 business days or as soon as possible. Clinical criteria have been expanded to require ART resumption in the event of non-infectious symptoms suggestive of severe acute retroviral syndrome for consistency with clinical care standards and other HIV cure-intent protocols.
6.	2.4.3 App – 1C	Post ART withdrawal monitoring has been added. Participants will have CD4/CD8+T cell counts, HIV viral load, and clinical assessments at 4, 8, and 24 weeks after restarting ART to ensure that viral load and CD4 counts remain at a safe level. If viral load is not below the level of quantification by Week 8, participants will be evaluated every four weeks until the viral load is confirmed to be less than the level of quantification. In addition, Plasma and PBMCs will be collected in four 10mL EDTA

#	Section	Description of Change
		tubes and cryopreserved at the time of ART resumption and at weeks 4, 8 and 24 after restarting ART.
7.	3.1.2.3	Inclusion criterion was added for HIV viral load requirements, which include options for patients with higher viral loads if it can be determined which antiretroviral regimen can suppress the virus, as this is more consistent with clinical practice.
8.	4.2.1	Dosing recommendations for BEAM and R-BEAM therapy have been eliminated to permit the use of biosimilars for rituximab, as sites are permitted to administer therapy per standard of care and their local institutional guidelines. In addition, rituximab biosimilars inclusion enables an alternative option in the event there is a supply shortage of rituximab at their institution.
9.	4.7	Criteria for withdrawing from the study was revised. "Progression of Lymphoma" was removed as a criterion and participants will instead be followed for correlative studies as outlined in Section 7.5.8.
10.	7.5.6 7.5.8.7 7.6.1.6 7.6.2.6 App – 1B App – 1D Appendix VII	The protocol has been updated to include optional bone marrow biopsy collections at 3 months, 12 months, and at study discontinuation for participants that do not have bone marrow involvement at baseline and that consent to optional studies. In addition, clarifications were added to distinguish requirements / purpose of required (restaging for those with bone marrow involvement) vs optional bone marrow biopsies (for research).
11.	7.5.8.2	The University of California San Francisco (UCSF) is conducting the SCOPE study which includes an optional GI biopsy at the same timepoints as this study. The SCOPE study is an observational, prospective study of HIV-1 infected volunteers designed to provide a specimen bank of samples with carefully characterized clinical data. Specimens banked as part of the SCOPE study will be used to examine questions involving virologic, immunologic, and host factors involved in HIV-1 infection, progression, non-progression, response to treatment, control of HIV-1 virus, and evolution of drug resistance. Participants that agree to enroll into both the SCOPE study and AMC-097 at the same time (co-enroll) and agree to optional tissue collections will have their biopsy results shared for both studies to reduce the number of biopsies performed and facilitate enrollment to these optional studies.

#	Section	Description of Change
12.	7.7 App – 1B	Follow-up requirements have been revised to remove UC Davis as the responsible party for contacting participants and/or their providers during study required follow-up. Each site will contact the participants they enrolled.
13.	App – 1B App – 1D 4.6 7.7	Added optional blood sample collections every 12 months for years 3-15 for HIV viral load, and DNA and immunologic correlative studies to monitor participant's HIV and vector parameters in the body.

III. Administrative and Editorial Changes:

#	Section	Description of Change
14.	Global	The protocol version was changed from 8.0 to 9.0 and the date from 10SEP2020 to 07FEB2022.
15.	Global	Editorial and administrative changes were applied to spelling, grammar, punctuation, and table/figure numbering.
16.	Global	Replaced "subject" with "participant" throughout.
17.	Protocol Synopsis 1.3.2.5 1.3.2.6 2.3 9.1	The definition of ANC and Platelet engraftment has been clarified to include the underscore line with the greater than symbol. The ">" (greater than) is changed to '>/=' (greater than or equal) to be consistent with other sections of the protocol which state 'absolute neutrophil count of **at least** 500 cells/mm^3 and platelet count of **at least** 20,000 cells/mm^3
18.	2.4.1 2.4.2 2.4.3	Subsections for ART resumption criteria, ART monitoring, and post-ART monitoring have been added for clarity.
19.	3.5 Appendix VII	Corrected the EDC participant ID obtained after registration from nine digit to eleven digits.
20.	5.1	Removed definition of CD4+T cells for brevity.

#	Section	Description of Change
21.	7.4.2	Updated conditioning therapy to include R-BEAM as an option for consistency with Section 4.2.1.
22.	Appendix I-App – 1D	Sample collections for CCR5-Tropism were added for consistency with the screening evaluations in Section 7.1. Collections for immunology studies were updated to indicate specimens are to be collected in four 10mL EDTA tubes and one 5 mL redtop tube at 3, 6, and 12 months post-transplant and treatment discontinuation for consistency with Appendix VII. In addition, footnotes were added for GI biopsy collections to reflect that an specimen collections are optional and that GI biopsies may be delayed until the participant's CD4 count has reached 300 cells/mm3 and the biopsy repeated 2 months after the first collection for consistency with Section 7.5.8.2 and Appendix I.
23.	Appendix VI	AMC Data and Safety Monitoring Plan was updated to version 9.0. Key revisions include revision to state that the IRB review plan is identified in the protocol, and will continue to reference situations that apply for both domestic and international trials, as the AMC is preparing to open international trials where the requirements for US IRB review and international IRB review will be specific to the region.

AMC PROTOCOL #097:

A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT02797470
Investigational Agent:	Autologous CD34+ cells transduced with a pre-selective marker and triple combination of anti-HIV genes (NSC 784725)
IND #:	16129 Sponsor-Investigator: Mehrdad Abedi, MD
Protocol Chair:	Mehrdad Abedi, MD
Protocol Co-Chair:	Joseph Anderson, PhD Ariela Noy, MD

Version 9.0, 07FEB2022

NCI Version Date 07FEB2022

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol # 097 – A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells (Version 9.0, 07FEB2022),** as written according to AMC, NCI, International Conference on Harmonization guideline for Good Clinical Practice E6, the Declaration of Helsinki, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DDMMMYYYY)

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LIST OF TABLES AND FIGURES

PROTOCOL ROSTER

AMC Protocol # 097
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PROTOCOL SYNOPSIS

Title: A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells

Phase of Study: Phase I

Methodology Open label

Participating Institutions: This protocol will be open initially to UC Davis, UC San Diego, and UC San Francisco Medical Centers. Upon completion of the first cohorts additional AMC sites will be added dependent on the recruitment rate. A decision on any additional participating trial sites will be made after consultation with the AMC Hematologic Malignancy Working Group. Memorial Sloan Kettering Cancer Center was added as a site in AUG 2019.

Accrual Target: This study will enroll a minimum of 2 participants and a maximum of 18 participants.

Population: Male or female participants greater than 18 years of age, with HIV-1 related lymphomas that are refractory/resistant to first line of therapy or relapse after achieving a remission and are eligible for an autologous HSCT as a part of their routine therapy are eligible for this study. Participants must be on a multi-drug anti-HIV regimen (excluding zidovudine [AZT, ZDV, Retrovir®, or agents containing zidovudine (e.g., Combivir® and Trizivir®)] and efavirenz [EFV, Sustiva®, or agents containing efazirenz (e.g., Atripla®)]) and have an HIV-1 viral load < 50 copies/mL by RT-PCR at the time of study enrollment.

Regimen: For the first 2 cohorts, both transduced (autologous CD34+ cells transduced with a pre-selective marker and a triple combination of anti-HIV genes) and un-manipulated product will be infused within 4 to 24 hours of each other. After DSMB approval, only transduced product will be administered to the rest of the participants. In case of non-engraftment, the back-up product stored at the respective site will be infused. The number of cells infused to each participant depends on the cohort in which the participant is enrolled. The number of cells in the transduced products is based on CD34 counts after transduction of the stem cells and before freezing.

Study Cohorts	Ratio of Transduced vs Un-transduced Stem Cells	Minimum Number of Transduced/Un-transduced Cells Acceptable. CD34 cells/kg	Range for Number of Transduced Cells/Unmanipulated. CD34 cells/kg
1	1:1	1×10^6:1×10^6	1 to 5 X 10^6: 1 to 5 X 10^6
2	5:1	2×10^6:1×10^6	2 to 5 X 10^6:1×10^6

3	1:0	2 X 10^6: 0	2 to 10 X 10^6: 0
3+	1:0	3.0 X 10^6: 0	3.0 to 10 X 10^6: 0

Duration: The initial follow-up period for this clinical trial will be two years; however, all participants will be followed for 15 years for safety, as mandated by FDA for all gene therapy study participants.

Primary Objective: To evaluate the clinical safety of our approach using our development candidate (i.e., anti-HIV gene modified hematopoietic stem cells). See Section 1.2 for endpoint definitions.

Secondary Objectives: To evaluate immune reconstitution with HIV-1 resistant immune cells, viral load and HIV-1 status, integration sites of vector sequences in circulating cells, presence of any *in vivo* clonal expansion of transduced cells, and any immune reaction to transduced cells.

Major Secondary Objectives

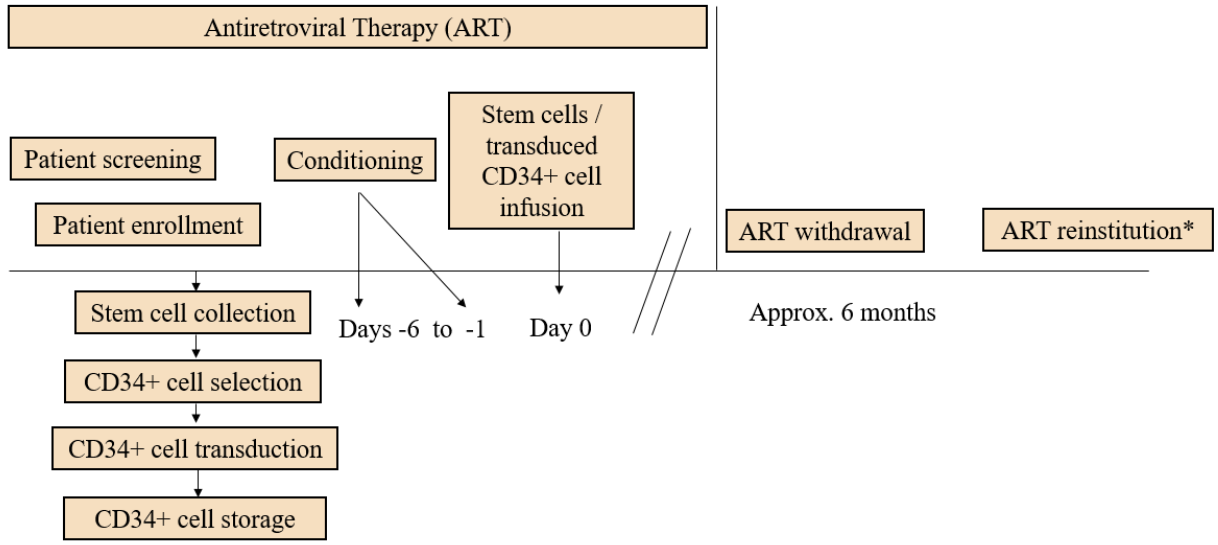
- To determine the efficacy of our approach using our development candidate.
- To determine the presence, quantity, and duration of gene modified HIV-1 resistant peripheral blood cells and gut mucosal immune cells.
- To study the integration sites of vector sequences in circulating cells.

Minor Secondary Objectives

- To study progression-free survival.
- To study overall survival.
- To study complete response rate and duration.
- To study partial response rate and duration.
- To study time to neutrophil engraftment (first measurement of 3 consecutive laboratory values obtained on different days) of ANC > /= 500 cells/mm^3.
- To study time to platelet engraftment (first measurement of 3 consecutive laboratory values obtained on different days) of platelets > /= 20,000 cells/mm^3 without platelet transfusions 7 days prior).
- To study hematologic function at Day 100 (ANC > 1500, Hb > 10g/dl without transfusion and platelets > 100,000)
- To study CD4 recovery at the conclusion of the trial.
- To study safety in terms of toxicities, infections, transfusions, and infusion-related reactions.
- To study HIV-1 viral load over time.

	• To study persistence of vector-transduced cells over time.
Exploratory Objectives:	To explore the role of anti-retroviral therapy (ART) interruption on expansion of HIV-1 resistant HIV-1 target cells, including immune cells, both in the peripheral blood and the gut mucosa.
Statistical Methodology	Three participants will be enrolled in each cohort with potential expansion of the cohort to 6 with the maximum of 18 participants. The primary endpoint of the study is safety. Safety is defined as timely engraftment (the collective establishment of a persistent absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 20,000 cells/mm^3 for 3 consecutive measurements of laboratory values obtained on different days) within one month post-transplant, in the absence of any study candidate-specific grade 3 and 4 non-hematopoietic organ toxicity, excluding alopecia, or any clonal expansion.

PROTOCOL SCHEMA



*ART reinstitution will occur if / when participants satisfy one of the ART resumption criteria in section 2.4.1.

LIST OF ABBREVIATIONS

ACSR ..... AIDS and Cancer Specimen Resource
AdvantageEDC[SM] ..... AMC internet data entry system
AE ..... adverse event
AIDS ..... acquired immunodeficiency syndrome
AMC ..... AIDS Malignancy Consortium
AML ..... acute myelocytic leukemia
ANC ..... absolute neutrophil count
ART ..... antiretroviral therapy
ATI ..... analytic treatment interruption
AZT ..... zidovudine
BCNU ..... carmustine
BEAM ..... carmustine, etoposide, cytarabine, and melphalan
R-BEAM ..... rituximab, carmustine, etoposide, cytarabine, and melphalan
BID ..... bis in die (twice daily)
BSA ..... body surface area
BMT ..... bone marrow transplant
CBC ..... complete blood count
CCR5 ..... c-c chemokine receptor type 5
CDUS ..... Clinical Data Update System
CEF ..... CMV-EBV-influenza virus
CFR ..... Code of Federal Regulations
CFSE ..... carboxyfluorescein succinimidyl ester
CFU ..... colony forming unit
CI ..... confidence interval
cm ..... centimeter
CMP ..... comprehensive metabolic panel
CMV ..... cytomegalovirus
CNS ..... central nervous system
COA ..... certificate of analysis
CR ..... complete response
CRF ..... case report form
CT ..... computed tomography scan
CTA ..... clinical trial agreement
CTCAE ..... Common Terminology Criteria for Adverse Event Reporting
CTEP ..... Cancer Therapy Evaluation Program
CTEP-AERS ..... CTEP Adverse Event Reporting System
CTL ..... cytotoxic T lymphocyte
CTMS ..... Clinical Trials Monitoring Service

CXCR4 ..... chemokine receptor type 4
CXR ..... chest X-ray
DARF ..... drug accountability record form
DC ..... dendritic cells
DHHS ..... Department of Health and Human Services
DLCO ..... diffusing capacity of the lung for carbon monoxide
DLT ..... dose-limiting toxicity
DMSO ..... dimethyl sulfoxide
DNA ..... deoxyribonucleic acid
DSMB ..... data and safety monitoring board
EBMT ..... European bone marrow transplant
EBV ..... Epstein-Barr Virus
ECOG ..... Eastern Cooperative Oncology Group
EDTA ..... ethylenediaminetetraacetic acid
EFV ..... efavirenz
EGFP ..... enhanced green fluorescent protein
ELISA ..... enzyme linked immunosorbent assay
EU/mL ..... endotoxin units per milliliter
FACS ..... fluorescence activated cell sorting
FACT ..... Foundation for the Accreditation of Cellular Therapy
FBS ..... fetal bovine serum
FDA ..... Food and Drug Administration
FDG-PET ..... fluorodeoxyglucose-positron emission tomography
FEV-1 ..... forced expiratory volume
ft ..... flow through
FVC ..... forced vital capacity
g/dl ..... grams per deciliter
GALT ..... gut associated lymphoid tissue
GAPDH glyceraldehyde-6-phosphate
GCP ..... good clinical practice
GI ..... gastrointestinal
GMP ..... good manufacturing practice
HAV ..... hepatitis A
Hb ..... hemoglobin
HIV ..... human immunodeficiency virus
HCT ..... hematopoietic cell transplant
HIPAA ..... Health Insurance Portability and Accountability Act
HLA ..... human leukocyte antigen
HPC ..... hematopoietic progenitor cells
HSC ..... hematopoietic stem cells

HSCT ..... hematopoietic stem cell transplantation
HSV ..... herpes simplex virus
HTLV ..... human T cell lymphotropic virus
ICH ..... International Conference on Harmonization
IDB ..... Investigational Drug Branch
IFN ..... interferon
IHC ..... immunohistochemistry
IL ..... interleukin
IND ..... investigational new drug application
INR ..... international normalized ratio
IPI ..... International Prognostic Index
IRB ..... institutional review board
kg ..... kilogram
LAL ..... limulus amebocyte lysate
LN ..... liquid nitrogen
LAM-PCR ..... linear amplification-mediated PCR
LDH ..... lactate dehydrogenase
LTR ..... long terminal repeat
LVEF ..... left ventricular ejection fraction
MCP ..... monocyte chemotactic proteins
mg ..... milligram
MIP ..... macrophage inflammatory protein
µL ..... microliter
MDS ..... myelodysplastic syndrome
mL ..... milliliter
mm^3 ..... cubic millimeter
MOI ..... multiplicity of infections
MOP ..... manual of procedures
mRNA ..... messenger ribose nucleic acid
MUGA ..... multiple gated acquisition scan
NCI ..... National Cancer Institute
NCT ..... National Clinical Trials [Registry]
ng ..... nanogram
NIH ..... National Institutes of Health
NHL ..... Non-Hodgkin Lymphoma
NK cells ..... natural killer cells
NRG mouse ..... NOD-Rag1null IL2rgnull, NOD rag gamma mouse
NSC ..... National Service Center
NT ..... non-transduced cells
ODMC ..... Operations and Data Management Center

OHAM ..... Office of HIV and AIDS Malignancy
OI ..... opportunistic infections
OS ..... overall survival
PB ..... peripheral blood
PBMC ..... peripheral blood mononuclear cells
PCP ..... *Pneumocystis carinii* pneumonia
PCR ..... polymerase chain reaction
PDL ..... poly-d-lysine
PET ..... positron emission tomography
PFS ..... progression-free survival
PFT ..... pulmonary function test
PHI ..... protected health information
PI ..... principal investigator
PIO ..... Protocol Information Office
PT ..... prothrombin time
PTT ..... partial thromboplastin time
QC ..... quality control
QA ..... quality assurance
qPCR ..... quantitative polymerase chain reaction
RAC ..... Recombinant DNA Advisory Committee
RCL ..... replication competent lentivirus
RNA ..... ribose nucleic acid
RPR ..... rapid plasma reagin
RT-PCR ..... reverse transcription polymerase chain reaction
SAE ..... serious adverse event
SOC ..... system organ class
SD ..... standard deviation
SEB ..... staphylococcal enterotoxin-B
SGOT ..... serum glutamic oxaloacetic transaminase
SGPT ..... serum glutamic-pyruvic transaminase
SMART ..... Strategies for Management of Antiretroviral Therapy
SOP ..... standard operating procedure
shRNA ..... short hairpin ribose nucleic acid
STI ..... structured (or strategic) treatment interruption
TAR ..... tat activation response region
TAX (1TAX) ..... transactivating protein
Tat ..... trans-activator of transcription
TNFα ..... tumor necrosis factor-alpha
TRIM5α ..... tripartite motif containing protein 5 alpha
TTR ..... time to tumor response

Treg ..... regulatory T cells
VDRL ..... Venereal Disease Research Laboratory
VZV ..... varicella zoster virus
ULN ..... upper limit of normal
USP ..... United States Pharmacopeia
ZDV ..... zidovudine

1.0 OBJECTIVES

1.1 Hypothesis

Our hypothesis states that anti-HIV gene expressing stem cells can safely reconstitute the hematopoietic system of the recipient and can produce a pool of mature myeloid and lymphoid cells that harbor anti-HIV genes capable of resisting HIV-1. As a secondary objective, we will interrogate two physical compartments of immune system, (i.e., peripheral blood cells and gut mucosa) for the presence, quantity, and duration of gene modified HIV-1-resistant immune cells. In addition, we will determine the integration sites of vector sequences in circulating cells and monitor for any clonal expansion of hematopoietic cells.

We also hypothesize that transduced HIV-resistant immune cells will have a selective survival advantage as compared to non-transduced cells in the face of a viral load, as demonstrated by our preclinical *in vivo* experiments, and suggested by previous clinical trials using comparable stem cell gene therapy approaches. As an exploratory endpoint, we therefore want to test the efficacy of our stem cell gene therapy for HIV-1 in the context of structured HIV-1 treatment interruptions.

1.2 Primary Objective

The primary endpoint of the study is safety, defined as timely engraftment (the collective establishment of a persistent absolute neutrophil count of at least 500 cells/mm^3 and platelet count of 20,000 cells/mm^3 without transfusion for 3 consecutive measurements of laboratory values obtained on different days) by one month post-transplant, in the absence of any grade 3 and 4 non-hematopoietic organ toxicity that can be attributed (possibly, probably, or definitely) to lentiviral transduced stem cell transplant, excluding alopecia, or any clonal expansion and excluding expected toxicities that are associated with the pre-transplant conditioning regimen (see Appendix X for full list).

1.3 Secondary Objectives

1.3.1 Major secondary objectives

1.3.1.1 To determine efficacy of the candidate product, defined as establishment of > 5% mononuclear blood cells expressing anti-HIV genes in the peripheral blood at 3 months post-transplant.

1.3.1.2. To determine the presence, quantity, and duration of gene modified HIV-1 resistant peripheral blood cells and gut mucosal immune cells.

1.3.1.3 To study the integration sites of vector sequences in circulating cells.

1.3.2 Minor secondary objectives

1.3.2.1 To study progression-free survival.

1.3.2.2 To study overall survival.

1.3.2.3 To study complete response rate and duration.

1.3.2.4 To study partial response rate and duration.

1.3.2.5 To study time to neutrophil engraftment (first measurement of 3 consecutive laboratory values on different days) of ANC >/= 500 cells/mm^3).

1.3.2.6 To study time to platelet engraftment (first measurement of 3 consecutive measurements laboratory values obtained on different days) of platelets > /=20,000 cells/mm^3 without platelet transfusions 7 days prior).

1.3.2.7 To study hematologic function at Day 100 (ANC > 1500, Hb > 10g/dl without transfusion and platelets > 100,000)

1.3.2.8 To study CD4 recovery at the conclusion of the trial.

1.3.2.9 To study safety in terms of toxicities, infections, transfusions, and infusion-related reactions.

1.3.2.10 To study HIV-1 viral load over time.

1.3.2.11 To study persistence of vector-transduced cells over time.

1.4 Exploratory Objectives

1.4.1 To evaluate the presence and the magnitude of expansion of HIV-1 resistant immune cells in the peripheral blood and gut mucosa of transplanted participants, subsequent to withholding ART.

2.0 BACKGROUND

2.1 Study Disease

HIV-1/AIDS continues to be a major public health problem worldwide. Based on recent estimations, there are approximately 33.3 million people living with HIV-1/AIDS with 2.6 million new HIV-1 infections per year, and 1.8 million annual deaths due to AIDS. It is estimated that more than one million people are living with HIV-1 in the USA and that more than half a million have died after developing AIDS. Despite the advances in anti-retroviral therapy (ART), eradication of HIV-1 from infected patients is still an elusive goal. Lifelong therapy is associated with potential long-term toxicity, adherence problems, and development of drug resistance (1-6). Interruption of ART therapy at any stage will result in a rebound in HIV-1 replication and rapid deterioration of a patient's immune system. Even new drug classes such as integrase inhibitors and CCR5 antagonists, despite their promise, have failed to eradicate HIV-1 (5-6, 9-10). Patients who are successfully treated with ART often do not achieve full recovery of immune responses, may develop HIV-1-related cancers, and exhibit increased levels of immune activation (7-8). Such a chronic inflammatory status can result in immune exhaustion (and subsequent infections) and may precipitate multiple clinical complications such as cardiovascular and cerebrovascular disease, diabetes, chronic kidney disease, osteoporosis, and cancer, and collectively, accelerated aging. While the cause of this chronic inflammatory status is not completely clear, evidence suggests the role of innate immunity, ART interruption, non-compliance, effect of HIV-1 on endothelial cells, interruptions in the coagulation system, incomplete immune recovery, microbial translocation, co-infections, residual viremia, etc.

2.1.1 Gene therapy for HIV-1 patients with lymphoma

Therefore, the idea of a cell-based gene therapy approach to cure HIV-1 would be especially compelling (11). Gene therapy has the potential to not only control viral replication and prevent CD4+ T cell depletion, but also provide a pool of immune cells with sustained intrinsic protection. HIV-1 gene therapy is not a new idea, and currently, gene therapy clinical trials are ongoing (12-14). However, there are major differences in the types of genes utilized as well as the cells targeted, which may be either peripheral blood T cells or hematopoietic stem cells (HSC).

Gene therapy targets can be classified according to the same concept as applied to other anti-HIV-1 therapeutic strategies: Class I therapeutics inhibit HIV-1 entry and replication; Class II therapeutics inhibit viral regulatory and structural protein expression; and Class III therapeutics inhibit viral assembly and release. Most of the current anti-HIV gene therapy approaches (including our proposed protocol) focus on Class II and especially Class I gene targets that have been shown to perform as best available antivirals by far. Recently, a similar comparison has resulted in a similar conclusion in *in vivo* studies (15).

While T cells are easy to obtain, their long-term engraftment is limited despite current lympho-depletion approaches. In addition, questions have recently been raised on the expansion of T cells in response to a high viral load (16-17). Furthermore, T cell gene therapy, despite its relative ease, cannot alleviate the main concerns about HIV-1 therapy such as the presence of low-level viral replication caused by dormant HIV-1 reservoirs. Therefore, the benefits of current T cell gene

therapy protocols with the need for multiple, life long, continued cell infusions will not exceed the advantages of current ART therapy. Targeting human stem cells, as described here, on the other hand, can address many of these concerns. Such a stem cell therapy would require only a single treatment that would replace, in the long run; the reservoirs of active and latent HIV-1 with anti-HIV gene modified cells resistant to infection, thus alleviating the need for long-term ART and would ultimately cure these patients. In addition, unlike challenges in *in vivo* expansions of gene therapy modified T cells (as described above), anti-HIV gene modified stem cell derived HIV-1 target cells have shown that they do respond to an HIV-1 viral load with significant expansion of T cells (15,18). The best evidence supporting the feasibility of this comes from a case report of an HIV-1 patient transplanted with stem cells from a host homozygous for the CCR5 delta-32 mutation. The transplant resulted in reduction of HIV-1 viral load over time and the replacement of microglial and Kupffer cells, common reservoirs of latent HIV-1, by donor-derived HIV-1 resistant cells (18). This strongly suggests that the patient is now cured of HIV-1. Previous trials of HIV-1 gene therapy into HSCs have been plagued by low transduction efficiencies and loss/silencing of the anti-HIV genes over time (14, 18). Furthermore, single anti-HIV genes harbor the risk of developing resistant HIV-1 mutants (12). Finally, in some of these trials, the use of retroviral vectors (versus lentiviral vectors in our proposal) increases the risk of oncogenesis (13). Lessons learned from two recent computational models of HIV-1 replication and development of resistance to gene therapy regimens support our notion that the combinatorial anti-HIV gene therapy protocols and higher numbers of anti-HIV gene modified immune cells are critical factors in the success of gene therapy protocols for HIV-1 (19-20). Furthermore, they showed that when 1-2 anti-HIV targets are used, the success will be significantly dependent on the potency of the approach, while multiple combinatorial gene therapy approaches can eliminate such a requirement.

2.1.2 Bone marrow transplant for HIV-1 related lymphomas

The prognosis for patients with refractory and relapsed non-Hodgkin's lymphoma (NHL) is poor with overall survival rates of less than 20% for patients treated with non-transplant salvage therapies. Based on these randomized trials, high-dose therapy with hematopoietic stem cell transplantation (HSCT) has been established as the standard of care for patients with relapsed but chemotherapy-sensitive NHL (21-23).

This initial transplant experience was marked by what appeared to be an increased risk of opportunistic infection (OI). Since the availability of ART, however, the transplant experience has evolved considerably, and several groups have now demonstrated the feasibility of such an approach.

In a trial published by City of Hope, patients with induction-failure NHL, chemotherapy-sensitive disease, and International Prognostic Index (IPI) high-risk disease were eligible for treatment. Twenty participants were enrolled in the trial. All of the participants successfully achieved adequate autologous stem cell collections. Participants were treated with either high-dose chemotherapy or intensive chemo-radiotherapy. At a median follow-up of 31.8 months, 17 of 20

participants were alive and free of evidence of disease. Treatment-related complications were comparable to those seen in the non-HIV-1 infected patient population (24).

In a similar trial by the AIDS Malignancy Consortium (AMC), 27 participants with either HIV-1-related NHL or Hodgkin's lymphoma were enrolled and 20 of them subsequently underwent autologous hematopoietic cell transplantation (HCT) with a dose-reduced busulfan and cyclophosphamide regimen. At a median follow-up time of 23 weeks, 10 participants were alive and free of disease (25). In a recent trial by the AMC, 43 participants with HIV-1 CCSR aggressive NHL or Hodgkin's lymphoma were enrolled and 40 underwent autologous HCT using BEAM regimen (35). In this trial, 39 participants were alive 100 days post-HCT and 36 of the 39 of these participants were free of disease; and 24 of 32 participants achieved recovery of hematological function by 24 months post-HCT. Other groups have also demonstrated the feasibility of performing autologous HCT in this patient population (26-28).

More recently, the European Bone Marrow Transplant (EBMT) Lymphoma Working Party, in a much bigger trial, published treatment outcomes for 68 participants with HIV-1-related lymphoma (including 18 participants with Hodgkin lymphoma) that underwent autologous HCT at 20 different institutions. Sixty-five participants were treated with the carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen and the remainder were treated with radiation therapy-based regimens. At a median follow-up of 32 months, the 3-year estimated progression-free and overall survivals for the group were 56% and 61% respectively, with low overall cumulative incidence of non-relapse mortality of 4.4% and 7.5% at three and 12 months respectively. Relapse or progression was identified in 20 participants after a median time of 4.1 months from autologous HCT with the predicted cumulative incidence of relapse of 30% at 24 months (29).

A subsequent EBMT study for patients with Hodgkin's disease and non-Hodgkin's lymphoma used a comparison matched control design stratified by HIV-1 status. The results of this comparative study revealed that HIV-1 patients undergoing autologous HCT for lymphoma showed similar relapse rates, progression free survival, and overall survival (30).

Based on these data, the practice of autologous HSCT is routinely used in many centers in the country as part of the treatment of relapsed/refractory (but still chemo-sensitive) NHLs.

2.2 Study Agent: Autologous CD34+ Cells Transduced with a Pre-Selective Marker and a Triple Combination of Anti-HIV Genes

Our proposed novel anti-HIV therapeutic candidate combines multiple anti-HIV genes into a single lentiviral vector that is designed to block HIV-1 infection at different stages of the HIV-1 life cycle (entry, uncoating, and viral transcription). This vector also contains a pre-selective molecule, which marks transduced cells and allows for the purification/enrichment of the transduced population away from untransduced cells. This approach not only provides strong pre-integration inhibition of HIV-1 infection, but also decreases the generation of viral escape mutants. The major anti-HIV components of our

vector are a CCR5 shRNA, a chimeric TRIM5α, and a TAR decoy. Due to the natural HIV-1-resistant phenotype conferred by the delta-32 bp CCR5 mutation found in a small percent of humans, CCR5 knockdown utilizing shRNAs is an excellent approach for HIV-1 gene therapy. However, utilizing only a single CCR5 shRNA will not afford protection against CXCR4 or other tropisms of HIV-1. Therefore, we have incorporated two other highly potent anti-HIV genes into our lentiviral vector, which protect against all tropisms of HIV-1. The second molecule, a human/rhesus macaque chimeric TRIM5α molecule, acts at the post-entry/pre-integration stage of the HIV-1 life cycle. Old world monkey TRIM5α isoforms, which include the rhesus macaque isoform, are strong inhibitors of HIV-1 infection, however, human TRIM5α does not inhibit HIV-1. Therefore, we have utilized a chimeric isoform of human TRIM5α where we have incorporated the critical amino acids of the rhesus macaque isoform necessary to inhibit HIV-1 infection. This chimeric human TRIM5α now only contains 13 amino acids from the rhesus macaque isoform; however, it is now able to potently inhibit HIV-1 infection. The third molecule, a TAR decoy, acts at the pre-transcription stage of the HIV-1 life cycle and scavenges the HIV-1 Tat protein away from its normal function in HIV-1 proviral transcription. This removal of Tat from the transcriptional complex disrupts HIV-1 proviral transcription and does not allow new viral mRNA, and therefore, new virus particles to form. The pre-selective molecule, a truncated and mutated form of human CD25, is used to mark the cell surface of transduced cells, so they can be purified away from untransduced cells with CD25 immunomagnetic separation. This modified human CD25 molecule has been fully truncated of its intracellular amino acids to avoid any possible intracellular signaling. Two-point mutations have also been made to inhibit any IL2 binding, and also to inhibit the incorporation of this molecule into the mature IL2 receptor complex.

The three anti-HIV molecules expressed together in a single lentiviral vector have demonstrated complete protection from productive HIV-1 infection and prevented integration of multiple strains of HIV-1-1 (including macrophage and T cell tropic HIV-1 strains) in both transduced cultured cells and transduced CD34+ HSCs derived into macrophages *in vitro* (17). *In vivo* safety and efficacy studies in a humanized mouse model for HIV-1 showed excellent results including maintenance of normal total human CD4+ cell levels with a pre-integration block of HIV-1 infection (18). Our preclinical *in-vitro* and *in-vivo* safety and efficacy data are mature enough to start the regulatory approval process for a stem cell gene therapy clinical trial. The successful development of a multi-gene pre-selective anti-HIV vector, excellent safety and efficacy results in both *in vitro* and *in vivo* testing of the vector transduced cells even for resistant strains of HIV-1, production of high titer GMP-grade lentiviral vector, and superior transduction efficiencies into HSCs are highlights of our proposed therapeutic candidate, which make it unique and more promising than other currently available gene therapy for HIV-1 approaches.

Extensive preclinical data supporting this study is included in our IND document and the investigator's brochure.

2.3 Study Design and Rationale

This is an open-label, single-arm, multi institution, Phase I study of maximum of 18 participants. The study is designed to fulfill the mission of a Phase I study as "a trial to study the safety, and determine the dose limiting toxicity (DLT) to a new treatment." All participants will be treated with anti-HIV gene transduced CD34+ cells.

Table 2-A: Study Cohorts

Study Cohorts	Ratio of Transduced versus Untransduced Stem Cells
1	1:1
2	5:1
3	1:0
3+*	1:0 but with a higher transduced cell count only in case of DLT due to insufficient engraftment in cohort 3

*. See section 2.3.1

Three participants will be treated at each cohort level, with the option of 3-6 additional participants in the highest dose level cohort. Participants will be recruited to the groups in order that they were screened. Participants will be monitored on a weekly basis for the first 4 weeks and then every other week thereafter. A cohort will be expanded from 3 to 6 participants if at least one participant in the cohort experiences engraftment failure or grade 3 or 4 non-hematopoietic toxicity, excluding alopecia. The enrollment of the participants within the cohorts will be staggered so each participant needs to show at least early signs of engraftment for neutrophils (ANC) >/= 500 cells/mm^3 and platelets >/= 20,000 cells/mm^3 before the next participant is enrolled. The enrollment of participants between the cohorts will be staggered, so every participant in the same cohort needs to have at least 30 days of follow up from the time of stem cell transplant for the AMC Data and Safety Monitoring Board (DSMB) to review the side effects and before we can proceed to the next cohort.

Achievement of high levels of engraftment with anti-HIV genes will be needed to secure a reasonable anti-HIV response. Therefore, in the third cohort, the participants will receive only the transduced product. The un-manipulated portion of product will remain frozen as a backup. In this cohort, the backup product will only be given to the participant if delayed engraftment occurs, especially in the setting of ongoing complications such as bleeding or infection.

For safety reasons and based on FDA request, participants enrolled in the first cohort of the study will receive both transduced and un-transduced product at equal number. This is to prevent a prolonged cytopenia in case the transduced cells fail to engraft and recover the peripheral blood in a timely manner. In the second cohort, once the safety of the product is established, we will increase the ratio of the transduced cells to untransduced cells, with the goal to give 5 times (or higher) more transduced cells.

Participants with relapsed/refractory HIV-1 related lymphoma in need of autologous bone marrow transplantation will be enrolled. Upon documentation of disease response, their peripheral stem cells will be collected using standard mobilization approaches. Because of the unpredictability of the number of cells collected for each patient and the significant

variability of the number of cells obtained after transduction and selection process, a set of criteria has been created to explain the minimum and the range of cells infused to each patient (Table 4-A).

- A target cell number of 10 x 10^6 CD34+ cells/kg will be collected, with a minimum of 5 x 10^6 CD34+ cells/kg only if we cannot collect enough cells after multiple attempts.
- A minimum of 1.5 x 10^6 of unmanipulated CD34+ HSC/kg will be collected upfront and will be frozen in a minimum of 3 cryo bags and stored at each institution's local stem / progenitor cell facility per site SOPs. Even though the minimum amount of unmanipulated cells infused in the first two cohorts are 1.0 x 10^6 CD34+ cells/kg, additional 0.5 x 10^6 CD34+ cells/kg of recipient weight will be collected to ensure a safe transplant in the unlikely situation that the transduced product is not usable.
- The minimum total number of CD34+ cells (manipulated + unmanipulated) infused to the patient is 2 x 10^6 CD34+ cells/kg of recipient weight independent of the cohort to assure the safety of transplant.
- In cohorts 1 and 2, a minimum of 1 x 10^6 of unmanipulated CD34+ HSC/kg will be infused, and the rest of the cells will be stored as back-up. Additional CD34 cells from the transduced product given based on each cohort is expected. In cohort 3, all of the untransduced cells will be stored and used only in the case of delayed engraftment.
- Additional cells can be collected and stored after the target number for CD34 (10 x 10^6 CD34+ cells/kg) is achieved based on the discretion of participant's transplant physician in consultation with the study principal investigator. These cells can be given to the patient, but the ratio of total manipulated to unmanipulated cells needs to follow the guidelines in Table 4-A.
- In case of any failure in the transduction process, all of the unmanipulated cells will be infused to the patient.

Apheresis product, from the first day of collection, will be split into two parts: One part (1.5 x 10^6 of CD34+ HSC/kg) will be cryopreserved (unmanipulated), and the second part, if additional cells are available, will be sent immediately to the GMP facility for gene transduction. We expect that we will need several days of collection for each participant. Once 1.5 x 10^6 CD34+ cells/kg is collected, then no more products will be divided for back up, and for the rest of the collections, the entire product from subsequent collections will be used for gene transduction. After transduction, this product will be frozen. Release tests will be performed on aliquots (see Section 6.1.11).

2.3.1 Three+ (3+) expansion cohort (protocol version 8)

The ultimate goal of the study is to replace the full hematopoietic system of the recipient with a gene modified anti-HIV hematopoietic system. The design of this clinical trial is different from other dose escalating clinical trials as we are not testing an increasing dose of our product and therefore routine phase I, 3+3 design is not applicable in this trial. The purified manipulated cells may not have the same robust engrafting capabilities as unmanipulated HSCs and, therefore, if in the third cohort 2 patients develop DLT due to insufficient engraftment, an additional 3 patients will be treated with a higher dose of gene-modified CD34 cells (3.0 x10^6

CD34 cells/kg of recipient body weight) to assess whether a higher dose of cells will improve engraftment. Any additional engraftment issue on this expanded cohort deemed to be related to product will result in stopping of the trial.

2.4 ART Withdrawal / Analytic Treatment Interruption (ATI)

The presence of sizable untransduced CD34 cells in the infused product will result in a population of hematopoietic cells in the participant after transplant that will remain sensitive to HIV-1 and still can drive a significant viral load with its associated complications. In the City of Hope clinical trial, significant expansion of HIV-1 resistant hematopoietic clone was observed when the participant was off his ART. Based on the above rationale and supporting observation, we are proposing to withdraw ART after 6 months post-transplant and when the CD4 counts reaches ≥ 300 cells/mm^3.

At six months post-transplant, or later, ART will be voluntarily withheld for participants with a CD4 count of 300 or higher with no detectable viral load (by single copy PCR) until one or more of the criterion in Section 2.4.1 prompting resumption of treatment. We do understand that the time to achieve a T-cell count of 300 may take longer than six months for HIV-1 infected participants post-transplant. Therefore, for participants in which the CD4 T-cell count has not risen to ≥ 300 cells/mm^3 at the time of the planned ART interruption, ART will continue until the T-cell count has risen to ≥ 300 cells/mm^3.

In addition, **participants will be tested for the virus that causes COVID-19 prior to ART interruption** and if positive by PCR, will remain on ART until they recover, and the study team approves them to proceed with ATI. **Participants on ATI will be offered COVID testing if symptoms associated with COVID-19 develop** and will restart ART if they test positive by PCR.

The duration for ART withdrawal has been selected as it is an appropriate duration for assessment of any selective survival advantage of anti-HIV gene expressing immune cells, and as this is an accepted and safe duration for possible viremia rebound in previously ART controlled HIV-1 participants. Interruption of ART in previous clinical trials has led to a consistent re-emergence of viremia in approximately 2 weeks, with re-establishing a set point in 4-6 weeks (33). This approach has been proven to be safe for participants.

Designed as an exploratory endpoint in our study, this duration of treatment interruption will allow determining whether participants' viral loads return to their pre-ART set points. Multiple clinical trials testing therapeutic vaccination for HIV-1 as a strategy for modifying the role of ART for controlling HIV-1 disease have used a similar interruption (formerly known as Structured, or Strategic, Treatment Interruption (STI)) for 12 weeks due to its safety profile.

2.4.1 ART Resumption Criteria

Several safety parameters will be monitored and will be used to restart therapy earlier, if needed. These include:

1. CD 4+ T cell criteria: A decline of CD4+ count to less than 200 cells/mm^3 in 2 consecutive measurements laboratory values obtained on different days, 2 weeks apart, or more than 50% drop in absolute CD4 count.
2. Viral load criteria: ART will be initiated for any one of the following outcomes:

- viremia > 50,000 copies RNA/mL for four weeks
- viremia > 10,000 copies RNA/mL for 6 weeks
- viremia > 2000 copies RNA/ml for 12 weeks
- viremia > 400 copies/RNA for 24 weeks

Operationally, this will allow for an acute viremic state that will need to resolve within 12 weeks, with high-level viremia only being allowed for a brief period. After the spike, the viral load should fall as the numbers of susceptible target cells are deleted, leaving just the transformed cells. Post-treatment control (defined as viremia <400 copies RNA/mL) should be achieved prior to Week 24 post-virus rebound.

For any initial viral load greater than 400 copies/mL during weekly monitoring, participants must return within 3 business days for a repeat test.

3. Clinical criteria: ART will also be re-initiated for any symptoms suggestive of a severe acute retroviral syndrome, particularly signs of altered mental status or viral meningitis (severe headache, neck stiffness), but including unexplained rash, lymphadenopathy, fevers, and occurrence of additional opportunistic infection (OI). ART will also be re-initiated if a participant tests positive for COVID-19 by PCR.
4. If, in the opinion of the subject or the primary care physician, restart is desired for other reasons. It will be requested, but not required, to discuss this decision with the PI and research team beforehand, if feasible.

2.4.2 ART Withdrawal Monitoring

Participants will be closely monitored weekly when they are off ART, and treatment can be restarted at the discretion of the participant, their HIV-1 physician, or the site PI. All patients on ART withdrawal will receive anti-OI prophylactic antibiotics.

Despite a long history with the application of ATI for testing the therapeutic impact of candidate immunomodulatory treatment strategies, some studies have indicated that treatment interruptions, when devised with a medication sparing intent and without close clinical observation, may carry certain risks and are not always successful long-term (31). The host of published data on ATIs has recently been summarized in a Cochrane report (32). An important conclusion of this report is that ATIs continue to have applicability to the testing of new therapeutic concepts or drugs in well-characterized participant populations in the context of well-controlled clinical settings. However, ATIs without the addition of any other treatment modality, such as immunotherapy or with an ART sparing interval, are no longer supported.

Based on recent trial results, the U.S. Department of Health and Human Services (DHHS) HIV-1 Treatment Guidelines (2015) state that, apart from unplanned ATI or short-term ATI due to drug toxicities, long-term ATIs are not recommended (34). The guidelines provide important guidance, advising that if therapy has to be discontinued, participants should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound,

acute retroviral syndrome, increased risk for HIV-1 transmission, decline of CD4+ T-cell count, HIV-1 disease progression or death, development of minor HIV-1-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4+ T-cell count. Treatment interruptions possibly result in rapid reductions in CD4+ T-cell counts. The risks of repeated treatment interruptions are not clearly defined in the guidelines; however, data from the NIH's Strategies for Management of Antiretroviral Therapy (SMART) study suggest that cycles of treatment interruption at low CD4+ T cell counts could result in increased risk of death or disease progression. These risks continue to exist for short, prolonged, and repeated cycles of ATI.

Participants in the current study will be monitored on a weekly basis during the 12-week ATI and beyond. Participants will also be counseled with regard to the risks (outlined in the HIV-1 Treatment Guidelines) prior to ATI and weekly during ATI. During ATI, participants will be tested for COVID-19 if they experience symptoms consistent with COVID-19 and will restart ART COVID-19 positive by PCR. In addition, drug resistance data will be carefully reviewed by the investigator prior to allowing a participant to enter a second treatment interruption. Complications, such as acute retroviral syndrome when suspending ART or immune reconstitution syndrome when restarting ART, are more common in the setting of their *de novo* occurrence (i.e., when HIV-1 is first contracted and when ART is first initiated in the ART naïve patient). Even in these circumstances, their occurrence is rarely clinically significant with the potential exception of cryptococcal meningitis and reactivation mycobacterium tuberculosis disease in the case of immune reconstitution inflammatory syndrome. Irrespective, participants will be alerted to the potential for each of these respective events and instructed on alerting the study team of any sentinel symptoms so that clinical observation can be intensified. Additionally, participants with a history of mycobacterium tuberculosis latent or remote infection, cryptococcal meningitis, or clinically significant cardiovascular disease will be excluded from participating in the study without careful review by the protocol leadership and a more intensive discussion with the participant about the potential risks of reactivation or clinical manifestations of these respective conditions.

Based on this background, treatment interruption following engraftment will be delayed until CD4+ T-cell counts recover to $\geq$ 300 cells/mm^3 to provide a buffer above the 200 cell/mm^3 threshold for restarting ART prior to the end of the pre-specified 12-week period. Any clinically significant deterioration observed or reported during the treatment interruption including, but not limited to, signs of altered mental status or viral meningitis (severe headache, neck stiffness), the emergence of fever to greater than 38.5^{o}C, severe lethargy, or signs/symptoms of a possible OI, any OI including esophageal thrush or pneumonia, or any deterioration that in the opinion of the study team or the participant's primary provider would place the participant at risk for significant morbidity will be monitored and will be used to restart therapy earlier, if needed. While understandably non-specific, the safety of the participant will be the primary consideration attending any clinical management criteria during the course of this clinical trial. Consideration for

reinstating an ATI once interrupted due to the side effects will only be considered after consultation with the FDA.

The rationale for establishing a threshold for restarting ART prematurely if the CD4+ T-cell count goes below 200 cells/mm^3 is based on the expectation that selective expansion of transformed cells is likely to occur in the setting of loss of non-transformed cells and an overall decline in total CD4 count. The anticipated risk of this strategy is expected to be mitigated by the limited duration of a low CD4 count accompanying high viremia. Clinical experience has demonstrated that the risk of OI occurrence increases over time. As an example, in the experience of the clinical investigators, unintentional interruption of *Pneumocystis carinii* pneumonia (PCP) prophylaxis is rarely associated with reactivation PCP sooner than several months. Additionally, while risk of OI occurrence is tightly associated with decline in CD4+ T-cell count, the level of viremia interacts with the rate of risk as well. Reinstitution of potent ART, which rapidly suppresses viremia within days to weeks in the setting of close clinical monitoring, will minimize the risk to the participant of significant clinical events. While an independent association of the level of viremia and risk of OI or other morbidities has not been established, the team will err on the side of caution and use the escalating viral load criteria described above as a threshold. This will be implemented more to be confident of the ability to control attendant inflammation and potential consequences, rather than suggesting that HIV-1 viremia is associated independently with increased risk of OI.

Please refer to Appendix 1: App – 1C for the schedule of assessment for the ATI portion of the study, Appendix XII for the ATI disclosure form for participants, Appendix XI for ATI risk mitigation and counseling forms, and Appendix XIII for PrEP information sheets for participants.

2.4.3 Post ART Withdrawal Monitoring

Once ART is reinitiated, participants will be evaluated at Weeks 4 and 8 on ART. If viral load is not below the level of quantification by Week 8, participants will be evaluated every four weeks until the viral load is confirmed to be less than the level of quantification. A follow up visit will occur 24 weeks after resumption of ART.

Routine safety studies, CD4+/CD8+ T cell counts, and viral load will be performed at Weeks 4, 8, and 24, and as needed between Week 8 and Week 24 to monitor safety and evaluate decrease of viral load to below level of quantification as described above. Plasma and PBMCs will be collected and cryopreserved at the time of ART resumption and at Weeks 4, 8 and 24 on ART. Please refer to Appendix 1: App – 1C for the schedule of assessment for the ATI portion of the study.

2.4.4 Change in ART withdrawal criteria (protocol version 8)

The previous goal of ART withdrawal when T-cell count has risen to ≥ 500 cells/mm^3 was not achievable for most participants. Some patients achieved a CD4 count of ≥ 300 cells/mm^3. Resuming ART when CD4 is < 200 cells/mm^3 is appropriate for safety reasons. Below 200, we expect participants to be prone to

OIs, hence most providers use this as a threshold to begin prophylactic antibiotic.

This change in the CD4 criteria will allow participants to begin controlled ART withdrawal earlier around 6 months to a year and not wait for two years to do so.

ART withdrawal in these participants will provide critical information about the kinetics of the selection of HIV-resistant transplanted clones of CD4 T-cells and the potential kinetics of HIV reservoir decay in that setting. This will inform the design of future studies when models of the threshold for a potential requirement for a proportion for transformed cells required for cure might be identified. In other words, the information collected during a structured STI may provide sufficient information to model what fraction of the transplanted product should be HIV resistant stem cells in order to achieve an extinction of the HIV reservoir. Although it is not anticipated that any of the participants from earlier cohorts will achieve control of their infection following an STI, we have observed an expansion of the transformed CD4 clone in participants who became viremic due to ART non-compliance. Ultimately, the goal of our treatment intervention is that the proportion of transformed CD4/HIV-resistance cells in recipients is sufficient such that they no longer need ART to control HIV infection. STI is the most certain way to establish that desired endpoint. Including participants from the earlier cohorts will assist in guiding the design of future clinical trials to achieve that goal.2.5 Correlative Studies

2.5.1 Biologic rationale and proposed mechanism of action for the study agent

Survival in patients infected with HIV has improved dramatically with the advent of ART. However, neither a cure nor a vaccine exists. Infected individuals develop AIDS related malignancies such as lymphoma that are in general more aggressive and present with higher disease stages. Even after successful curative therapy of their malignancy, their survival depends on high compliance with ART therapy to prevent the relapse of lymphoma. Lack of immunological response despite virological suppression, issues with non-compliance or drug resistance, side effects of medications, and development of a well characterized but poorly understood chronic inflammatory status associated with different chronic illnesses are just a few of the complications that continue to negatively affect the quality of life and survival in patients with HIV related lymphomas. Hematopoietic stem cell (HSC) gene therapy for HIV may offer an alternative one-time treatment, with the possibility of controlling both the lymphoma as well as HIV itself by eliminating reservoirs of HIV that are responsible for persistence of the disease. Our proposed novel anti-HIV therapeutic candidate, autologous HSCs transduced with a triple combination of anti-HIV genes transferred by a single lentiviral vector is aimed at blocking HIV infection at different stages of the HIV life cycle. This approach provided strong pre-integration inhibition of HIV-1 infection, eliminated the generation of viral escape mutants, and prevented the integration of multiple, including resistant strains of HIV in various cell types in vitro. *In vivo* safety/efficacy studies in a humanized mouse model displayed excellent results including a selective survival advantage of anti-HIV gene modified cells and maintenance of normal human CD4+ cell levels. We also use a novel method of transduction that improves our transduction efficiency to a more clinically relevant level. Furthermore, for the first time in any HIV gene therapy approach, we are

proposing to use a selectable surface marker on transduced cells to purify and transplant only anti-HIV vector transduced HSCs. Significantly, this improvement in transduction efficiency and selection for anti-HIV transduced HSC, resulted in decreased viremia in our model. We have successfully filed an application to the NIH Recombinant DNA Advisory Committee (RAC) and have been awarded an FDA IND approval and have started to manufacture the clinical GMP reagents for our clinical trial. We will be targeting HIV related lymphoma patients that require transplant as a part of their standard of care. This provides us an ethically acceptable setting to test the safety and efficacy of our product. By using a highly effective combinatorial anti-HIV gene therapy approach, developing a novel and significantly improved transduction process, revising transplant procedures to transduce HSCs before freezing and, most importantly, selecting and transplanting only the HIV resistant transduced HSCs, we expect to replace the patient's immune system with HIV resistant cells, thus depleting viral load in the absence of ART.

2.5.2 Specific hypothesis

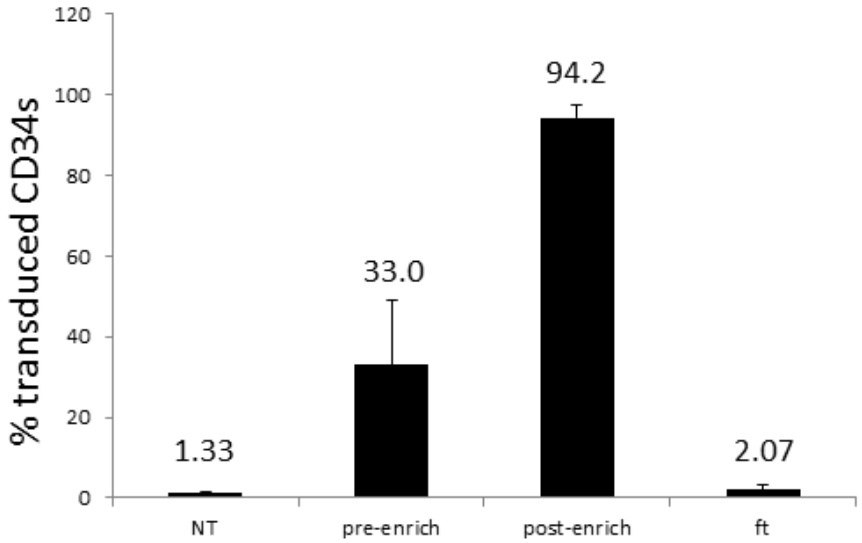
Anti-HIV gene expressing stem cells can safely reconstitute the hematopoietic system of the recipient and can produce a pool of mature myeloid and lymphoid cells that harbor anti-HIV genes capable of resisting HIV-1. As a secondary objective, we will interrogate two physical compartments of immune system, (i.e., peripheral blood (PB) cells and gut mucosa) for the presence, quantity and duration of gene modified HIV-1-resistant immune cells. In addition, we will determine the integration sites of vector sequences in circulating cells and monitor for any clonal expansion of hematopoietic cells.

2.5.3 Relevant preclinical data

We have obtained strong preclinical data in both our *in vitro* and *in vivo* experiments demonstrating safety and efficacy of our tCD25 pre-selective combination anti-HIV lentiviral vector. This vector encodes a chimeric human/rhesus macaque TRIM5α isoform, a CCR5 shRNA, and a TAR decoy each of which inhibit HIV in a different stage of its life cycle. It also expresses a truncated/mutated form of human CD25 which is used as a selectable marker to purify transduced HSC away from untransduced HSC so an enriched population of HIV-resistant HSC can be transplanted into patients.

SAFETY/FEASIBILITY/TOXICITY STUDIES: To evaluate the levels of enrichment of 1TAX vector transduced HPC, flow cytometry was performed on CD25 immunomagnetic bead purified cells. As displayed in Figure 2-B, enrichment levels ranged from 89.6% to 98.3% with an average of 94.2% (Post-enrich). This was compared to initial transduction efficiencies, which ranged from 19.8% to 60.4% with an average of 33.0% (Pre-enrich). Human HPC do not normally express CD25 and this is displayed as background expression, ~1.33% (Non-transduced, or NT). Flow through (ft) levels from the Stem Cell Technologies magnetic columns, ~2.07%, demonstrated that the majority of 1TAX vector transduced cells were collected during the enrichment procedure.

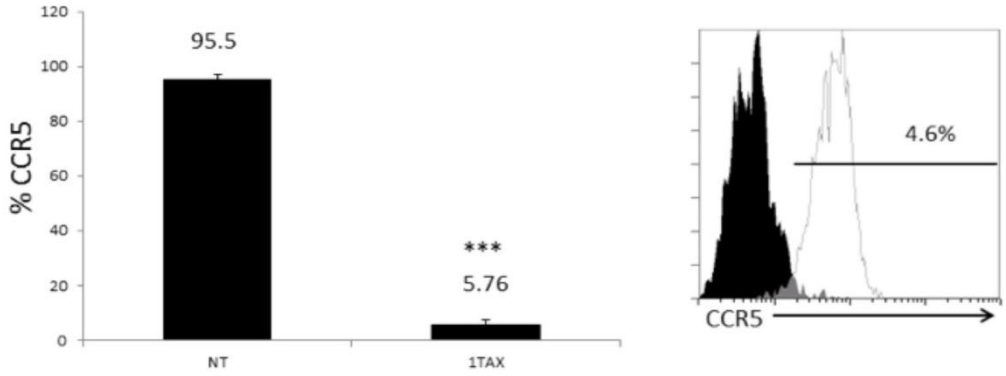
Figure 2-B: Enrichment of 1TAX vector transduced cells: Human CD34+ HPC were transduced with the 1TAX vector, purified by CD25 immunomagnetic beads, and analyzed by flow cytometry for CD25 expression. Non- transduced cells (NT), flow through (ft)



Enrichment of 1TAX vector transduced cells: Human CD34+ HPC were transduced with the 1TAX vector, purified by CD25 immunomagnetic beads, and analyzed by flow cytometry for CD25 expression. Non- transduced cells (NT), flow through (ft)

Safety was observed in 1TAX vector transduction of HPC using colony forming unit assays and differentiation of these colonies into phenotypically normal macrophages. No significant differences in colony formation or expression of normal macrophage cell surface markers was observed in 1TAX vector transduced HPC compared to NT cells. Genetic stability of integrated 1TAX vector including the lack of deletions and rearrangements was also observed. The correct sequence of the integrated 1TAX vector was observed in transduced HPC. Expression of all three anti-HIV genes was detected in 1TAX vector transduced HPC. Potent down regulation of CCR5 expression was observed in 1TAX vector transduced cells (>94%, $p<0.001$) (Figure 2-C).

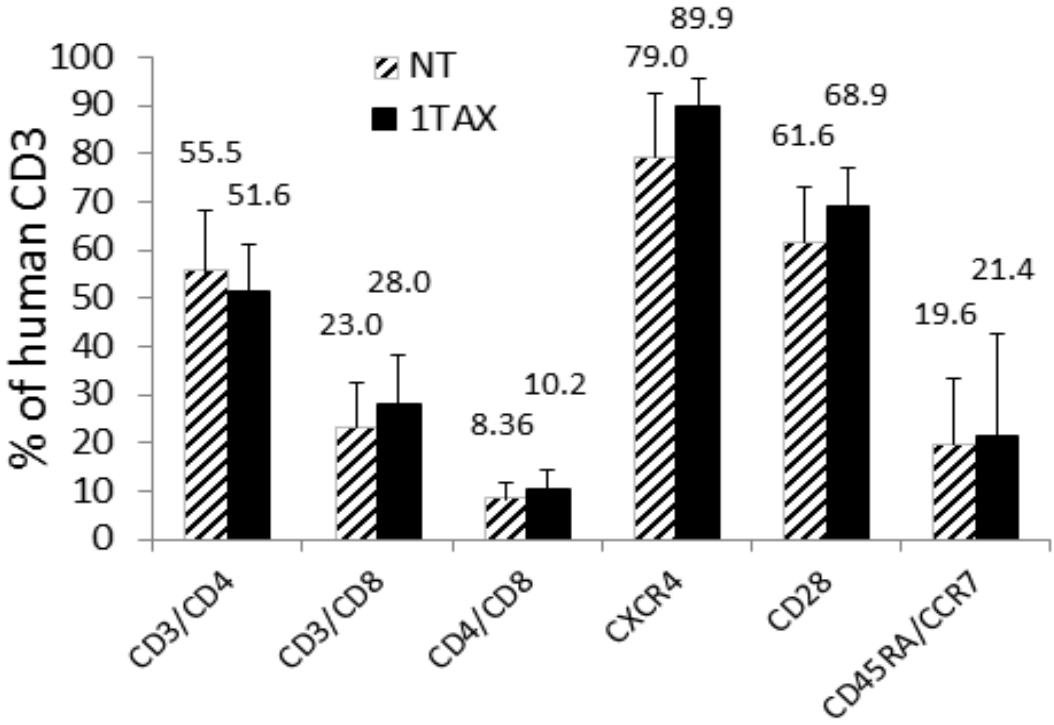
Figure 1-C: Down regulation of CCR5 expression on 1TAX cells: Ghost-R5/X4/R3 cells transduced with the 1TAX vector were analyzed by flow cytometry for CCR5 cell surface expression. A representative histogram is displayed with NT cells (unshaded) and 1TAX vector transduced cells (shaded). Experiments were performed in at least triplicate. *** p<0.001



With the transduction of lentiviral vectors, there is the possibility for integration to occur in an area of the genome which may immortalize that specific transduced cell. Therefore, to determine if any immortalization occurred with 1TAX-transduced HPC, a long-term culture assay was performed similar to previously described (Modlich et al., 2009). No visual immortalization had occurred in either the 1TAX transduced or NT HPC cultures upon scoring 192 individual wells. To further evaluate the tumorigenicity of 1TAX vector transduced HSC, a NOD-RAG1-/-IL2rgamma-/- (NRG) knockout mouse model was used. Human CD34+ HSC were transduced with the 1TAX vector, enriched by CD25 immunomagnetic bead separation and transplanted into NRG pups (N=8). Engrafted mice were then left in the UC Davis vivarium for 6 months and transferred to the UC Davis Comparative Pathology Laboratory where they were euthanized and evaluated for any tumors. Gross necropsy and histologic examination of all major organs was performed. The anatomic pathologist and director of the comparative pathology lab confirmed that there were no tumors noted grossly or histologically.

To evaluate the in vivo safety and toxicity of 1TAX vector transduced HSC, human CD34+ cells transduced with the 1TAX vector were transplanted into NRG pups (N=10). Twelve weeks post-transplantation, mice were screened for engraftment in the peripheral blood by flow cytometry. 1TAX transplanted HSC (55.5%) (N=10) displayed similar CD3+/CD4+ human T cell engraftment as NT HSC (51.6%) (N=7) transplanted mice. The phenotypic profile of peripheral blood 1TAX T cells was analyzed by multi-color flow cytometry. No significant differences in the percentage of the CD3+ T cell markers, human CD4+ (p=0.50), CD8+ (p=0.32), CD4+/CD8+ (p=0.34), CXCR4 (p=0.08), CD28 (p=0.17), and CD45RA+/CCR7+ (p=0.84), were observed when comparing NT and 1TAX vector transduced cells (Figure 2-D).

Figure 2-D: Phenotypic profile of 1TAX vector transduced peripheral blood T cells: Human CD34+ HSC were transduced with the 1TAX vector and transplanted into NRG mice. The peripheral blood of engrafted mice was analyzed by multi-parametric flow cytometry for T cell phenotypes



NRG mice engrafted with 1TAX transduced and enriched cells were then evaluated for human immune cells in other hematopoietic sites such as the spleen, thymus, and bone marrow. 1TAX transplanted HSC (54.4%) (N=10) displayed similar CD3+/CD4+ human T cell engraftment levels as NT HSC (59.7%) (N=7) transplanted mice. No significant differences in the percentage of the CD3+ T cell markers, human CD4+ (p=0.36), CD8+ (p=0.64), CD4+/CD8+ (p=0.48), CXCR4 (p=0.20), CD28 (p=0.08), and CD45RA+/CCR7+ (p=0.62), were observed when comparing NT and 1TAX vector transduced cells. 1TAX vector transplanted HSC (41.7%) (N=10) displayed similar CD3+/CD4+ human T cell engraftment levels as NT HSC (42.9%) (N=7) transplanted mice. No significant differences in the percentage of the CD3+ T cell markers, human CD4+ (p=0.79), CD8+ (p=0.18), CD4+/CD8+ (p=0.13), CD3-/CD8+ (p=0.0.58), CXCR4 (p=0.09), CD28 (p=0.43), and CD45RA+/CCR7+ (p=0.34), were observed when comparing NT and 1TAX vector transduced cells.

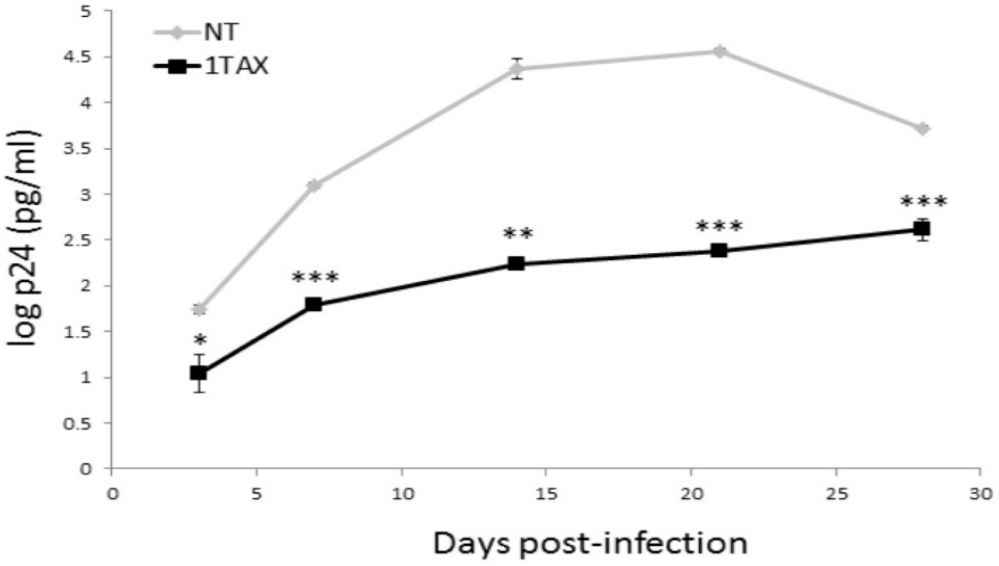
The levels of 1TAX B cells in the spleen and bone marrow and 1TAX macrophages in the bone marrow of engrafted NRG mice were also analyzed by flow cytometry. No significant differences in the levels of spleen B cells (p=0.47), bone marrow B cells (p=0.27), or bone marrow macrophages (p=0.22) were observed in 1TAX compared to NT cell engrafted mice.

These results demonstrate that 1TAX vector transduced and enriched HSC are safe, are not toxic, and are able to successfully engraft in NRG and undergo normal multi-lineage hematopoiesis in the peripheral blood and lymphoid organs all while not causing tumorigenicity.

EFFICACY STUDIES: The ultimate goal of HIV gene therapy is to transplant a HIV-resistant immune system into HIV infected patients. To evaluate the efficacy of 1TAX vector transduced HSC in inhibiting HIV infection, both in vitro and in vivo challenge experiments were performed.

First, an *in vitro* HIV-1 model system incorporating human CD34+ HPC derived macrophages was used. To evaluate the anti-HIV efficacy of enriched 1TAX vector transduced cells, *in vitro* HPC derived macrophages were challenged with a CCR5-tropic BaL-1 strain of HIV-1. As displayed in Figure 2-E, significant resistance (over 2 logs on days 14 and 21 post-infection) to HIV-1 infection was observed in 1TAX vector transduced cells compared to NT cells (day 3 $p=0.033$, day 7 $p<0.001$, day 14 $p<0.005$, day 21 $p<0.001$, and day 28 $p<0.001$) as determined by p24 antigen Enzyme Linked Immunosorbent Assay (ELISA).

Figure 2-E: HIV-1 challenge of 1TAX HSC derived macrophages: A) Nontransduced (NT) (♦) and 1TAX vector transduced (■) HSC derived macrophages were challenged with a CCR5-tropic BaL-1 strain of HIV-1. On multiple days post-infection, cell culture supernatants were sampled and assessed for HIV-1 using a p24 antigen ELISA kit. Experiments were performed in triplicate. * p<0.05, ** p<0.01, *** p<0.001



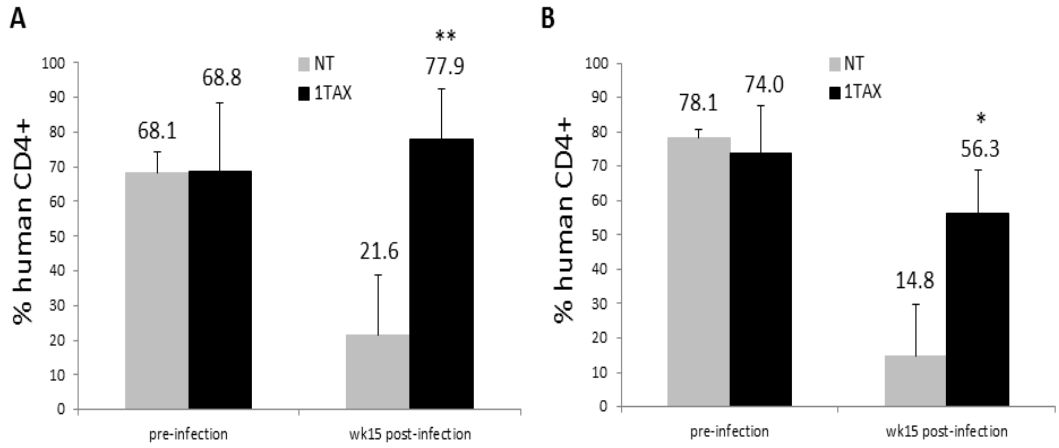
An *in vitro* selective survival experiment was performed to determine if anti-HIV gene modified cells were capable of surviving during the course of an HIV-1 infection. In cultures containing a 1:1 and 2:1 ratio of combination vector transduced cells to untransduced cells, the pre-infection Enhanced Green Fluorescent Protein (EGFP) percentage being, ~46% and ~73% respectively, increased to >84% EGFP positive cells by day 21 post-infection for both BaL-1 and NL4-3. This increase was statistically significant (BaL- 1 50% p value=0.001, BaL-

1 75% p value=0.05) (NL4-3 50% p value=0.001, NL4-3 75% p value=0.001). These results are in contrast to cultures containing EGFP-alone control vector transduced cells where the EGFP percent positive cell population remained relatively constant on day 21 post-infection (~42% and ~72% for ratios of 1:1 and 2:1, respectively) compared to the pre-infection EGFP percentages of 46% and 70% (BaL-1 50% p value=0.23, BaL-1 75% p value=0.69) (NL4-3 50% p value=0.62, NL4-3 75% p value=0.95).

To determine if viral inhibition was occurring at the stages of pre-entry (due to the CCR5 shRNA) and post-entry/pre-integration (due to TRIM5α), cells challenged with both BaL-1 and NL4-3 were further analyzed by quantitative polymerase chain reaction (qPCR) for genomic HIV-1 provirus. A highly potent block of HIV-1 provirus formation was demonstrated. Anti-HIV vector transduced cells contained undetectable levels, similar to background levels in uninfected cells, of HIV-1 provirus as compared to control untransduced and EGFP-alone vector transduced infected cells at multiplicity of infections (MOIs) of 0.01 and 0.05 for BaL-1 and NL4-3 strains of HIV-1. These data confirm that the anti-HIV vector conferred a strong block to HIV-1 integration, therefore preventing HIV integration.

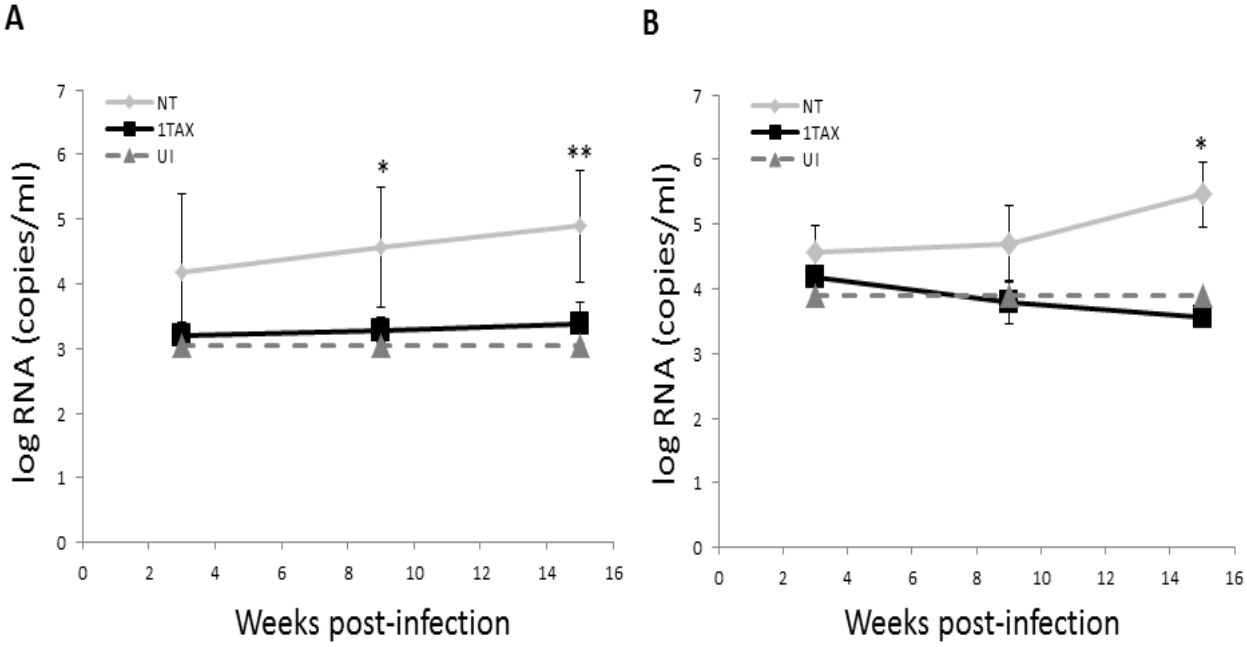
The hallmark characteristics of progressive HIV infection include a decline in CD4+ cells and an increase in plasma viremia. To evaluate the in vivo anti-HIV efficacy of 1TAX transduced cells, a humanized NRG mouse model was used. NRG mice engrafted with 1TAX HSC were infected with either a CCR5- tropic BaL-1 or CXCR4-tropic NL43 strain of HIV-1. On specific weeks post-infection, the peripheral blood of infected mice was analyzed by flow cytometry for CD4+ T cells and qPCR for plasma viremia. Mice engrafted with NT HSC (N=7) and infected with BaL-1 displayed a depletion of CD4+ T cells from pre-infection levels (68.1%) to 15 weeks post-infection (21.6%). This was in comparison and significantly different (p=0.0019) than mice engrafted with 1TAX HSC (N=7) and infected with BaL-1 which did not display CD4+ T cell depletion with pre-infection levels of 68.8% and 15 weeks post-infection of 77.9% (Figure 2-F A). Similar results were observed in NT and 1TAX engrafted mice infected with NL43. NT mice (N=4) displayed a decrease in CD4+ T cell levels from pre-infection (78.1%) to 15 weeks post-infection (14.8%) and 1TAX mice (N=4) displayed a decrease in CD4+ T cell levels from pre-infection (74.0%) to post-infection (56.3%) (Figure 2-F B). A significant (p=0.028) depletion of CD4+ T cells was observed on week 15 post-infection when comparing NT and 1TAX mice. Even though a decrease in CD4+ T cells (pre-infection to post-infection) was observed in 1TAX mice infected with NL43, this decrease was not significant (p=0.23). These results demonstrate that maintenance of CD4+ T cell levels could be achieved when an enriched population of 1TAX-transduced HSC is transplanted into NRG mice.

Figure 2-F: Maintenance of human CD4+ T cells in vivo in 1TAX cell engrafted NRG mice infected with HIV-1: NRG mice engrafted with either untransduced (NT) or 1TAX vector transduced cells were infected intraperitoneally with a (A) CCR5-tropic BaL-1 or a (B) CXCR4-tropic NL43 strain of HIV-1. Various weeks post-infection, mice were bled via tail vein and analyzed by flow cytometry for total human CD3+/CD4+ cell percent. Bar graphs display averages and standard deviations from seven mice per cohort for the BaL-1 infections and four mice per cohort for the NL43 infections for CD3+/CD4+ cell levels pre-infection and 15 weeks post-infection. * p<0.05 and ** p<0.002



To evaluate the levels of HIV-1 viremia in BaL-1 and NL43 infected NT and 1TAX mice, qPCR was performed on peripheral blood plasma on various weeks post-infection. As displayed in Figure 2-GA, inhibition of HIV-1 infection (~1.5 logs) was observed in 1TAX cell engrafted mice (solid black line) compared to NT cell engrafted mice (solid grey line). A significant difference in plasma viremia was observed on week 9 (p=0.0092) and week 15 (p=0.0043) post-infection. Levels of plasma viremia in 1TAX mice infected with BaL-1 were similar to those of background-uninfected mice (dashed grey line). As for the NL43 infections, inhibition of HIV-1 infection was observed (~2 logs) in 1TAX cell engrafted mice (solid black line) compared to NT cell engrafted mice (solid grey line) (Figure 2-GB). A significant difference (p=0.0073) was observed on week 15 post-infection. Again, levels of plasma viremia in 1TAX mice infected with NL43 were similar to those of background-uninfected mice (dashed grey lines). These results highlight the ability of 1TAX vector transduced HSC to generate a HIV-resistant immune system when transplanted into NRG mice.

Figure 2-G: Reduction in HIV-1 plasma viremia in NRG mice engrafted with 1TAX vector transduced HSC: NRG mice engrafted with either untransduced (NT) or 1TAX vector transduced cells were infected intraperitoneally with a (A) CCR5-tropic BaL-1 or a (B) CXCR4-tropic NL43 strain of HIV-1. Various weeks post-infection, mice were bled via tail vein and analyzed by qPCR for plasma viremia using a primer/probe set specific for the HIV LTR. Log RNA copies/mL for NT (♦) (solid grey lines), 1TAX vector transduced (■) (solid black lines), and background levels from uninfected (UI) mice (▲) (dashed grey lines). Line graphs display averages and standard deviations from seven mice per cohort for the BaL-1 infections and four mice per cohort for the NL43 infections. * p<0.05 and ** p<0.005.



Here, as we were able to initially enrich for 1TAX vector transduced cells prior to transplantation, we were able to generate a human immune system in the NRG mice which was resistant to HIV infection. This allowed for only a small percentage of NT and unprotected cells being transplanted with the majority of the transplanted cells protected. Combined, these results and preclinical data highlight the potential of our therapeutic candidate to succeed in our Phase I human clinical trial.

2.5.4 Reason for selection of the assay methodology

To evaluate the differentiation and persistence of anti-HIV HSC in recipient participants including functional and phenotypic changes in immune cell populations following HSC transplant, and to measure viral load and HIV response. Correlative studies, especially for gene therapy protocols, are critical to evaluate the feasibility, safety, and efficacy of the therapeutic intervention.

The correlative studies can be divided into immunological and HIV studies, DNA monitoring studies, and monitoring for oncogenesis and hematopoietic clonality. We will evaluate various aspects of the anti-HIV lentiviral therapy including DNA monitoring, oncogenesis/clonality, and immunological studies. Long-term

expression of anti-HIV genes and stability of the integrated vector will also be evaluated. The primary objectives of the immunology studies in this protocol are to monitor the reconstitution of the immune system, especially the homeostasis and function of T cell immunity in HIV-infected participants transplanted with anti-HIV gene transduced stem cells. A large number of clinical trials have shown that chronic HIV infection results in depletion of key T cell subsets.

2.5.4.1 DNA monitoring studies

The DNA monitoring core will evaluate engraftment (critical for efficacy) and safety of our approach in peripheral blood and gut tissue of transplanted participants. We will evaluate sites of vector integration, immune responses to foreign genes, potential silencing of anti-HIV genes (CCR5 shRNA, chimeric TRIM5α, and TAR decoy), and toxicity of the cells including tumorigenicity. Pre-transplant samples will be collected from the UC Davis GMP facility and also from leftover infusion bags. Post-transplant, both peripheral blood and biopsies will be obtained according to the timeline in Appendix I.

Approximately 20 mL of ethylenediaminetetraacetic acid (EDTA) anti-coagulated blood specimens will be collected for DNA monitoring studies (see Appendix VII for additional details of DNA monitoring studies).

Objective 1 Determine the levels of *in vivo* gene marking and vector copy number in 1TAX vector transduced cells.

Total DNA will be extracted from the peripheral blood of participants transplanted with the 1TAX vector transduced cells. qPCR will be performed with a vector-specific primer/probe set specific for the chimeric TRIM5α transgene. The levels of glyceraldehyde-6-phosphate (GAPDH) expression will also be evaluated as an internal control.

Objective 2 Determine integrated 1TAX vector sequence and stability.

To evaluate integrated 1TAX vector sequence and stability, sequencing will be performed. Total DNA will be extracted from the participant's peripheral blood. PCR amplification and sequencing (with vector specific primers) of integrated 1TAX vector will be performed. Sequences obtained will be evaluated for rearrangements, deletions, and additions.

Objective 3 Evaluate expression of the anti-HIV genes:

To determine if all three anti-HIV genes (CCR5 shRNA, chimeric TRIM5α, and TAR decoy) are being expressed long-term, qPCR will be performed. Total RNA will be extracted from the participant's peripheral blood. qPCR with gene specific primers will be performed to determine expression levels. GAPDH expression levels will be used as an internal control.

Objective 4 Evaluate clonality of 1TAX transduced cells in duodenal tissue:

In any gene therapy protocol, there is a risk of insertional oncogenesis due to random insertion of the vector. We will routinely monitor participants for any evidence of clonality. This is important for stem cell transplantations in lymphoma patients since there is an inherent risk of secondary malignancies (about 5-8%) due to the chemotherapy both as a treatment for controlling the malignancy and as a transplant preparative regimen. We will perform LAM-PCR every 6 months for 1TAX vector integrant sites and look for evidence of increasing oligoclonality or monoclonality, defined as 2-fold increase over two successive timepoints to > 20% of total transduced cells.

Objective 5 Determine if an immune response develops in participants due to the expression of the chimeric TRIM5α transgene.

The chimeric TRIM5α anti-HIV gene contains a 13-amino acid patch which is foreign to native human TRIM5α. Therefore, it is possible for an antibody based immune reaction to occur against cells expressing this region. However, this is highly unlikely in a myeloablative setting when immune tolerance can be induced against more prominent antigens such as human leukocyte antigen (HLA). Also, in our preliminary data, no stimulation was observed in cells pulsed with this amino acid region. Still and in accordance with the FDA, we will monitor participant serum for any antibody production by ELISA.

2.5.4.2 Immunological studies

The immunological studies will be done in 2 compartments: peripheral blood and gut mucosa.

A large number of clinical studies have demonstrated that chronic HIV infection results in preferential depletion of key T cell subsets, namely naïve and various T memory cells. An increased level of T cell activation has also been demonstrated in association with disease pathogenesis in AIDS patients as measured by HLA-DR and CD38 co-expression on CD8+ T cells. More recently, other cell surface markers have also been tested including CD69 and CD71. In addition to the imbalanced Th1/Th2 subsets, HIV infection also induces impairment in Th17 and regulatory T cells (Treg), an imbalance that reflects a systemic immunologic defect more pronounced in advanced HIV disease and after effective viral suppression with ART.

In the current proposal, homeostasis and differentiation of major T cell populations, and HIV-specific T cell responses will evaluate the adaptive

antiviral T cell functions. Furthermore, Type-1 and Type-2 T cell responses to common pathogens including CMV and EBV antigens will be assessed. Additional components of the innate immune system, including NK, NK-T cells, and dendritic cells will be examined in order to characterize functional immunologic changes following transplant. Furthermore, antigen-specific T cell responses will evaluate the adaptive antiviral T cell functions.

Approximately 40 mL EDTA anti-coagulated blood specimens and 5 mL of non-anticoagulated blood (serum) will be collected for immunological studies.

Out of the 40mL blood, about 2-mL whole blood will be used as fresh for phenotyping assays to determine the absolute counts of T cells, B cells and NK cells. The rest of blood will be:

- Isolate plasma and peripheral blood mononuclear cells (PBMC) (38 mL):
    - 10 mL plasma will be collected and stored in 1 mL aliquots for cytokine assays in later days (Year 3 and Year 4).
    - 10-20x10^6 cells will be used in assays immediately as fresh (listed as Functional assay in Section 2.5). Out of these cells, a minimum of 5x10^6 PBMC will be used for phenotyping assays of immune cell populations. A minimum of 10x10^6 PBMC will be needed for T cell function assays (T cell responses to pooled HIV peptides stimulations, to CEF (CMV-EBV-influenza virus), as well as culture median only (negative control) and to one of the positive mitogenic stimulations (positive controls, PMA or SEB (Staphylococcal enterotoxin-B)).
    - The rest of PBMC will be cryopreserved in 10% DMSO-FBS and stored in liquid nitrogen for testing in a later time, tentatively scheduled in Year 3 and Year 4. The expected number of PBMC in cryopreservation is 20-30x10^6, but could be less, especially for earlier time points post-transplant. In this case, we will make sure at least 5x10^6 cells will be preserved for any possible need of retesting.

From the plasma (10 mL) and serum samples (3 mL), aliquot as stored samples till batched assays, tentatively scheduled for Year 3 and Year 4. Cytokines studies will focus on the increased inflammatory status seen in patients with controlled HIV associated with immune exhaustion. They include but not limited to TNF-alpha, interferon gamma, IL2, IL10 and also other markers of chronic immune activation/exhaustion such as soluble PDL1/2.

Reconstitution of immune system in peripheral blood

Our laboratory will use established polychromatic flow cytometry panels to enumerate lymphocyte subsets and antigen specific cytokine expression in CD4 and CD8 T cells. Isolated PBMC from 40 mL EDTA anti-coagulated blood specimens will be collected from each participant at baseline, and at 3, 6, 12, and 24 months post HSCT for the following studies. The processing for participants enrolled at UC Davis will be done at UC Davis Medical Center. Critical assays will be performed with fresh whole blood and freshly isolated PBMC. Additional PBMCs will be stored in liquid nitrogen for later time assays (and necessary re-test).

- Chimerism of engrafted transformed cells:

  A portion of whole blood sample (~5mL) and a minimum of 10 x 10^6 PBMC will be tested in the flow cytometric assays to:

  a. Determine the proportion of circulating chimeric CD34+ cells expressing CD25.

  b. Determine the proportion of circulating chimeric non-lymphoid immune cells expressing CD25 will be explored employing a variety of antibody subsets to identify the most robust subset believed to reflect engrafted and persistent transformed populations.

  c. Consideration will be given to sorting these populations for PCR verification of TRIM5α genotype.

- Mixed lymphocyte reactions:

  In patients who are losing engraftment of the transduced cells, mixed lymphocyte reactions will be monitored in order to determine whether unmodified, post-SCT PBMC recognize and kill engrafted, modified cells. A mixed lymphocyte reaction will be performed using post-SCT PBMCs obtained when more than 50% drop in transduced cell chimerism is determined by PCR. PBMC obtained from 20 cc of peripheral blood will be mixed with pre-SCT modified stem cells (generated from remaining CD34+ depleted CD4+ T cells from pre-SCT leukapheresis). This will be performed in the immunology core. Gene modified cell killing and markers of T and NK cell activation and function will be determined in the ex vivo experiments using flow cytometric analysis.

  To study the homeostasis of T Lymphocytes and their subsets, a small portion of whole blood sample (~2-mL) and a minimum of 5x10^6 PBMC will be tested in the flow cytometric assays to:

  a. Determine memory and naïve CD4 and CD8 T cells and T cell activation:

     A multi-parameter test will be performed to detect viable CD3, CD4, CD8, CCR7, CD45RA, CD38, HLA-DR, CD27, CD57, Ki67 and viable cell stain. Naïve, central memory and effector T cells will be

analyzed by expression of CCR7/CD45RA on T cells that are gated on viable-cell/CD3 and CD4 or CD8 staining. T cell activation will be measured using combinations of CD38/HLA-DR as well as CD27, CD57 and/orKi67.

b. Determine the Treg, NK, NK-T cells, and DC subsets:

These will be examined with antibodies to CD45, CD11c, CD123, CD3, CD4, CD8, CD25, CD16, CD56, IL-7R, FoxP3, and viable cell stain. Expression of CD25+/ FoxP3+/IL-7R- will be used to identify Treg in viable CD3/CD4 cells. NK and NK-T cells will be identified by markers of CD3, CD16/CD56, and CD8. Expression of homing molecules (integrin α4β7, CD62L, CCR9, CD18, CD31 and CD54) and inhibitory and activating receptors on NK cells will also be included in this panel pending on specimen availability.

c. Pending specimen availability, homeostasis of B cell classes and expression of T cell homing molecules (integrin α4β7, CD62L, CCR9, CD18, CD31, and CD54) will also be accessed (at baseline and month 12).

- Functional responses upon reconstitution of T Cell Immunity

Isolated PBMC will be cultured with mitogen or HIV-specific antigens and used in the following studies. For participants enrolled at UC Davis, the processing starts as soon as possible after blood collection, usually within 1-hour. For participants enrolled at other sites: EDTA blood samples will be sent to UC Davis with chilled packaging via FedEx Priority Overnight shipping:

a. Total Th1/Th2/Th17 subsets upon mitogen stimulation:

The detection panel will be: viable stain, CD3, CD4, CD8, and intra-cellular Granzyme-B, IFNγ, TNFα, IL2, IL4, IL10, and IL17a. Th1/Th2/Th17 subsets will be identified as IFNγ/TNFα/IL2, IL4/IL10, or IL17a, respectively, on viable CD4 T cells.

b. HIV antigen specific T cell responses:

PBMC stimulated with HIV-gag peptides will be examined with a panel of viability stain, CD3, CD4, CD8, and intra-cellular IFNγ, TNFα, IL2, IL4 and IL17a. The profile of cytokine(s) produced in viable CD4 or CD8 T cells will be analyzed and correlated to Granzyme- positive T cells. T cell responses to Staphylococcal enterotoxin-B (SEB) will be used as positive controls. Another control antigen, CMV-EBV-influenza virus (CEF) peptides antigens will be used as an indicator of T cell responses to pathogens common to human participants.

c. T cell proliferation responses to HIV gag stimulations:

If additional PBMC are available ($15x10^6$ cells more), proliferation responses will also be tested using CFSE (Carboxyfluorescein succinimidyl ester) assays. Furthermore, at one-year post transplant, based on the American Society of Blood and Marrow Transplantation (ASBMT) guidelines, participants will be immunized with inactivated vaccines. Acquisition of immunity against a neoantigen can therefore be assessed in these patients by their response to immunization with a replication incompetent antigen such as tetanus toxoid.

Analysis of the extra-vascular compartment of the immune system (gut mucosa):

Immune restoration in the duodenum is profoundly blunted with absolute numbers of CD4+ T cells in the lamina propria changing little after prolonged viral suppression. We believe that a thorough evaluation of immune effects of our product will be enhanced by demonstration of transduced cells in duodenal tissue. It is anticipated that transduced cells will home to the lamina propria and will be particularly enriched during HIV treatment interruption. Presence of transduced immune cells in gut associated lymphoid tissue (GALT) will likely be a hallmark of the success for our gene therapy protocol. Our HIV team members are leaders in the area of gut immunity and reconstitution in response to HIV infection, with a long track record of performing upper endoscopy safely in HIV research participants, having performed over 100 procedures on 60 research participants over the last 4 years.

To demonstrate homing/persistence of transduced lymphocytes in this compartment, the distal duodenum will be sampled at 6 months post-transplant (or when CD4 count reaches above 300 cell/mm^3) and will be repeated two months after the first GI biopsy. This will facilitate addressing two important questions, namely the uptake of the transduced population of lymphocytes into the extravascular compartment and the degree of enrichment that occurs following selective survival pressure on these lymphocytes during ART withholding. The categorical residence of transduced cells and both their functional integrity and that of the local immune system in general will be assessed for both IHC and digestion into single cell suspension for flow cytometry.

The distal duodenum will be sampled by a designated gastrointestinal (GI) physician at each center at 6 months post-transplant (or when CD4 count reaches above 300 cell/mm^3) and will be repeated two months after the first GI biopsy. This will be under separate consent form for the study and the participation therefore is not mandatory for enrollment in the main study (see Appendix V).

- Tissue biopsies will be immediately processed at the time of endoscopy for cryopreservation and for both subsequent IHC and digestion into

single cell suspension for flow cytometry. Cryopreserved samples can be used for HIV quantitation and sequencing, RNA microarray, and quantitation of transduced cells by PCR of the inserted vector.

- IHC will be performed to enumerate critical populations of the mucosal immune system, specifically CD4+ and CD8+ T cells and T-regulatory cells.
- Flow cytometry will be performed in unstimulated CD4+ and CD8+ T cells and T-regulatory cells.
- Functional assays of immune function will be performed by incubating duodenal cells with mock challenge; SEB, CEF, and HIV gag peptides for intracellular cytokine measurement by flow cytometry of TNFα, IFN-γ, IL-2, IL-17a, and CD103.

These experiments are expected to demonstrate both the persistence of the transduced lymphocyte population, as well as improved immunologic function in this compartment, which can be compared to the time series of parallel immune function assays performed on PBMCs over the same time period.

2.5.4.3 Virologic studies

A. ART resistance and co-receptor usage: These studies will be performed at baseline, 2 and 10 weeks and then 6, 12, and 24 months post-transplant.

B. To characterize changes in the HIV reservoir and viral diversity: Additional blood samples will be collected at baseline, 2 and 10 weeks and then 6, 12- and 24-months post-transplant for HIV reservoir characterization. These studies will include quantitative PCR analysis of PBMC-associated HIV DNA, RNA (including unspliced and multiply spliced forms) and 2-LTR circles. In addition, single genome sequencing of HIV gp120 and HIV pol will be performed to understand sequence evolution following transplantation and detection of minority resistance variants. Single-copy HIV from plasma will also be determined at each of these time points. Samples will be sent to the Timothy Henrich Laboratory at University of California, San Francisco.

2.5.5 1TAX lentiviral vector stability

The marker is a stably integrated lentiviral vector harboring a combination of anti-HIV genes and a pre-selective marker gene. As the 1TAX vector is stably integrated, it will remain permanently in the transduced cells.

2.5.6 Technical performance characteristics, positive and negative controls, and methods of scoring for the assays

Study T lymphocytes and their subsets

The flow cytometry data is highly reproducible and accurate. Variability will be observed from participant to participant; however, samples will be evaluated and

compared from the same participant to decrease variability.

Flow cytometry positive controls will be obtained from normal healthy donors. Negative controls are isotype stained cells.

The flow cytometry data will be scored by percent + cell populations staining for the specific immune cell surface markers.

Functional responses upon reconstitution of T cell immunity

The functional cytokine secretion data is highly reproducible and accurate. Variability will be observed from participant to participant; however, samples will be evaluated and compared from the same participant to decrease variability.

The functional cytokine secretion positive controls will be obtained from normal healthy donors. Negative controls are unstimulated cells from the same participant.

The functional cytokine secretion data will be scored based on the levels of cytokines as measured in ng/mL.

Monitoring for insertional oncogenesis and clonality of hematopoiesis after gene therapy

We will use LAM-PCR (Linear Amplification Mediated PCR), a highly accurate method that is able to specifically identify the sites of integration of the 1TAX vectors. Variability will be observed even in the same participant samples as the vector is capable of integrating in 1000s of places in the targeted genome.

There are no positive or negative controls for this assay. This is specific for 1TAX vector integration sites. It is not possible to specifically integrate a 1TAX lentiviral vector into the chromosome of a host genome.

Insertional oncogenesis and clonality will be scored based on the sites of integration of the 1TAX vector and the number of events correlating to each specific integration site.

DNA monitoring studies for in vivo gene marking, vector stability, and anti-HIV gene expression

These assays are highly accurate and specific due to the use of primers specific for the 1TAX vector and expressed genes. Variability will be observed between participant to participant due to the different levels of engraftment. This will affect the levels of *in vivo* gene marking and anti-HIV gene expression. Variability will be minimized by comparing the results of these assays within each sample from the same participant. 1TAX vector stability should be consistent as we have not observed any deletions or rearrangements in our preclinical data.

The positive control for *in vivo* gene marking is the transfer plasmid used for vector production, which includes the psi sequence. The negative control is a plasmid that does not contain the vector specific psi sequence. 1TAX vector stability positive control is again the transfer plasmid used for vector production. The negative control for 1TAX vector stability is genomic DNA from untransduced cells. The positive control for anti-HIV gene expression is total RNA from 1TAX vector

transduced HEK-293T cells. The negative control for anti-HIV gene expression is total RNA from untransduced cells.

In vivo gene marking will be scored by 1TAX vector copies per cell. Vector stability will be scored based on the correct size of the PCR product in comparison to the positive control transfer plasmid. Anti-HIV gene expression will be scored by relative gene expression as compared to GAPDH expression (housekeeping gene).

Monitoring for immune response to TRIM5α

The reproducibility of this assay will vary from participant to participant. This assay is designed to detect any immune response which may occur with the expression of the chimeric TRIM5α transgene and so we may never detect any immune response in participants. Accuracy will be assessed by baseline plasma levels obtained from participants prior to transplantation.

The positive control for the TRIM5α ELISA is an anti-chimeric TRIM5α antibody generated in rabbits. The negative control is plasma from a normal healthy donor.

The immune response to the chimeric TRIM5α will be scored based on the levels of anti-chimeric TRIM5α antibody in ng/mL.

Monitoring of transduction efficiency and stem cell capabilities of transduced hematopoietic stem cells in immunocompromised mouse models

Transduction efficiencies have been consistently reproduced to exceed 50% of the cell population. Variability is expected from participant to participant sample as we have observed in our preclinical data.

The positive control for transduction efficiency is transduced HEK-293T cells. The negative control is an isotype control for flow cytometry.

Transduction efficiency will be scored based on CD25+ cell expression by flow cytometry.

2.5.7 The site performing the correlative studies

UC Davis will perform the correlative studies. Dr. Pollard's lab will perform the immunological core studies and Dr. Anderson's lab will perform the DNA monitoring core studies. Specialized immunologic and virologic assays will also be performed in the laboratory of Dr. Timothy Henrich at University of California, San Francisco. Basic immunology studies will be performed according to the standard of care by CLIA-certified local laboratories at each participating institution.

2.5.8 Additional sample for safety investigation

In the unusual circumstance where an unexpected or sudden change in the subject's clinical status occurs where product safety concerns raise a relevant question requiring additional blood samples outside the specified time points, participants may be asked for an additional blood sample (maximum of 30 mL of EDTA whole blood in a purple top tube), at the local PI's discretion in consultation with the protocol chair. The samples will be shipped to Dr. Pollard's Laboratory at UC Davis (see Appendix VII), and will be analyzed per the protocol correlative studies

relevant for the safety concern, such as mixed lymphocyte reactions. It is not anticipated that this will occur with every subject or on more than one occasion outside of the current schedule of events.

3.0 PARTICIPANT SELECTION

A rostered AMC investigator must document that each protocol participant meets meet all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

General participant population eligible for this trial: Male or female participants greater than 18 years of age with HIV-1 related lymphoma that are refractory/resistant to first line of therapy, or have relapsed after achieving a remission, and are eligible for an autologous HSCT as a part of their routine therapy are eligible for this study.

The type of the chemotherapy and the number of cycles prior to the study, as well as the timing of stem cell collection in relation to the last chemotherapy, will be determined based on the transplant physician discretion and each individual institution guidelines. **There should be a minimum of 2 weeks from the last day of any chemotherapy (except the one used for stem cell mobilization) before a participant can be enrolled on this trial.** While screening studies may be performed within 8 weeks of the stem cell collection, enrollment in the screening segment should occur before stem cell collection and no more than 1 week prior to stem cell collection.

NOTE: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart. All questions regarding eligibility should be directed to the study chair.

Participant ID Number: 097 - ___ ___ ___ - ___ ___ ___

Patient's Initials (L, F, M): ___ ___ ___

3.1 Eligibility Criteria

3.1.1 Inclusion criteria associated with type and status of lymphoma, one of the following must be applicable:

____ 3.1.1.1 Biopsy-proven intermediate or high-grade non-Hodgkin's lymphoma, meeting one of the following criteria (timeline 8 months prior to enrollment in the screening segment*):

- In partial remission,
- Relapsed after initial complete remission,
- Failed induction therapy, but responds to salvage therapy (i.e., chemosensitive disease),
- In complete remission with high-risk features as specified by the International Prognostic Index (See Appendix VIII).

____ 3.1.1.2 Biopsy-proven advanced stage follicular lymphoma, that have failed at least two lines of therapy multi-agent chemotherapy, but responds to

salvage therapy (i.e., chemosensitive disease) (timeline 8 months prior to enrollment in the screening segment*).

____ 3.1.1.3 Biopsy-proven advanced stage Mantle cell lymphoma with Ki-67 > 10% in first complete remission (timeline 8 months prior to enrollment in the screening segment*).

____ 3.1.1.4 Biopsy-proven Hodgkin's lymphoma, meeting one of the following criteria (timeline 8 months prior to enrollment*).

- In first, or greater relapse after initial complete remission,
- In partial remission,
- Failed induction therapy, but responds to salvage therapy (i.e., chemosensitive disease).

____ 3.1.1.5 Biopsy-proven Burkitt's lymphoma, meeting one of the following criteria (timeline 8 months prior to enrollment*):

- In second complete remission after relapse following initial complete remission,
- Failed induction therapy, but responds (very good partial remission, complete remission, or near complete remission) to salvage therapy (i.e., chemosensitive disease).

____ 3.1.1.6 Biopsy proven plasmablastic lymphomas, or peripheral T cell lymphoma (with the exception of ALK+ type in first or second complete remission) (timeline 8 months prior to enrollment*).

*__NOTE__: Patients meeting the following criteria are exempt from the 8-month timeline and do not require additional biopsy:

- Patients who have never achieved a complete remission on the last biopsy-proven site of disease and went on to the next therapy then achieved a complete remission.
- Patients who relapsed quickly (within 3 months of their last chemotherapy) and now have achieved a complete remission with salvage therapy.

3.1.2 Inclusion criteria associated with HIV-1 status

____ 3.1.2.1 HIV-1 infection, as documented by any federally approved, licensed HIV rapid test performed in conjunction with screening (or ELISA, test kit, and confirmed by Western blot or other approved test). Alternatively, this documentation may include a record demonstrating that another physician has documented the participant's HIV status based on either: 1) approved diagnostic tests, or 2) the referring physician's written record that HIV infection was documented, with supporting information on the participant's relevant medical history and/or current management of HIV infection.

____ 3.1.2.2 Must be on a multi-drug anti-HIV regimen (excluding zidovudine [AZT,

ZDV, Retrovir®, or agents containing zidovudine (e.g., Combivir® and Trizivir®)], and efavirenz [Sustiva®, or agents containing efavirenz (e.g., Atripla®)]).

Participants on zidovudine [AZT, ZDV, Retrovir®; including Combivir® and Trizivir®] and efazirenz [Sustiva®; including Atripla®] must switch to an alternative regimen without anticipated drug-drug interactions or myelosuppressive properties based on known viral resistance patterns and/or ART history, such as raltegravir and Truvada (emtricitabine and tenofovir) at least two weeks prior to the transplant.

_____ 3.1.2.3 Participant taking ARTs must satisfy one of the following:

- Undetectable HIV viral load (< 50 copies/mL). For patients who have had negative viral loads in the past 6 months and no known HIV viral load >500 copies/mL within the last 6 months, minor fluctuations of viral load (isolated escalations up to 500 copies/mL) are acceptable. The participant's history of negative viral loads may be documented with recent laboratory results and/or a record from the participant's HIV care provider.
- If viral load is detectable at < 2000 copies/mL a review of previous antiretroviral regimens or previous genotypic or phenotypic testing which indicate the ability to fully suppress virus by addition of sensitive drugs must be performed. This review will be carried out by the protocol ID team or the ID specialist caring for the patient.
- If viral load is detectable at ≥ 2000 copies/mL, a current HIV genotype and/or phenotype must be obtained. If a HAART regimen to which the patient's virus is sensitive can be determined based on genotype and previous antiretroviral experience, then the patient will be considered eligible in this regard. This review will be carried out by the protocol ID team or the ID specialist caring for the patient.

3.1.3 General Inclusion Criteria (timeline: within 8 weeks prior to enrollment in the screening segment, unless otherwise specified)

____ 3.1.3.1 Karnofsky performance status of 70-100%. ECOG performance status < [2] (see Appendix II)

____ 3.1.3.2 SGOT and SGPT ≤ 2.5 times upper limit of normal (ULN). Serum bilirubin ≤ 2.5 times ULN except for participants who are on atazanavir or indinavir, or with elevated indirect bilirubin related to bilirubin conjugation issues such as Gilbert's disease, provided that the participant's direct bilirubin is within normal institutional limits.

____ 3.1.3.3 Participants who are hepatitis C virus antibody positive, or hepatitis B virus surface antigen positive must be free of clinical evidence of cirrhosis as determined by the principal investigator in consultation with the institutional Gastroenterology Service. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.4 Participants with Hepatitis B should be on appropriate anti-viral therapy at the time of the transplant, and their viral load should be negative. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.5 Serum creatinine ≤ 2 times ULN. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.6 Creatinine clearance ≥ 60 mL/min by the modified Cockcroft-Gault Formula. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.7 PT/PTT ≤ 2 times upper limit of normal (ULN), or international normalized ratio (INR)/PTT ≤ 2 times the ULN. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.8 FEV-1 or DLCO (corrected for hemoglobin) ≥ 50% predicted. Timeline: within 4 weeks prior to enrollment.

____ 3.1.3.9 LVEF ≥ 50% by 2D ECHO or MUGA scan. Timeline: within 4 weeks prior to enrollment.

____ 3.1.3.10 Not pregnant or nursing, with negative serum pregnancy test. Pregnant women are excluded from this study because the conditioning regimen has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with BEAM, breastfeeding should be discontinued. These potential risks may also apply to other agents used in this study. Timeline: within 3 weeks prior to enrollment.

____ 3.1.3.11 Participants should agree to practice effective contraceptive precautions and to use at least one method of contraception for the duration of the study and for 3 months post-transplant.

____ 3.1.3.12 Age ≥18 years. Because only adult transplant centers are participating as study sites.

____ 3.1.3.13 Life expectancy of greater than 3 months.

____ 3.1.3.14 Ability to understand and the willingness to sign a written informed consent document.

____ 3.1.3.15 Receipt of a stable ART regimen for at least 3 weeks prior to enrollment.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a participant from study enrollment (timeline for all the exclusion criteria is within 8 weeks prior to enrollment in the screening segment):

____ 3.2.1 Participants with > 5% involvement of bone marrow by malignant cells (either by manual count or flow cytometry) prior to stem cell collection.

____ 3.2.2 Participants with any abnormal cytogenetics in the bone marrow not related to the lymphoma, and not deemed to be constitutional.

____ 3.2.3 Participants with unexplained anemia and/or thrombocytopenia.

____ 3.2.4 Participants with clear evidence of myeloproliferative disorders, or myelodysplastic disorders in the marrow.

____ 3.2.5 Presence of any active CNS disease at the time of evaluation (parenchymal or leptomeningeal).

____ 3.2.6 Any history of HIV-1 associated encephalopathy.

____ 3.2.7 Participants with persistently low CD4 counts less than 200 and a history of any AIDS-defining infection in the last 6 months before screening are excluded from the study.

____ 3.2.8 Symptomatic/active bacterial, or fungal, or any other opportunistic infection.

____ 3.2.9 Active CMV retinitis, or other active CMV-related organ dysfunction.

____ 3.2.10 Relapse of pneumocystis carinii pneumonia within the past year before enrollment.

____ 3.2.11 Intractable, severe diarrhea, defined as > 1.500 cc diarrheal fluid per day, or diarrhea causing persistent severe electrolyte abnormalities, or hypoalbuminemia.

____ 3.2.12 History of active myocardial ischemia, cardiomyopathy, uncontrolled dysrhythmia, or congestive heart failure within the last 6 months before enrollment.

____ 3.2.13 Dementia of any kind.

____ 3.2.14 Seizures within the past 12 months before enrollment.

____ 3.2.15 History of Grade III hemorrhagic cystitis due to prior cyclophosphamide chemotherapy.

____ 3.2.16 History of other prior malignancy, except squamous cell carcinoma of the cervix or anus, superficial basal cell or squamous cell skin cancer, or other malignancy curatively treated more than 5 years ago before enrollment.

____ 3.2.17 Active psychosocial condition that would hinder study compliance and follow-up.

____ 3.2.18 Any perceived inability to directly (and without the means of a legal guardian) provide informed consent.

____ 3.2.19 Any medical or physical contraindication, or other inability to undergo HPC collection.

____ 3.2.20 Participants who are receiving any other investigational agents.

____ 3.2.21 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

Physician Signature: _____ Date: _____

(Optional unless this section is used as an eligibility checklist)

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll a minimum of 2 participants and a maximum of 18

participants.

3.3.2 Accrual rate

Approximately 1 participant per month.

3.4 Recruitment Methods

Participants will be recruited from UC Davis, AIDS Malignancy Consortium (AMC) sites as well as from other referring clinics (throughout California and beyond) and will be enrolled and treated on protocol at either UC Davis or AMC sites. Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll participants who are representative of the respective target population. Screening of participants will be done by PIs as well as other members of the transplant team at either institution.

All procedures will be performed at the UC Davis Cancer Center, UCSF Adult Hematology and BMT Clinic, the UCSD Moores Cancer Center, and Memorial Sloan Kettering Cancer Center. The UC Davis IRB, UCSF Committee on Human Research, the UCSD Human Research Protections Program, and the Memorial Sloan Kettering Cancer Center Institutional Review Board/Privacy Board will oversee study conduct at their respective sites. After the first 3 participants are recruited to the protocol and dependent on the pace of participant recruitment to the protocol, a decision will be made by principal investigator and in consultation with AMC Steering Committee to extend the recruitment to other AMC sites.

Since it would not be possible to contact all of the participants associated with the study to obtain consent, the lead site (UC Davis) is requesting a waiver of HIPAA Authorization for recruitment purposes only. The PIs/research team will identify potential participants while at clinical appointments and access medical records to verify eligibility prior to the treating physician and research coordinator approaching the potential participant. Consent to participate and HIPAA Authorization to access additional information in the medical records will be obtained prior to enrollment into the study. For a description of the Cancer Center's plan to safeguard the Protected Health Information (PHI) from improper use and disclosure as well as assurance that the PHI will not be inappropriately reused or disclosed to any other person or entity (See Section 11.3).

All the information disseminated to participants (handouts, brochures, etc.) and any advertisements will be first approved by the IRB for the site. Screening requirements outlined in Section 7.1 and Appendix I will be used to meet inclusion or exclusion criteria that are defined for the study (see Section 3.1 and 3.2). Participants will be informed of their eligibility only by their treating physicians. Only participants who have signed all appropriate documentation and who meet participant eligibility requirements will be enrolled. We are completely aware of the difficulties in recruiting participants with this rather rare condition (i.e., HIV-1 related relapsed lymphoma). Therefore, we have proposed an ambitious effort to enroll participants not only from our catchment area of Northern California, but also from other areas of California, as well as from other states. Accrual will be facilitated by a dedicated community advocate, who will initiate and retain interactions with the target community and provide education about the trial. This advocate will interact with clinical research centers as well as other referring clinics across

California. He/she will use all available communication tools and specifically the internet to identify and reach out to the target populations for this study through support groups or specific websites, as community outreach materials and methods are specifically approved by the reviewing IRB. All information intended for distribution on the internet or any other media for the purpose of advertising for the study will be approved by the IRB in advance. We have already established a network of collaborators throughout the country and have received verbal and written commitment from some of these centers to propose the study to eligible participants and to facilitate the transfer of their care to our study centers. Entry criteria for cancer studies will be disease, not gender- or ethnicity-specific. Although, participants under 18 and pregnant or nursing women will not be eligible. Information will be disseminated to participants and physicians (e.g., handouts, brochures, etc.), and any advertisement or instruction will be approved by the IRB for the site.

3.5 Participant Enrollment Procedures

Sites must have this protocol approved by their Institutional Review Boards (IRB) and Institutional BioSafety Committee (IBC) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

3.5.1 Registration for screening

After an informed consent form has been signed by the participant, the participant must be registered for screening (AMC-097, Segment A) on-line via AdvantageEDC^{SM}. After successful registration into screening, the participant will receive an eleven-digit participant ID and will then enter the screening process (Screening and Pre-entry visits).

3.5.2 Enrollment

After the screening evaluations have been obtained and the participant is determined to be eligible, the participating site will complete the protocol-specific eligibility checklist. **Sites should email the completed (signed by site PI) eligibility checklist to mabedi@ucdavis.edu and hs-CellularTherapyResearch@ucdavis.edu for approval by the protocol chair (or a designated sub-investigator at UC Davis) before enrolling the participant into AMC-097 Segment B (on-line via AdvantageEDC).** Enrollment should occur no more than 1 week prior to, but before stem cell collection (enrollment 1 day prior to or on the day of stem cell collection is strongly encouraged). There should also be a minimum of 2 weeks from the last day of any chemotherapy (except the one used for stem cell mobilization) before a participant can be enrolled on this trial. Once the eligibility checklist is submitted, a system generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

Participants must be enrolled into AMC-097 Segment B prior to receiving HCT.

4.0 TREATMENT PLAN

Protocol agent will be administered on an inpatient basis. Reported adverse events and potential risks are described in Section 5.0 and Section 6.1.16. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The final product is autologous CD34+ cells transduced with a triple combination of anti-HIV genes that will be re-suspended in participants' serum, cryopreserved and then thawed and infused directly into central vein of the participants though a central catheter, 1 day after finishing their conditioning chemotherapy. Different number of non-transduced, un-manipulated product will be co-infused similarly according to the study cohort.

Autologous CD34+ cells isolated via clinical grade magnetic cell separation from mobilized peripheral blood apheresis products of HIV-1 lymphoma participants will be transduced with a 1TAX lentiviral vector carrying a triple combination of anti-HIV genes, tested and cryopreserved. CD34+ cell isolation, transduction, and qualification of the final product will be carried out in the UC Davis GMP facility following established Standard Operating Procedures (SOPs) and appropriate Quality Control (QC) and Quality Assurance (QA). The final product will be tested for identity, viability, purity, sterility, absence of mycoplasma and endotoxin, and for integrated transgene copy numbers per genome. A Certificate of Analysis (COA) will be generated (see Section 6.1). After completed testing, the autologous, cryopreserved product will be thawed and used for infusion into the HIV-1 lymphoma participant who has undergone a conditioning regimen.

4.1 HSC Mobilization and Peripheral Stem Cell Collection

See Section 2.3 for additional details of collection.

Prior to stem cell mobilization, eligibility and suitability of the autologous donor will be confirmed based on the screening data and the individual institution guidelines. The infectious disease profile and the rest of the blood donor test will be performed with FDA licensed blood donor tests.

In all patients, ART will be withheld 3 days prior and during stem cell collection. This is to decrease the possibility of ART therapy to interfere with the transduction of stem cells before transplant.

The stem cell mobilization regimen will be based on the individual participant's need, decided by the transplant physician. Both chemo mobilization and/or growth factor mobilization is allowed. HSC/progenitor cells will be collected by participating institutions, according to the institutional standards.

The quality, as well as the quantity, of stem/progenitor cells may be different in each collection. While it is difficult to assess the quality of stem cells, their quantity can be easily measured by the number of CD34 cells at the end of each day collection.

We aim to collect a minimum of 5 x 10^6 CD34 cells/kg of body weight of the recipient (ideally 10 x 10^6 CD34 cells/kg).

Assignment of the mobilized stem cells for the transduced group and the non-transduced group will be done according to the guidelines below:

1. *Minimum number of required unmanipulated cells will be collected first (1.5 x 10^6 CD34 cells/kg of recipient)* and will be immediately frozen and stored in harvesting center Progenitor Laboratories as per site SOP.
2. Additional cells available will be assigned to transduced portion of stem cell collection, which will be transferred to the UC Davis GMP facility by courier in temperature controlled transport containers, undergo CD34+ cell selection and transduction culture, followed by freezing and storage in the GMP facility. We prefer to receive the samples on the same day but they can be held for up to 24 hours and shipped with the next day collection based on the communications of the transplant physicians in the collection facility and the PI or Co-PI of the study.

Stem cell collection goals: Ideally, we aim to collect 10 x 10^6 CD34+ cells/kg of body weight of the recipient (for both manipulated and unmanipulated product). A minimum of 5 x 10^6 CD34+ cells/kg of body weight of the recipient is needed to proceed with the study.

1.5 x 10^6 CD34 cells/kg of body weight of the recipient will be used as the *unmanipulated product* and will be frozen. The rest of the product will be used for stem cell transduction. Additional cells can be collected and stored after the target number for CD34 (10 x 10^6 CD34+ cells/kg) is achieved based on the discretion of the subject's transplant physician and in consultation with the study principal investigator. These cells can be given to the patient, but the ratio of total manipulated to unmanipulated cells needs to follow the guidelines in Table 4-A.

The collection will continue until we achieve our collection targets. Table 4-Abelow provides the dose of *transduced* versus *untransduced* cells in each cohort of the study.

Table 4-A: Dose of Transduced Versus Untransduced Cells

Cohort Level	Ratio of Transduced Versus Untransduced Stem Cells.	Minimum Number of Transduced/ Untransduced Cells Acceptable. CD34 cells/kg	Range for Number of Transduced Cells / Unmanipulated Cells. CD34 cells/kg
1	1:1	1 X 10^6:1 X 10^6	1 to 5 X 10^6: 1 to 5 X 10^6
2	5:1	2 X 10^6:1 X 10^6	2 to 5 X 10^6:1 X 10^6
3	1:0	2 X 10^6: 0	2 to 10 X 10^6: 0
3+ expansion	1.0	3 x10^6 : 0	3 to 10 X 10^6: 0

4.2 Agent Administration

4.2.1 Preparative regimen for transplant

All participants enrolled in this protocol will be hospitalized, in all clinical centers, in accordance with the procedures for recipients of HSCT as defined by the treating institutions. They will receive BEAM or R-BEAM regimen as a standard of care preparative regimen administered per institutional guidelines. Physicians may use

their discretion and institutional guidelines in determining the appropriate body weight (actual, adjusted, or ideal) for the conditioning regimen dose calculation.

The BEAM and R-BEAM regimens for this study are comprised of the following intravenous medications:

- BCNU
- Cytarabine (Ara-C);
- VP-16
- Melphalan
- Participants with B cell Lymphoma may be administered rituximab prior to chemotherapy and post-transplant. Biosimilar agents are permitted at the investigator's discretion.

4.2.2 Stem cell infusion

For the first 2 cohorts, both *transduced* and *un-manipulated* product will be infused within 4 to 24 hours of each other at day 0, intravenously:

- The *transduced* product will be transported from the GMP facility of UC Davis, stored at the BMT unit of participating facilities and thawed in the BMT unit and immediately infused into the participants.
  - The stem cell lab at participating facilities will be receiving the frozen product via overnight courier, in a temperature-controlled transport container, prior to the start of the conditioning regimen.
- The *un-transduced* product will be stored at the participating facilities stem cell laboratories, thawed in the BMT unit and immediately infused into the participants, 4 to 24 hours after the infusion of transduced product is concluded.

Again, both procedures, including the route and duration of infusion, will be in accordance with the procedures for recipients of HCT as defined by the treating institution.

After DSMB approval, Participants in the third cohort will be administered **only** *transduced* product.

All the sites will follow site SOPs for thawing and infusing the transduced product, which will be coordinated before the start of the trial.

In case of non-engraftment, the back-up product stored at the respective site will be infused.

The number of cells infused to each participant depends on the cohort that the participant is enrolled in and is mentioned in Table 4-A above. The number of cells in the transduced products is based on CD34 counts after transduction of the stem cells and before freezing.

4.2.3 Antibiotic prophylaxis

All participants during transplant will receive antiviral (acyclovir or valacyclovir), antifungal (fluconazole) and anti-Pneumocystis jiroveci prophylaxis based on each

institution guidelines/preference. Antiviral and anti-Pneumocystis jiroveci prophylaxis will be continued for a minimum of one year and 6 months, respectively, after transplant. Antifungal prophylaxis will be continued for 30 days post-transplant. All prophylactic therapy will be restarted during ART withdrawal.

4.2.4 Antiretroviral therapy

Antiretroviral therapy will be stopped during transplant only for participants with excessive nausea or vomiting and for participants who are not able to take pills due to mucositis, etc. The therapy will be resumed once the transplant team feels confident that the toxicities are resolved, and participant has adequate oral intake. Potential interaction of ART with some of the chemotherapy agents and potential negative effects on stem cell engraftment and marrow recovery will be avoided by using ART that do not have those interactions or side effects. Participants on zidovudine [AZT, ZDV, Retrovir®, or agents containing zidovudine (e.g., Combivir® and Trizivir®], and efavirenz [Sustiva©, or agents containing efavirenz (e.g., Atripla®)], prior to transplant will be switched at least two weeks before the transplant to an alternative regimen without anticipated drug-drug interactions or myelosuppressive properties based on known viral resistance patterns and/or ART history, such as raltegravir and Truvada (emtricitabine and tenofovir). Antiretroviral drugs with long half-lives, such as efavirenz, will be avoided post-transplant in participants' combination therapy; if a drug regimen containing a long half-life drug is stopped, only a single drug will remain in the system for a prolonged period of time, and drug-resistant variants of HIV-1 can emerge very quickly.

4.3 Definition of Dose-Limiting Toxicity

Dose limiting toxicity in the trial is defined as lack of timely engraftment (the collective establishment of a persistent absolute neutrophil count of at least 500/mm^3 and platelet count of at least 20,000/mm^3 for 3 consecutive laboratory values obtained on different days) within one month post-transplant, or any grade 3 and 4 non-hematopoietic organ toxicity that can be attributed (possibly, probably, or definitely) to lentiviral transduced stem cell transplant, excluding alopecia, or any evidence of clonal expansion and excluding expected toxicities that are associated with the pre-transplant conditioning regimen, regardless of grade (see Appendix X for full list).

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Table 4-B: Criteria for dose escalation

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥ 2	If this threshold is exceeded in cohorts 1 or 2, dose escalation will be stopped. This dose level will be declared the maximally administered dose

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
	(highest dose administered). If 2 participants in the 3rd cohort develop DLT due to insufficient engraftment, an additional 3 patients will be enrolled in the cohort 3+ with an increase in minimum number of transduced CD34 cells from 2 to 3.0 X 10^6 cells/kg of recipient weight. If 2 or more DLTs occur in cohort 3+, the trial will be stopped.
1 out of 3	Enter at least 3 more participants at this dose level. If 0 of these 3 participants experience DLT, proceed to the next dose level. If 1 or more of this expansion group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤ 1 out of 6 at highest dose level at or below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

4.4 General Concomitant Medication and Supportive Care Guidelines

All concomitant medication, including blood products or general supportive guidelines, will be addressed by treating physicians and based on the institutional guidelines.

Section 4.2.4 explains the details of anti-retroviral therapy (ART) during the study period and in the follow up period.

All medications must be reported in the site's source documents from the time of study enrollment in Segment A through the treatment discontinuation visit. All medications will be reviewed and updated in the site's source documents at all visits where indicated in the schedule of evaluations. Only a subset of medications will be reported in the Concomitant Medications CRF as listed below:

- Anti-retroviral
- Antiviral
- Growth colony stimulation factors (GCSF)

4.5 Duration of Therapy

The investigational part of this clinical trial (i.e., infusion of gene modified hematopoietic

stem cells) will occur only once after conditioning regimen administration is concluded.

4.6 Duration of Follow Up

The initial follow-up period for this clinical trial will be two years post-transplant. For practical reasons, close and complete follow up of the participants needs to be limited. We have decided to use the 2-year limit for the close clinical follow-up since majority of the participants post an autologous transplant have recovered their immune system, and they are in a less risk of opportunistic infections as well as disease relapse after 2 years. However, all participants will be followed for 15 years albeit, in a less frequent and intensive form (every 12 months for years 3-15) for safety, as mandated by FDA for all gene therapy study participants. Additionally, every 12 months for years 3-15 we will request optional blood collections to monitor the patient's HIV and vector parameters in the body for participants that consent to optional studies.

4.7 Withdrawal of Participants

Participants will complete protocol treatment with HCT. Following HCT, participants may be withdrawn from the study prior to expected completion of that participant voluntarily or by their physician(s) for safety reasons, failure of the participant to adhere to protocol requirements, participant consent withdrawal. Patients who have progression of lymphoma within 24 months of gene therapy infusion will be followed for correlative studies as outlined in section 7.5.8.1. The goal is to monitor the patient's HIV and vector parameters in the body.

If early termination of the study should occur for any of the above-stated reasons, the study doctor(s) will have a discussion with the participant on how to stop safely, such as evaluation for risks from the study drugs, follow-up care, and any other procedures that might be recommended.

Even though participants may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such participants throughout the protocol defined follow-up period for that participant (though careful thought should be given to the full data set that should to be collected on such participants to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a participant withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of the participant follow-up period.

5.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 5.1) and the characteristics of an observed AE (Section 5.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting (via AdvantageEDC^{SM}).

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

5.1 Comprehensive Adverse Events and Potential Risks Lists

5.1.1 Adverse event list for genetically modified hematopoietic stem cells

Autologous stem cell transplant is a potentially toxic procedure and can result in multiple side effects. Autologous stem cell transplant is clinically indicated in all the participant of this study and is a part of standard of care for all these patients. Therefore, in this protocol we will focus on only side effects attributable (possibly, probably or definitely) to lentivector transduced stem cell transplant, excluding expected toxicities that are associated with the pre-transplant conditioning regimen (see Appendix X for full list). The complete product information of commercial chemotherapeutic agents to be administered as part of the protocol for stem cell transplant with BEAM or R-BEAM regimen can be found in FDA approved package insert for each agent.

Side Effects specific to participation in this protocol include but not limited to (see Section 6.1.19 for additional details):

Blood draw risks

Bruising, infection, and minor pain or discomfort comparable to a needle prick.

IV inserted in the vein risks

Inflammation, pain, bruising, bleeding, or infection.

Stem cell infusion

Problems that may occur during stem cell infusion are usually associated with infusion of DMSO and include low blood pressure, lightheadedness, fainting, fever, chills, tachycardia, bronchospasm, and hypoxia. These are temporary effects that are likely to subside after the infusion.

Allergic reactions

Proteins made from large amounts of non-human (protein) can sometimes lead to future allergic reactions. There is a small amount of a modified protein in the

modified cells for which there is a small chance of allergic reaction, but it is unlikely to be harmful to you even if it occurs. If an allergic reaction occurs, it is more likely that the modified cells will be destroyed. After the cell infusion, blood will be tested for any reaction that could affect the use of these agents in the future, but this reaction would not be directly harmful. This reaction is estimated at about a 4% chance of happening.

Possibility of another cancer or leukemia

The lentivirus used to modify the cells does not have the genes needed to reproduce itself, but it is possible in the future that it could combine with other genes in the body, or that it could activate an unknown virus to result in a known or unknown medical problem or disease, including the possibility of another cancer.

Reproductive risks

Since the effects of the proposed treatments on a fetus are unknown, any woman who should become pregnant while on this study will be removed from the study, and another method of treatment will be suggested. If male, the participant must practice effective birth control and must advise their partner to contact their physician should they become pregnant. We request the participants use at least one method of contraception for 3 months post-transplant.

Risk of antiviral therapy withdrawal

Participants may be asked to hold on taking their anti-HIV medications on at least three occasions. First, for 3 days before and during stem cell collection (to avoid the interaction of anti-HIV medications on stem cell transduction). The second time, during and/or immediately after chemotherapy for transplant in participants who cannot tolerate oral intake due to severe nausea/vomiting or mucositis. The third time (only in the third cohort), sometime after the first 6 months after the transplant when their immune system has recovered at least to some extent measured by CD4 T cells, participants in the third cohort will be asked if they would agree to voluntarily hold their anti-HIV medications until the onset of the criteria that will prompt resumption of treatment (see Section 2.4.1). The rationale for the third withdrawal is to expand the anti-HIV-1 immune system. Each time the participant stops anti-HIV medications, there is a potential risk that HIV-1 infection can become reactivated, and suppress their immune system, and make them susceptible to severe and potentially life-threatening infections. Clinicians, including an HIV doctor, will closely monitor the participant's immune system, and will restart their anti-HIV medications as soon as level of viral reactivation and suppression of the immune system reaches certain thresholds accepted by experts in the field. However, this may not completely eliminate the risk of complications.

Unknown risks

The experimental treatments may have side effects that no one knows about yet. The researchers will tell participants of new information that might make participants change their mind about participating in the study.

5.2 Classification of AEs by Severity and Relationship to Study Drug Administration

5.2.1 Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

5.2.2 Life-threatening Adverse Event: Any AE that places the participant or participant, in view of the Investigator, at immediate risk of death from the reaction.

5.2.3 Serious Adverse Event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect.

5.2.4 Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

5.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

5.2.6 Unexpected Adverse Event: Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol.

5.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports.

5.2.8 Attribution: The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:

Definite – The AE is clearly related to the investigational agent.

Probable – The AE is likely related to the investigational agent.

Possible – The AE may be related to the investigational agent.

Unlikely – The AE is doubtfully related to the investigational agent.

Unrelated – The AE is clearly NOT related to the investigational agent.

5.3 Expedited Adverse Event Reporting

5.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 5.3.3).

A 24-hour notification is to be made to AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

5.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

5.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific participant ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions - Disease Progression"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Table 5-A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

5.3.4 SAE reporting to FDA and IND sponsor-investigator

All SAEs that occur in trial participants following treatment initiation require a report to IND sponsor-investigator within one working day of awareness of the event, or immediately if the events are life-threatening or fatal. Participating institutions will make this report by submitting the Adverse Event Form in AdvantageEDC[SM]. The AMC ODMC will manage all SAE report submissions to the IND sponsor-investigator in accordance with its agreement with the IND sponsor-investigator, using the applicable forms designated for this purpose.

The sponsor-investigator will be responsible for reporting all serious and unexpected suspected adverse drug experiences to the FDA for the IND for this trial.

Participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to the AMC ODMC, and the sponsor-investigator or his designee will be responsible for reporting to FDA.

5.3.4.1 The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports.

The following describes the sponsor safety reporting requirements by timeline for reporting and associated type of event:

Within 7 calendar days

Any study event that is:

- associated with the use of the study drug
- unexpected,
- fatal or life-threatening

Within 15 calendar days

Any study event that is:

- associated with the use of the study drug,
- unexpected, and
- serious, but not fatal or life-threatening

-or-

- A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

- suggests a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity.

5.3.4.2 Additional reporting requirements

Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

5.3.4.3 Reporting process

Adverse events may be submitted on FDA Form 3500A, or in a narrative format. If supplied in a narrative format, the minimum information to be supplied is noted above.

5.4 Routine Adverse Event Reporting

All AEs that require expedited reporting via CTEP-AERS must also be reported in routine study data submissions (Adverse Event CRF). Routine reporting of all AEs attributed (possible, probable or definite) to lentivector transduced stem cell transplant, regardless of grade, must be reported on the Adverse Event CRF. Expected toxicities that are associated with the pre-transplant conditioning regimen (see Appendix X for full list) do not require routine reporting. All grade 3 or greater AEs, whether or not attributable to lentivector transduced stem cell transplant, will be recorded on the Adverse Event CRF.

Reporting of AEs must begin at the time of stem cell collection.

5.5 Clinical Laboratory Results

Clinical laboratory results that are outside of the institution's reference ranges must be reported as adverse events if they are deemed clinically significant by the investigator(s).

5.5.1 A clinical laboratory abnormality should be deemed clinically significant if any one of the following conditions is met:

- Is not an erroneous result as proven by repeat testing, if performed, within 48 hours.
- The laboratory abnormality is directly attributable to the lentivector transduced stem cell transplant, excluding expected toxicities that are associated with the pre-transplant conditioning regimen (see Appendix X for full list).
- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug(s), close observation, more frequent follow-up assessments, or further diagnostic investigation.
- Is associated with a serious adverse event or is otherwise judged by the Investigator to be of significant clinical impact.

In general, a laboratory abnormality that is not clinically significant will be consistent with CTCAE grade 1 (mild) or 2 (moderate) severity, as categorized by the relevant severity description in the Investigations System Organ Class (SOC) or Metabolism and Nutrition Disorders SOC. Investigators must designate laboratory abnormalities that are consistent with grade 3 or greater severity as clinically significant.

5.6 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

5.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine adverse event reporting via CDUS unless otherwise specified.

6.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 5.1. The complete product information of commercial chemotherapeutic agents to be administered as part of the protocol for stem cell transplant with BEAM or R-BEAM regimen can be found in FDA approved package insert for each agent.

6.1 Autologous CD34+ Cells Transduced with a Pre-selective Marker and Triple Combination of Anti-HIV Genes, IND Agent (NSC # 784725)

Autologous CD34+ cells transduced with a pre-selective marker and triple combination of anti-HIV genes is an investigational agent supplied to AMC investigators by GMP facility at UC Davis Medical Center.

6.1.1 Description

The final product is autologous CD34+ cells transduced with a triple combination of anti-HIV genes that will be re-suspended in participants' serum, cryopreserved and then thawed and infused directly into central vein of the participant though a central catheter, 1 day after finishing their conditioning chemotherapy. Different number of non-transduced, unmanipulated product will be co-infused similarly according to the study cohort.

Autologous CD34+ cells isolated via clinical grade magnetic cell separation from mobilized peripheral blood apheresis products of HIV-1 lymphoma will be transduced with a 1TAX lentiviral vector carrying a triple combination of anti-HIV genes, tested and cryopreserved. CD34+ cell isolation, transduction and qualification of the final product will be carried out in the UC Davis GMP facility following established Standard Operating Procedures (SOPs) and appropriate Quality Control (QC) and Quality Assurance (QA). The final product will be tested for identity, viability, purity, sterility, absence of mycoplasma and endotoxin, and for integrated transgene copy numbers per genome. A Certificate of Analysis (COA) will be generated. After completed testing, the autologous, cryopreserved product will be thawed and used for infusion into the HIV-1 lymphoma participant who has undergone a conditioning regimen.

6.1.2 GMP manufacturing, transduction, cryostorage and qualification of autologous CD34+ cells

All steps are controlled by Standard Operating Procedures (SOPs), overseen by QC and QA and are performed in a state of the art GMP facility at UC Davis Medical Center by qualified personnel.

6.1.3 The GMP manufacturing process of the cellular product consists of 7 phases

1. Receipt of donor apheresis product.
2. CD34+ cell selection.
3. In process testing (cell number, CD34+ analysis, viability).
4. Overnight transduction of the isolated CD34+ cells on a fibronectin matrix in the presence of cytokines (SCF, Flt-3 and TPO).

5. Harvesting of the transduced cells.
6. Freezing and storage of the transplantable, final product.
7. Qualification of the final product and generation of a COA (cell number, viability, sterility, endotoxin, mycoplasma, number of vector integrants per genome).

6.1.4 Transfer from the manufacturing facility to the clinical site

The fresh product will be transported to the AMC clinical sites. A validated transport container (Liquid Nitrogen, LN2 dry vapor shipper) will be used that can maintain the LN2 vapor phase temperature for at least 48 hours. Transport to the UC Davis Medical Center clinical site only takes 15 minutes. Transfer from the other sites throughout California will be done by a courier and usually within the same day. The cells will be thawed according to standard bone marrow transplant procedure SOPs and will be infused into the participant. Samples will be tested for viability. A final COA will be generated.

6.1.5 Plasmid production

Plasmid release tests: Identity (restriction enzyme digest), purity (Limulus amebocyte lysate (LAL) endotoxin assay), sequence (DNA sequencing).

Acceptance criteria: Confirmed identity (restriction enzyme digest with readout on gel, bands at appropriate positions), confirmed purity (endotoxin level below acceptable limit), and DNA base pair sequence of plasmid identical to required sequence.

6.1.6 Vector manufacturing

Vector release tests: Sterility (USP 14-day sterility according to 21CFR 610.12), LAL endotoxin assay, mycoplasma PCR, RCL (susceptible cell / cell line transductions), sequence of transferred genes (DNA sequencing), contaminating DNA (VSV-g DNA PCR).

Acceptance criteria: Sterility (USP 14 day sterility according to 21CFR 610.12) – no organisms seen, LAL endotoxin level below acceptable limit (less than 0.5 EU/mL), mycoplasma not detected by PCR, RCL not detected by HIV-1 p24 from transduction culture of susceptible cell lines and primary target cells, sequence of transferred gene identical to expected sequence, contaminating DNA within acceptable limits. In addition, stability testing (transducing titer) will be performed annually.

6.1.7 CD34+ cell isolation, culture, and transduction

CD34+ cell isolation: In process tests: Cell count, viability (dye exclusion) and CD34+ analysis using FACS.

Acceptance criteria: Viability greater than 70%, CD34+ cell content greater than 70%.

6.1.8 Labeling, receiving, storage, dispensing and return

Procedure for Labeling and Tracking the Product: The product is tracked and labeled according to FACT approved SOPs available in the clinical stem cell labs. The labels used for the product conform to current FACT standards.

Receipt of Drug Supplies: Shipping of the product is carried out in accordance to current FACT standards. The shipping container allows for controlled temperature (2-8 degrees C) to be maintained within the shipping period, the temperature is tracked using data loggers. The apheresis product slated for transduction is received in the UC Davis GMP facility with appropriate chain of custody documentation and is properly logged. The shipment is acceptable if the temperature was maintained within 2-8 deg C during shipping, and no damage to the container or its contents is visible. Chain of custody documentation is filled in and a copy of it is sent to the center that shipped the product. Transduction of the product begins immediately after receipt.

6.1.9 Stem cell transduction

The Collection of CD34+ cell may take multiple days. The product needed for the un-transduced portion of this protocol will be collected first and will be frozen and stored according to each institution's guidelines. Once the minimum required number of CD34+ cells in the product is collected, the collection for products aimed for transduction will start. The cells will be immediately transduced within 24 hours of collection each day and harvested 48 hours later. After harvest, the transduced cell population will be isolated using clinical grade CD25 antibodies coupled to magnetic beads and then cryopreserved. Multiple apheresis products may need to be collected and transduced until the required number of selected cells has been obtained. An aliquot of transduced, selected cells from each final product will be tested for viability, sterility, endotoxin, mycoplasma, vector copy number, and transduction efficiency post selection. Right before the stem cell infusion, the transduced product will be thawed, and an aliquot will be used from each bag for stability testing.

6.1.10 Storage

The cryopreserved, transduced, and selected products are stored at the cryopreservation facilities of each stem cell lab. The same FACT approved SOPs as used for cryostorage, labeling and tracking of other stem cell products apply and are modified accordingly for these research products. Storage of the products is segregated from other products designated for routine clinical use.

6.1.11 Dispensing

Criteria for final cellular product release tests

- Gram stain
- Sterility (USP 14-day sterility according to 21CFR 610.12)
- LAL endotoxin level
- Mycoplasma by PCR

- Viability (dye exclusion)
- Identity (described below)
- Potency (described below)
- Transduction efficiency (CD25 expression by flow cytometry)
- Number of vector copies (qPCR).

Acceptance criteria: Gram stain and sterility – no organisms seen, endotoxin below acceptable limits (less than 0.5 EU/mL), mycoplasma not detectable, viability greater than 70%, identity and purity-confirmed CD34+ purity greater than 70%, transduction efficiency: 1-99%, number of vector copies: less than 3 per genome.

6.1.12 Return

The cryopreserved products are shipped to the centers in an LN2 container. The shipping container allows for controlled temperature (-70 to -80 degrees C) to be maintained within the shipping period, the temperature is tracked using data loggers. Appropriate chain of custody documentation accompanies the shipment. The receiving center fills in the required portion of the chain of custody documentation, downloads the temperature data from the data logger and immediately returns a copy of the filled in document and temperature log to the UC Davis GMP facility. The shipment is acceptable if the temperature was maintained less than -140 degrees C during shipping, and no damage to the container or its contents is visible.

6.1.13 Criteria for final infused product release tests: (performed by transplant centers after thawing the product).

- Stat viability, 14-day sterility.
- Acceptance criteria: Stat viability greater than 70%.14-day sterility - no organisms seen. 14-day sterility is only available after 14 days; a positive culture action plan is followed in case of a positive culture result.

6.1.14 Stability

Vector stability will be assessed every year through the following tests: sequencing of transduced cells, transgene rearrangement/deletion PCR, levels of transgene expression, and vector titer.

The final product is stable for > 5 years.

6.1.15 Solution preparation

Final formulation will consist of a CD25+ cell enriched fraction in 70 mL bags containing 40ml total volume containing Normosol supplemented with 15% clinical grade human serum albumin and 10% clinical grade DMSO.

The product must be thawed according to institutional cellular product thawing protocols.

6.1.16 Route of administration

Intravenous infusion according to standard transplant protocols.

6.1.17 Method of administration

Intravenous infusion according to standard transplant protocols.

6.1.18 Special handling

The final CD25+/CD34+ cell product will be shipped frozen in LN2 to the respective AMC site for proper institutional cellular product thawing.

6.1.19 Side effects

No known side effects from 1TAX vector transduced cells according to the preclinical data.

6.1.19.1 Toxicities associated with conditioning regimen

Participants will receive BEAM or R-BEAM chemotherapy as a standard of care conditioning regimen for transplant. Therefore, these toxicities will not be discussed as a part of this protocol.

6.1.19.2 Gene therapy associated toxicities

Monitoring for insertional oncogenesis and clonality of hematopoiesis after gene therapy

In any gene therapy protocol using integrating lentiviruses there is a theoretical risk of insertional oncogenesis due to Replication Competent Lentivirus (RCL) or random or pseudo-random insertional mutagenesis. The latter could activate proto-oncogenes, inactivate tumor suppressor genes, or activate genes that could lead to cellular dysregulation (e.g., generation of an autocrine signaling loop). Based on our pre-clinical experience (in collectively more than 600 mice) and experience with vectors with very similar backbone in other clinical trials, we do not expect to observe gene therapy induced malignancies. However, we will routinely monitor participants for any evidence of transduced cell clonality. This is particularly important for HSCT based studies for cancer since there is an inherent increased risk of secondary malignancies in these participants (about 5-8%) due to the risk of chemotherapy, both as a treatment for controlling the malignancy and as preparative regimen for the transplant. We will routinely perform LAM-PCR every 3 months for the first 2 years of the study for vector integrants and look for evidence of increasing oligoclonality or monoclonality, defined as a 2-fold increase over two successive time points to >20% of total transduced cells. In the case that we identify oligo or monoclonality, we will initiate clinical and laboratory evaluations, including history and physical exam, blood counts, chemistries and appropriate imaging and bone marrow biopsy (if clinically indicated), sequencing of LAM-PCR product, flow cytometry with immunophenotyping of the cells and cytogenetic analyses. If none detected, then LAM-PCRs monitoring will be extended Q3 months for all

participants for additional 2 years with the prospective for lifetime routine monitoring.

Incidental production of replication-competent lentivirus (RCL) during vector production

This is highly unlikely during the vector production phase due to the design of the vector system; however, the vector product will undergo rigorous testing for RCL before release to prevent such a theoretical possibility and the incidental production of replication competent lentivirus after introduction of vector-transduced cells into the participant. RCL testing will also be done for the follow up of participants based on the FDA nonbinding recommendations:

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078723.pdf

Immune response to foreign Trim V alpha amino acid sequence

In the chimeric TRIM5α anti-HIV gene, there is a 13-amino acid patch, which is foreign to native human TRIM5α. Due to this amino acid sequence, it is possible for an antibody based immune reaction to occur against cells expressing this region. This is highly unlikely in the setting of a myeloablative bone marrow transplant when immune tolerance can be induced even against more prominent antigens such as major or minor HLA antigens. Furthermore, in our preliminary data, no immune stimulation was observed in cells pulsed with this amino acid region. Still, and in accordance with FDA guidelines, we will monitor participant serum for any chimeric TRIM5α antibody production using an ELISA test. Additional testing for cytotoxic T lymphocyte (CTL) reactivity will be performed if the ELISA test is positive. If it occurs, we do not expect a major negative effect in the participants since the immune reaction will most likely delete only transplanted cells that harbor the sequence. In the unlikely situation that the reaction eliminates other transplanted stem cells, the back-up product can be given to the participants.

6.1.20 Availability

The 1TAX vector will be available in sufficient quantity for transduction of all CD34+ cells from all 18 participants enrolled in the clinical trial.

6.1.21 Agent accountability

The product is tracked and labeled according to FACT approved SOPs available in the clinical stem cell labs. The labels used for the product conform to current FACT standards.

Shipping of the product is carried out in accordance to current FACT standards. The shipping container allows for controlled temperature (2-8 deg C) to be maintained within the shipping period, the temperature is tracked using data loggers. The apheresis product slated for transduction is received in the UC Davis

GMP facility with appropriate chain of custody documentation and is properly logged. The shipment is acceptable if the temperature was maintained within 2-8 deg C during shipping, and no damage to the container or its contents is visible. Chain of custody documentation is filled in and a copy of it is sent to the center that shipped the product. Transduction of the product begins immediately after receipt.

7.0 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I.

7.1 Screening Evaluations Required Within 8 Weeks Prior to Stem Cell Collection (unless otherwise noted)

7.1.1 Medical history, history of drug allergies, CDC HIV risk categories, history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics, and opportunistic prophylaxis should be obtained (must be on stable ART regimen for at least 3 weeks prior to enrollment in the screening segment).

7.1.2 Physical examination, including performance status (see Appendix II), vital signs (height, weight, body surface area), neurological exam, and physical staging of the disease as appropriate for the participant's lymphoma.

7.1.3 Chest X-ray (CXR)

7.1.4 Staging by a CT or a combined PET + CT is required for this study

7.1.5 EKG

7.1.6 PFTs; DLCO, FEVI, FVC (within 4 weeks prior to study enrollment)

7.1.7 Cardiac ejection fraction (by 2D ECHO or MUGA scan) (within 4 weeks prior to study enrollment)

7.1.8 Bone marrow biopsy and aspirate with flow cytometry for pathology

7.1.9 Laboratory tests, including:

7.1.9.1 Assessment for Cytomegalovirus immunoglobulin (CMV IgG) and CMV quantitative PCR.

7.1.9.2 Assessment for Hepatitis A antibody, Hepatitis B core antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody, and Hepatitis C antibody (within 3 weeks prior to study enrollment).

If Hepatitis B core antibody or Hepatitis C antibody is positive, complete Hepatitis B DNA PCR and Hepatitis C DNA PCR

7.1.9.3 Assessment for Herpes simplex virus (HSV) 1 & 2 IgG and PCR

7.1.9.4 Assessment for Toxoplasma immunoglobulin G (IgG)

7.1.9.5 Assessment for Varicella zoster virus immunoglobulin G (VZV IgG)

7.1.9.6 Assessment for Syphilis, Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL)

7.1.9.7 Assessment of HIV-1 and Human T-lymphotropic virus antibodies

7.1.9.8 Assessment of Creatinine Clearance (within 3 weeks prior to study enrollment)

7.1.9.9 Complete blood count (CBC) with differential, Platelet Count, comprehensive metabolic panel (CMP), Lactic Acid Dehydrogenase (LDH), and Uric Acid

7.1.9.10 Assessment of CD4 count

7.1.9.11 Assessment of Quantitative immunoglobulins (IgM, IgG, and IgA)

7.1.9.12 Serum pregnancy test for women of childbearing potential

7.1.9.13 Assessment of PT/PTT or INR/PTT (within 3 weeks prior to study enrollment)

7.1.9.14 HIV-1 RNA viral load to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory). (The HIV viral load assay must detect at minimum viremia < 50 copies/mL by RT-PCR) (within 6 months prior to study enrollment; see Section 3.1.2.2).

7.1.10 Optional donation to the AIDS and Cancer Specimen Resource (ACSR). (See Appendix IV for ACSR Informed Consent Form and Appendix III for ACSR Specimen Preparation and Shipping Instructions).

7.1.11 CCR5-tropism assay (We will use both commercially available assays (i.e., phenotypic assay performed by Monogram Biosciences and the genotypic assay performed by Quest Diagnostics) (See Appendix IX).

7.1.12 Immunology assays (correlative study, see Appendix I and Appendix VII).

7.1.13 DNA monitoring assays (correlative study, see Appendix I and Appendix VII).

7.1.14 Virology assays (correlative study, see Appendix I and Appendix VII).

7.2 Screening Evaluations required within 1 week of admission for stem cell transplant

7.2.1 Medical history, history of drug allergies, history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics, and opportunistic prophylaxis should be obtained.

7.2.2 Physical examination, including performance status (see Appendix II), vital signs (height, weight, body surface area), neurological exam, and physical staging of the disease.

7.2.3 CXR

7.2.4 Complete blood count (CBC) with differential, Platelet Count, comprehensive metabolic panel (CMP), Lactic Acid Dehydrogenase (LDH), and Uric Acid

7.2.5 Assessment of CD4 count

7.2.6 HIV-1 RNA viral load to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory). (The HIV viral load assay must detect at minimum viremia < 50 copies/mL by RT-PCR).

7.3 Required on the day of admission for transplant prior to start of chemotherapy

7.3.1 Medical history, history of drug allergies, history of current and past anti-retroviral regimens, if available; and history of any prior AIDS-defining conditions. Date of initial lymphoma diagnosis is required, with a copy of the pathology report in the medical record. Current concomitant medication list, including all anti-retroviral, anti-viral, antibiotics, and opportunistic prophylaxis should be obtained.

7.3.2 Serum pregnancy test for women of childbearing potential.

7.3.3 Basic immune assessment (i.e., CD4, CD8, and IgG) will be collected at the participating site.

7.4 Evaluations During Treatment

All the procedures in association with the transplant that are mentioned below will be performed based on each institute clinical protocols and SOPs. See Section 4.0 for the Treatment Plan.

7.4.1 Performance of apheresis procedure.

7.4.2 Conditioning (BEAM or R-BEAM) regimen to treat HIV-1-related lymphoma.

7.4.3 Treatment of conditioning regimen associated side effects such as nausea, diarrhea, mucositis, neutropenia fever, etc., and,

7.4.4 Prophylactic antibiotic choice and duration for fungal, viral, bacterial, and parasitic infections. Any deviation from the standard of care needs to be reported to the study PI in AdvantageEDC^{SM} and will be reviewed by the AMC DSMB when reviewing all participants on the cohort.

7.5 Post-Treatment Follow-up Evaluations

The schedule of follow up is shown in detail in Appendix I and Table 4-A and is summarized in the table below. During each follow up, in addition to regular history and physical exam, participants will be evaluated for study related side effects, status of their lymphoma and the status of HIV-1 using appropriate tests. Assessments during strategic ART withdrawal will be on a weekly basis and may be performed remotely, as described in Appendix XI. If required clinical and laboratory assessments (physical exam, medical history and medical review, toxicity assessments, CD4/CD8 counts and HIV VL) during ART withdrawal overlap with required post-treatment follow-up evaluations then these assessments do not need to be repeated.

Table 7A: Follow-Up Schedule

Study Visit	Target Day Post-Transplant
1 week	7 ± 3 days
2 week	14 ± 3 days

Study Visit	Target Day Post-Transplant
3 week	21 ± 3 days
4 week	28 ± 3 days
6 week	42 ± 3 days
2 months	60 ± 3 days
3 months	90 ± 3 days
4 months	120 ± 3 days
6 months	180 ± 10 days
8 months	240 ± 10 days
10 months	300 ± 10 days
12 months	360 ± 10 days
14 months	420 ± 20 days
16 months	480 ± 20 days
18 months	540 ± 20 days
20 months	600± 20 days
22 months	660 ± 20 days
24 months	720 ± 20 days

7.5.1 Update medical history. History to include concomitant medication changes, and any signs and symptoms. Adverse event assessment (adverse events must be recorded in AdvantageEDC^{SM} as per Section 5.4).

7.5.2 Physical examination, including performance status (see Appendix II), vital signs (height, weight, body surface area), neurological exam at every follow-up visit.

7.5.3 Toxicity assessment

7.5.4 Assessment of engraftment.

Note: this assessment will stop after 2 months. However, assessment of anti-HIV-1 transduced clonal cell expansion will continue as a part of correlative studies for the entire period of follow-up.

7.5.5 Restaging by a CT or a combined PET + CT, at 3, 6, 12, and 24 months' time points. See Section 8.1 and Section 8.2 for response parameters and frequency of response evaluations.

7.5.6 For participants with bone marrow involvement by the lymphoma: Bone marrow biopsy and aspirate with flow cytometry in participants to assess marrow as a part of restaging at 3 months and 12 months timepoints.

7.5.7 Laboratory tests, including:

7.5.7.1 Assessment for Cytomegalovirus by CMV quantitative PCR weekly for the first month post-transplant, and then at 2, 4, and 6 months post-transplant.

7.5.7.2 Complete blood count (CBC), comprehensive metabolic panel (CMP), Lactic Acid Dehydrogenase (LDH), and Uric Acid

7.5.7.3 Basic immune reconstitution assays, CD4 and CD8, and IgG levels. Performed at 4 weeks post-transplant; and at 2, 3, 4, 6, 8, 10, 12, 18, and 24 months post-transplant.

7.5.7.4 HIV-1 RNA viral load to be assessed by any FDA-approved viral load assay (evaluated at the local laboratory). The HIV viral load assay must detect at minimum viremia < 50 copies/mL by RT-PCRHIV viral load will be performed at 4 weeks, 3, 6, 8, 10, 12, 14, 16, 20, and 24 months post-transplant.

7.5.8 Correlative studies

For a complete list of correlative studies and their timeline see the study calendar (Appendix I) and also the tables on correlative section (Appendix VII).

7.5.8.1 Virology studies:

Blood samples will be collected at 2 and 10 weeks and then 6, 12- and 24-months post-transplant for HIV reservoir characterization. These studies will include quantitative PCR analysis of PBMC-associated HIV DNA, RNA (including unspliced and multiply spliced forms) and 2-LTR circles. In addition, single genome sequencing of HIV gp120 and HIV pol will be performed to understand sequence evolution following transplantation and detection of minority resistance variants. Single-copy HIV from plasma will also be determined at each of these time points.

7.5.8.2 GI biopsy (optional) will be performed voluntarily at 6 months post-transplant (or when CD4 count reaches above 300 cell/mm^3) and will be repeated two months after the first GI biopsy. The University of California San Francisco is conducting a cohort study called SCOPE that also includes an optional intestinal biopsy. The SCOPE study is an observational, prospective study of HIV-1 infected volunteers designed to provide a specimen bank of samples with carefully characterized clinical data.

Specimens banked as part of the SCOPE study will be used to examine questions involving virologic, immunologic, and host factors involved in HIV-1 infection, progression, non-progression, response to treatment, control of HIV-1 virus, and evolution of drug resistance. If participants choose to co-enroll in the SCOPE study at the same time as this study and agree to optional GI biopsies, then we will use their intestinal biopsy results for both studies. SCOPE is a separate study and requires a separate consent form. Participation in SCOPE is not a requirement of this study.

7.5.8.3 DNA and flow cytometry-based monitoring studies and assessment of anti-HIV-1 transduced clonal cell expansion and insertional mutagenesis and flow cytometric based assays for CD25 expression on CD34+ lymphoid and non-lymphoid immune cell populations. These studies will be performed at 2 weeks and then, 1, 2, 4, 6, 8, 10, 12, 18, and 24 months post-transplant.

7.5.8.4 Monitoring for immune response to TRIM5α. These studies will be performed at 1, 2, 6, 12, 18, and 24 months post-transplant.

7.5.8.5 Monitoring for mixed lymphocyte reactions: to determine whether unmodified, post-SCT PBMC recognize and kill engrafted, modified cells, a mixed lymphocyte reaction will be performed using post-SCT PBMCs obtained when more than 50% drop in chimerism of transduced cells in PB is determined. PBMC will be mixed with pre-SCT modified stem cells (generated from remaining CD34+ depleted CD4+ T cells from pre-SCT leukapheresis). Gene modified cell killing and markers or T and NK cell activation and function will be determined in the ex vivo experiments using flow cytometric analysis.

7.5.8.6 Immunological studies. These studies will be performed at 3, 6, 12, and 24 months post-transplant.

7.5.8.7 Optional bone marrow biopsy and aspirate at 3 and 12 months will be performed for research in participants without bone marrow involvement and that consent to optional studies.

7.6 Discontinuation Evaluations

7.6.1 Early discontinuation. Participants who discontinue protocol treatment early for any reason should have the following evaluations and laboratory tests within 30 days of discontinuation:

7.6.1.1 History and physical exam and assessment of adverse effect.

7.6.1.2 Laboratory evaluation for CBC, LDH, uric acid, and CMP.

7.6.1.3 CT or PET CT and bone marrow biopsy and aspirate with flow cytometry for participants with bone marrow involvement for documentation of disease staging. See Section 8.1 for response parameters.

7.6.1.4 Basic immune reconstitution assay (i.e., CD4, CD8 counts and IgG levels).

7.6.1.5 Correlative studies: immune reconstitution, virologic, and specialized immunologic and DNA monitoring studies.

7.6.1.6 Optional bone marrow biopsy and aspirate for participants without bone marrow involvement that consent to optional studies.

7.6.2 Off-study evaluations. Participants who complete all treatment per-protocol should have the following evaluations and laboratory tests within 30 days of discontinuation:

7.6.2.1 History and physical exam and assessment of adverse effect.

7.6.2.2 Laboratory evaluation for CBC, LDH, uric acid, and CMP.

7.6.2.3 CT or PET CT and bone marrow biopsy and aspirate with flow cytometry for participants with bone marrow involvement for documentation of disease staging. See Section 8.1 for response parameters.

7.6.2.4 Basic immune reconstitution assay (i.e., CD4 and CD8 counts, and IgG levels).

7.6.2.5 Correlative studies: immune reconstitution, virologic, and specialized immunologic and DNA monitoring studies.

7.6.2.6 Optional bone marrow biopsy and aspirate for participants without bone marrow involvement that consent to optional studies.

7.6.2.7 Follow for survival if stop during 2-year post-treatment (Section 4.7)

7.7 Post-Study Follow-up

At the completion of all follow-up evaluations described in Section 7.5 or Section 7.6, the Off-Study Summary Form should be completed in AdvantageEDC.

Follow for survival if stop during 2-year post-treatment (Section 4.7)

Based on the FDA requirements for gene therapy protocols, for all participants on this study who received the gene-modified stem cells, whether they completed the study or came off the study early, all participants will be monitored for 15 years post-transplantation. The study team at each respective institution will make yearly phone calls to the participants' primary care physician, their oncologist, or their HIV physicians to fill out a simple questionnaire about participant health, HIV status, and development of any other cancer or clonal abnormality.

For years 3-15, with participant consent, optional blood samples will be collected for HIV viral load, DNA, and immunological studies to monitor HIV and for research on vector parameters.

8.0 MEASUREMENT OF EFFECT

8.1 Response Parameters

The Lugano Classification by Cheson DB, et al., 2014 (36) will be used for response assessments.

- Time to Tumor Response (TTR): time from the first study treatment until documentation of first objective response.
- Response Duration: time from first documentation of response to documentation of first relapse or progression.
- Duration of CR: time from the first documentation of CR until first date that relapsed or progressive disease is objectively documented.
- Progression-Free Survival (PFS): time from start of study treatment to relapse, progression, or death from any cause, whichever occurs first. For this endpoint, persistent disease (not meeting criteria for progression) is not considered a failure. Participants who receive anti-cancer therapy other than the study drug (including consolidative radiation therapy or BMT) will be censored for all endpoints other than overall survival, including toxicity, response, and PFS.
- Overall Survival (OS): time from start of study treatment to death.

8.2 Frequency of Response Evaluation

- Physical examination for any evidence of disease relapse should occur at the time of each history and physical exam.
- In the absence of evident disease progression, response will be assessed formally at 3, 6, 12- and 24-months post-transplant per study calendar.
- F-FDG-PET/CT or CT scan is required for restaging of lymphoma.
- one marrow biopsy and aspirate with flow cytometry are required at 3 and 12-months post-transplant for all participants with bone marrow involvement at baseline. Additional bone marrow biopsy maybe required based on the discretion of participants' physicians.

8.3 Safety Measures

All AEs will be monitored by ongoing review of reported adverse events by the protocol chair and the AMC Operations and Data Management Center, and will be discussed during the monthly investigators' Lymphoma Working Group conference calls (see Section 9.3 for rules for early study termination).

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

Each cohort will enroll 3 participants but can be extended to 6 participants if recommended by DSMB (this will occur only if there is a treatment failure either from failure to engraft or from Grade 3 or 4 toxicities, excluding alopecia).

The **primary endpoint** of the study is:

- Safety defined as timely engraftment (the collective establishment of a persistent absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 20,000 cells/mm^3 for 3 consecutive days) at one-month post-transplant, in the absence of any study candidate-specific grade 3 and 4 non-hematopoietic organ toxicity, excluding alopecia, or any clonal expansion.

The **major secondary endpoints** of the study are:

- The efficacy of the candidate product, defined as establishment of > 5% mononuclear blood cells expressing anti-HIV genes in the peripheral blood at 3 months post-transplant.

  The 5% threshold of the study has been set by our external advisory committee based on the outcome of previously performed clinical trials with similar vectors. However, we expect to have much higher levels of engraftment of our product based on high vector titer levels, new selection method for harvesting only transduced stem cells, improved and novel method of transduction, and the new sequence of transduction followed by freezing that has provided a significant improvement in our transduction efficiency.

- To determine the presence, quantity, and duration of gene modified HIV-1 resistant peripheral blood cells and gut mucosal immune cells; and

- To study the integration sites of vector sequences in circulating cells.

In addition, the following minor endpoints will be studied as secondary endpoints:

- Progression-free survival
- Overall survival
- Complete response rate and duration
- Partial response rate and duration
- Time to neutrophil engraftment (first measurement of 3 consecutive laboratory values obtained on different days) of ANC > /= 500 cells/mm^3)
- Time to platelet engraftment (first measurement of 3 consecutive laboratory values on obtained different days) of platelets > /= 20,000 cells/mm^3 without platelet transfusions 7 days prior)
- Hematologic function at Day 100 (ANC > 1500, Hb > 10g/dl without transfusion, and platelets > 100,000.
- CD4 recovery at the conclusion of the study

- Safety in terms of toxicities, infections, transfusions, and infusion-related reactions
- HIV-1 viral load over time
- Persistence of vector-transduced cells over time

The **exploratory endpoint** of this proposal is to evaluate the presence and the magnitude of expansion of HIV-1 resistant immune cells in the peripheral blood and gut mucosa of transplanted participants, subsequent to withholding ART.

9.2 Sample Size/Accrual Rate

A minimum of 2 and a maximum of 18 participants will be enrolled in the study, with more than 7 participants being enrolled only if one or more participants in a cohort experience failure of engraftment or Grade 3 or 4 toxicity, excluding alopecia. The accrual rate is anticipated to be 1 participant per month.

With a sample size of 7, any toxicity occurring in as much as 20% of this patient population has a 79% chance of being seen in at least one of the participants in the study, and a toxicity occurring in as much as 10% of the population has a 52% chance of being observed in at least one participant.

Toxicity will be summarized as the proportion experiencing a given toxicity or group of toxicities, at or above a specified level of severity, with exact 95% CIs. The analysis set for toxicity will be participants who enrolled and received at least one active treatment with gene therapy.

9.3 Early Stopping Rules

The AMC DSMB is responsible for assessing trial data for dose escalation/cohort expansion and evaluating the stopping rules for this study. The composition and role of the AMC DSMB in this clinical trial is defined in the AMC DSMB charter. Based on pre-IND discussions with FDA, the following short term (day 30) and long term (day 90) stopping rules will be evaluated:

- Lack of timely hematopoietic engraftment in two out of 6 participants, within the first 30 days after stem cell infusion (as defined in Section 1.2). If this rule is met in cohort 3 (2.0×10^6 cells/μL), the DSMB will evaluate whether it is safe for the trial to proceed on cohort 3+ (3.0×10^6 cells/μL).
- Grade 3/4 non-hematopoietic toxicity, excluding alopecia, directly associated with the gene therapy product in two out of 6 participants in each cohort within the first 90 days of the trial.
- Death of one participant directly related to the gene therapy product (e.g., death due to lack of engraftment after day 20, but before day 30).

9.4 Cohort Escalation Design

The dose escalation in this trial is based on the increasing ratio of the administrated transduced product to untransduced mobilized peripheral stem cells. Please see the clinical trial design section for the details of dose escalation in each cohort.

9.5 Analysis of Secondary Endpoints

Secondary and exploratory endpoints will be summarized descriptively. Efficacy rates will be summarized by the proportion of participants who meet the criteria for efficacy (defined in Section 9.1), with 95% exact binomial confidence intervals (CIs). For dichotomous endpoints (e.g., the presence of gene modified HIV resistant peripheral blood cells and gut mucosal immune cells, complete response) the frequency, proportion, and exact 95% confidence interval for proportion will be calculated. Continuous measures (e.g., quantity and duration of gene modified HIV resistant peripheral blood cells and gut mucosal immune cells) will be summarized by mean (SD) and median (range), with log transformation if necessary, for skewed measures, as would be typical for cell counts. Time-to-event data (e.g., overall survival, progression free survival, duration of response) will be presented graphically by Kaplan-Meier plots and summarized by estimated median time to event (if that is estimable from the data) with 95% confidence interval.

Separate inferences for the three cohorts will not be possible, given the limited sample size, but descriptive summaries will be prepared for key variables to inform decisions about the next stage of clinical trials.

9.6 AMC Policy for Monitoring of Phase II Trials

This protocol will follow the AMC's policy for data monitoring (See Appendix VI), which serves to assure that:

- Only participants who meet the study eligibility criteria are enrolled.
- The informed consent process is conducted appropriately.
- Data is collected and analyzed as specified in the protocol.
- Adverse events are reviewed promptly and reported as required.
- Privacy and confidentiality of study participants are maintained.

Independent Data and Safety Monitoring Board

All gene therapy protocols according to NIH and FDA guidelines are included in the "high risk" category and therefore require a Data and Safety Monitoring Board (DSMB) for assessing the risk to the patient population. The AMC DSMB will be used as an independent group to monitor the potential efficacy and/or toxicities of the protocol. The members of the DSMB (at least 6 members) will be chosen with appropriate broad spectrum of expertise, including biostatisticians, HIV experts, gene therapy experts, bioethics experts, HIV patient advocates, and lay members. They will set the guideline to assess the study risk by description of anticipated adverse events, adverse event grading and plans for reporting adverse events. They will also institute a safety-monitoring plan

The AMC DSMB will be given a report by the PI(s) indicating the number of participants who have enrolled, a list of all adverse events, and the results of clinical measures. The AMC DSMB will review the safety data for the participants in each cohort after the 30 days post-transplant follow up period to identify whether DLT occurred, and if a decision should be made to proceed with the study for the subsequent participants according to the DLT definition and dose escalation rules in Section 4.3. At the time of each review, the AMC DSMB will be asked to recommend continuation or discontinuation of the trial. If, in the opinion of the AMC DSMB there is any indication of compromise of the safety of

the participants, the AMC DSMB will contact the PI(s) and the study will be halted.

10.0 ROLE OF DATA MANAGEMENT

10.1 CRF Instructions

Access to the internet data entry system for this study, AdvantageEDC[SM], and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.amcoperations.com. Participating institutions are responsible for submitting data and/or data forms via AdvantageEDC[SM] in accordance with the AMC Data Entry Guide and specific form instructions and in compliance with 21 CFR 11, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

10.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix VI, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

10.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Food and Drug Administration (FDA) regulations (21 CFR Part 50 and 56) and Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46), as well as the International Conference on Harmonization guideline for Good Clinical Practice E6 (R1) and Declaration of Helsinki must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before participant enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IRB according to local procedures. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature and significance of the risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

11.2 Multi-Site Research

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals will be obtained at each site (including approval by the site's IRB of record and Institutional Biosafety Committee as applicable).
- All modifications will be approved by FDA first and they will be communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented.

- All engaged participating sites will safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The DSMB will communicate the information below to all the engaged participating sites:

- Problems.
- Interim results.
- The closure of a study.

11.3 Data Management and Confidentiality

Provisions to protect the privacy interests of participants

Prior to study enrollment, participants will be contacted by a member of the research team in a private setting such as the clinic exam room. The research team will explain the study treatment, procedures, and the timing of each to the participants. The participants will be offered the opportunity to ask questions. After study enrollment, participants' privacy interests will be respected at all times, and requests for specific privacy requirements will be met if at all possible, taking into consideration the study protocol requirements and the participants' welfare.

HIPAA

A HIPAA authorization will be obtained for every participant (or Legally Authorized Representative, if applicable) enrolled to the study, and it will be done at the time the participant is consented to the study. The HIPAA Authorization approved by the UC Davis Compliance Office or the participating site's compliance office will be used.

After a study participant has signed a study-specific HIPAA authorization and an IRB-approved study consent form, the research team is permitted to access all sources of their medical information and protected health information (PHI). This includes the participant's electronic medical record (EMR) as well as any scans or medical/PHI documentation in paper form.

Privacy risks

The Sponsor-Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

Data and/or specimens will be labeled with a code that the research team can link to personal identifying information when acquired. The code sheet will be secured and kept separate from the dataset.

The researchers will store study records and other information in a secure location and will grant access only to those with a need to know. However, just like with other personal information kept by health care providers, banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands,

it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.

11.4 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB of the treating institution. A copy of the written approval of the IRB must be sent to the ODMC.

11.5 Vulnerable Populations

This study is not designed to enroll any participants from the following vulnerable populations: pregnant women, neonates, prisoners, persons who have not attained the legal age for consent to treatments or procedures involved in the research, or cognitively impaired adults.

11.6 Non-English-Speaking Participants

Non-English-speaking participants are not excluded from participation in this trial. For potential participants who do not speak English, local IRB policy for translation of informed consent forms and/or documentation of a short form consent must be followed.

11.7 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 11-A: Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	1	+	3	=	4
Not Hispanic or Latino	1	+	13	=	14
Ethnic Category: Total of all participants	2	+	16	=	18
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	1	=	1
Black or African American	1	+	3	=	4
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	1	+	11	=	12
Racial Category: Total of all participants	2	+	16	=	18

11.8 Compensation for Research-Related Injury

Participants are instructed that it is important they promptly tell the person in charge if they believe that they have been injured because of taking part in this study. For participants who are injured as a result of being in this study, individual institutions will provide necessary medical treatment based on their own policies. Depending on the circumstances, the costs of the treatment may be covered by the University or the study sponsor or may be billed to the participant's insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

11.9 Economic Burden to Participants

Standard of care and other routine costs involved with this study will be billed to the participant or the participant's insurance carrier, Medicare, or Medi-Cal, where appropriate. These costs are consistent with the routine care participants would receive outside of the study and may include standard medical tests and examinations (such as blood work and physical exams, pharmacy charges, scans, etc.). Whenever possible, preauthorization will be obtained. If the costs are not covered, these costs will be discussed with the participant prior to proceeding with the study. The participant will be responsible for any costs not covered by his/her insurance.

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APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study.

App – 1A: Pre-Transplant Screening; Mobilization Period

Required Studies/Testing	Within 8 Weeks Prior to Enrollment (Stem Cell Collection)	Within 1 Week Prior to Admission for Transplant	On the Day of Admission for Transplant Before Start of Chemotherapy
History & Physical with assessment of physical staging of the disease, Height and Weight, BSA, neurologic examination, review of current and prior anti-retroviral regimens, concomitant medications, and history of any AIDS defining conditions	X	X	X
Hepatitis Panel[5] (HAV Ab, HBsAg, HBcAb HBsAb, Hepatitis C Ab), HSV 1 & 2 IgG and PCR, Toxoplasma IgG, VZV IgG, Syphilis (RPR or VDRL), HIV-1 and HTLV antibody	X		
CXR	X	X	
EKG	X		
PFTs; DLCO, FEVI, FVC[4]	X		
Creatinine Clearance[5]	X		
CMV Immunoglobulin level and CMV quantitative PCR	X		
Bone marrow biopsy and aspirate with flow cytometry for pathology	X		
HIV-1 RNA[10], CD4 Count	X	X	
HepB DNA PCR and HepC DNA PCR[1]	X		
Cardiac Ejection Fraction (by 2D ECHO or MUGA scan)[4]	X		
B –HCG Test for Females of Childbearing Potential	X		X
Quantitative immunoglobulins (IgM, IgG, and IgA)	X		
Staging CT or PET CT	X		
Karnofsky Performance Score/ECOG Performance Status	X	X	
CBC with differential, Platelet Count, CMP, LDH and Uric acid	X	X	
CCR5-tropism assay[2]	X		
Immune reconstitution assays, basic[3]			X

Required Studies/Testing	Within 8 Weeks Prior to Enrollment (Stem Cell Collection)	Within 1 Week Prior to Admission for Transplant	On the Day of Admission for Transplant Before Start of Chemotherapy
PT/PTT assessment[5]	X		
Immunology assays, correlatives[8]	X		
DNA monitoring assays, correlatives[9]	X		
Virology assays, correlatives[8]	X		
Banking of CD34+ depleted PBMC from apheresis samples[6]	X		
Optional donation to the ACSR[7]	X		

1- Only if the core Ab is positive for HepB or the HepC Ab is positive, respectively.

2- We will use both commercially available assays (i.e., phenotypic assay performed by Monogram Biosciences and the genotypic assay performed by Quest Diagnostics) (See Appendix IX).

3- CD4, CD8, and IgG will be collected at the participating site as standard of care.

4- To be collected within 4 weeks prior to study enrollment.

5- To be collected within 3 weeks prior to study enrollment.

6– CD34+ depleted cells obtained from GMP Facility.

7– See Appendix IV for ACSR Informed Consent and Appendix III for ACSR Specimen Preparation and Shipping Instructions.

8- On all visits where immunological and viral correlatives are to be completed, 40 mL of blood (total) will be drawn in lavender top (EDTA) tubes and 5 mL of blood will be drawn in red top tubes.

9- On all visits where DNA monitoring correlatives are to be completed, 20 mL of blood will be drawn in lavender top (EDTA) tubes.

10- Within 6 months before study enrollment. See Section 3.1.2.2.

App – 1B: Post-Transplant Follow Up

Study Assessments/Testing Post Transplant	Weeks Post-HCT					Months Post-HCT													Discontinuation Early Disc., and Off-Study	Years Post-HCT[6]
	1	2	3	4	6	2	3	4	6	8	10	12	14	16	18	20	22	24	Within 30 days of discontinuation	3-15, once/yr
History & Physical, including performance status, height, weight and BSA, neurological exam, concomitant medication review, and Toxicity Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of engraftment	X	X	X	X	X	X[4]														
CBC, LDH, Uric Acid, CMP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CT or PET-CT restaging							X		X			X						X	X	
Required bone marrow biopsy and aspirate with flow cytometry (for restaging), if bone marrow involvement at baseline[2]							X					X							X	
Optional bone marrow biopsy and aspirate with flow cytometry (for research) for those without bone marrow involvement at baseline[2]							X					X							X	
GI biopsy									X[5]	X[5]										
Immune Reconstitution Assays, basic[1]				X		X	X	X	X	X	X	X			X			X	X	X[10]
Immune Reconstitution Assays, correlative studies							X		X			X						X	X	
CMV PCR	X	X	X	X		X		X	X											
HIV-1 viral load				X			X		X	X	X	X	X	X		X		X	X	X[10]
Virologic and specialized immunologic assays, correlative studies[3,8]		X				X[7]			X			X						X	X	X[10]
DNA monitoring, correlative studies[4,9]		X		X		X		X	X	X	X	X			X			X	X	X[10]

Study Assessments/Testing Post Transplant	Weeks Post-HCT					Months Post-HCT													Discontinuation Early Disc., and Off-Study	Years Post-HCT[6]
	1	2	3	4	6	2	3	4	6	8	10	12	14	16	18	20	22	24	Within 30 days of discontinuation	3-15, once/yr
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Telephone follow-up for HIV status and development of secondary malignancies																			X	X[6]

1. At these time points basic immunological tests (i.e., CD4, CD8, and IgG will be done). If collection timepoints overlap with collections as part of ATI / ART resumption, then labs will not need to be repeated.
2. Bone marrow biopsy and aspirate with flow cytometry will be performed as a part of restaging for participants with bone marrow involvement by the lymphoma. Optional bone marrow biopsy and aspirate with flow cytometry will be performed for participants without bone marrow involvement that consent to optional studies.
3. Samples will be collected and stored for possible HIV-1 nucleotide sequence analyses for ART drug resistance; Samples will also be collected and stored to explore the impact of anti-HIV transduced stem cells on genetic makeup of HIV-1 populations (e.g., co-receptor usage, genetic changes in tat or TRIM5α targets). If needed, we will use both commercially available assays (i.e., phenotypic assay performed by Monogram Biosciences and the genotypic assay performed by Quest Diagnostics).
4. Assessment for hematological engraftment will stop at 2 months. However, assessment of anti-HIV-1 transduced clonal cell expansion will continue as a part of correlative studies for the entire period of follow up.
5. GI biopsies (upper endoscopy) will be offered to all the participants of the study as a voluntary option at 6 months post-transplant (or when CD4 count reaches above 300 cell/mm^3) and will be repeated in two months after the first GI biopsy.
6. The follow-up in years 3-15 will be performed by phone calls to participants or their health care provider. The telephone contact for follow-up is not required for participants who discontinue protocol treatment early for any reason (early discontinuation) but is required for participants who complete all treatment per-protocol.
7. To be collected at 10 weeks post-transplant.
8. On all visits where immunological and viral correlatives are to be completed, 40 mL of blood (total) will be drawn in lavender top (EDTA) tubes and 5 mL of blood will be drawn in red top tubes for immunological studies and 40 mL of blood (total) will be drawn in lavender top (ETA) tubes for viral studies.
9. On all visits where DNA monitoring correlatives are to be completed, 20 mL of blood will be drawn in lavender top (EDTA) tubes.
10. Participants that consent to optional studies will have blood samples (30 mL) collected to monitor the participant's HIV and vector parameters.

App – 1C: Analytic Treatment Interruption

The schedule during the ATI period will be defined by clinical course and the characteristics of any virus rebound. ART will be initiated for clinical events, sustained drop in CD4+T cell counts or sustained increased in viremia as described in Section 2.4.1. Prior to these events, participants will be followed. If required clinical and laboratory assessments (physical exam, medical history and medical review, toxicity assessments, CD4/CD8 counts and HIV VL) during ART withdrawal overlap with required post-treatment follow-up evaluations then these assessments do not need to be repeated. Clinical assessments, and ATI counseling may be performed remotely to minimize in-person visits during the ATI.

Assessments	**Within One Week Prior to ATI**	**Weeks 1-12**	**Extended ATI (Weeks 13+)**	**Post ATI[1]**			
		Weekly	**Weekly**	**ART Resumption**	**W4**	**W8**	**W24**
COVID Testing[2]	X						
ATI		X	X				
Clinical Assessments[3]		X	X	X	X	X	X
T cell counts (CD4 and CD8)		X	X	X	X	X	X
HIV Viral Load[4]		X	X	X	X	X	X
Plasma and PBMCs[5]				X	X	X	X
Pre-ATI counseling and disclosure[6]	X						
Ongoing ATI counseling[6]		X	X				

1. Once ART is restarted, participants will be followed at the time of ART restart, and at 4, 8, and 24 weeks after restart.
2. Participants will be tested for the virus that causes COVID-19. If the test is positive, participants will remain on ART until they recover, and the study team approves them to proceed with ATI. Participants on ATI will be offered COVID testing periodically or if symptoms develop. ART will be restarted if participants test positive for COVID-19 by PCR.
3. Clinical assessments include: review of medical history, review of concomitant medications, performance status, height, weight, body surface area, neurological exam, and toxicity assessment.
4. During ATI participants with an initial viral result greater than 400 copies/mL must have repeat testing within 3 business days. Participants will be evaluated every four weeks between weeks 8 and 24 until the viral load is confirmed to be less than the level of quantification.

5. Plasma and PBMCs will be collected in four (4) 10 mL EDTA tubes and cryopreserved at the time of ART resumption and at Weeks 4, 8 and 24 on ART.
6. Participants must be provided the participant HIV interruption participation disclosure sheet (Appendix XII) and have pre-ATI counseling performed (Appendix XI) prior to ATI. ATI risk mitigation counseling must be performed weekly during ATI.

App – 1D: Sample Collection guidance

Correlative Laboratory	Baseline	2 Weeks	4 Weeks	2 Months	10 Weeks	3 Months	4 Months	6 Months	8 Months	10 Months	12 Months	18 Months	24 Months	Discont.r	Follow-up Years 3-5
Immunology (Pollard Lab)															
DNA (Anderson Lab)															
Virology (Henrich Lab)															
Optional GI Biopsy[1], [2] (Pollard Lab)								**X**	**X**						

CCR5-Tropism assays (Monogram Bioscience)															
Optional Bone Marrow Biopsies[3]															

1 Participants must sign the separate consent form to participate in these optional studies

2 If the participant's CD4 count is not >300 cells/mm3 at the 6-month timepoint, GI biopsies may be delayed until the participant's CD4 count has reached 300 cells/mm3, and biopsies will be repeated 2 months after the first collection.

3 For participants with bone marrow involvement at baseline that consent to optional collections.

KEY:

5mL redtop tube

4mL purple top (EDTA) tube

10mL purple top (EDTA) tube

APPENDIX II: PERFORMANCE STATUS SCALES

Karnofsky Performance Scale		ECOG Performance Status Scale	
Percent	**Description**	**Grade**	**Description**
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead.	5	Dead.

APPENDIX III: AIDS AND CANCER SPECIMEN RESOURCE (ACSR) SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

A. GENERAL

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website: www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Mondays** through **Wednesday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON FRIDAYS OR SATURDAYS** in the ACSR.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

Blood specimens

Draw two 8.5 cc (mL) yellow top [acid citrate dextrose (ACD)] tubes from study participant. With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 097
- AMC Participant ID#
- Date and time of collection
- Specimen type, (i.e., WB=Whole Blood, P=Plasma, S=Serum, or Tissue)
- Specimen purpose: Donation

Specimen shipment

- Seal the tops of the two 8.5 cc yellow tops with parafilm.
- Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and “self-seal.”
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Affix the FedEx airbill on blank side of the shipper making sure that it is marked “FedEx PRIORITY OVERNIGHT.”
- Mark “OTHER” in the airbill under “Packaging.” Please use the FedEx # available on the AMC member’s only website.

- Under airbill section "Special Handling" indicate, "YES-SHIPPERS DECLARATION NOT REQUIRED."
- Place "From/To" information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

Sylvia Silver, DA

GW Biorepository

George Washington Medical Center

Ross Hall, Room 118

2300 I St, NW

Washington, DC 20037

Phone: (202) 994-2945

Fax: (202) 994-5056

Email: ssilver@gwu.edu

- Make certain that shipper is already either pre-labeled with 'UN#3373' stamp or make a paper label with 'UN#3373" and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in mL and affix to the shipper.
- Affix airbill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON THURSDAY OR FRIDAY

Preparation of plasma and mononuclear cells

Refer to the ACSR's SOP on Separation of Plasma and Mononuclear Cells on the AMC Operations web site for instructions on preparing plasma and PBMC aliquots. It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Freeze the cell suspension in 0.5 mL aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written**

on package.

Preparation of tissue samples

Tissue specimens to be fresh frozen should be placed in OCT and then on dry ice immediately. The specimens may stay on dry ice until being transferred to a -80ºC freezer.

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer. *NOTE: Specimens can only be accepted Monday through **Thursday**. Therefore, specimens can only be shipped **Sunday-Wednesday** for delivery the next day. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Sylvia Silver, DA

GW Biorepository

George Washington Medical Center

Ross Hall, Room 118

2300 I St, NW

Washington, DC 20037

Tel: (202) 994-2945

Fax: (202) 994-5056

Email: ssilver@gwu.edu

C. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace[SM], a component of the AMC AdvantageEDC[SM] system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

APPENDIX IV: ACSR INFORMED CONSENT

Study Title for Study Participants:	Collecting Blood and Tissue Sample Donations for Research for HIV/AIDS-Related Cancers
Official Study Title:	Biospecimen Collection and Donation to the AIDS and Cancer Specimen Resource (ACSR)

What is the usual approach to donate blood and/or tissue to the ACSR?

You are being asked to donate blood and/or tissue for future research. You are being asked to donate your blood and/or tissue samples to the ACSR because you have HIV infection and are being considered for participation in an AIDS Malignancy Consortium (AMC) clinical trial. The AMC works with the ACSR to collect donated samples from persons with HIV infection for research studies. People who do not take part in an AMC clinical trial can also donate samples to the ACSR.

What are my other choices if I do not take part in this study?

It is your choice to donate or not donate your blood and/or tissue samples. You may still take part in the AMC clinical study if you choose not to donate blood or biopsy samples to the ACSR.

You may also choose to donate:

- Blood but not tissue, or
- Tissue but not blood.

What is the AIDS and Cancer Specimen Resource (ACSR)?

The ACSR is a biorepository (biobank) that collects human biological specimens (samples) from persons who have HIV or cancers related to HIV/AIDS. The ACSR stores the samples and some of the donor's medical information for use by researchers in future research studies. The National Cancer Institute (NCI) has set up the ACSR to assist researchers locate samples needed for their studies.

The ACSR has an independent research panel that approves researchers' requests to use the ACSR's stored samples for research studies. The ACSR only gives samples and medical information to researchers after their projects have been approved. Researchers may use the samples to study cancers and other diseases associated with HIV disease. This information may help us learn more about the causes of HIV-related diseases and cancers and to develop better ways to screen, diagnose, and treat them.

Why is this study being done?

The purpose of this study is to collect samples for the ACSR for future research studies. Researchers may study samples from the ACSR in combination with hundreds or thousands of other samples to explore how biologic or genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The samples may be used to learn more about how HIV-related diseases and cancers develop. The samples may also lead to new tests or discoveries. Finally, researchers may use the samples to study the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. These studies could make it possible to identify many of the changes that are associated with diseases such as cancers. It may

also help us tailor treatments to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

What extra tests and procedures will I have if I take part in this study?

1) If you agree to donate blood, the medical team will draw about 2 tablespoons of blood to give to the ACSR. This takes about 10 minutes.
2) If you agree to donate tissue, your leftover tissue biopsy material will be donated to and stored by the ACSR.
3) Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not include your name or any information that could personally identify you.

We will only give the ACSR tissue that is left over after making decisions about your treatment or diagnosis. The study doctor will not take any extra biopsies just for the ACSR.

We cannot tell you right now what future research these samples would be used for. Instead, we are asking that you give approval to give your samples for future testing without contacting you again. The results of whatever research is done on your samples will *not* be told to you or your doctor. The results of the tests will *not* be placed in your study records.

How long will ACSR keep my samples?

Your blood and/or tissue sample will be stored until it is used for research. The samples may be stored indefinitely.

What possible risks can I expect from taking part in this study?

- Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
- Confidentiality: The ACSR will receive study samples with code numbers. There will be no personal identifiers on the samples. Then the samples will be re-labeled with a barcode and stored for future testing. While the ACSR and researchers who study ACSR samples will have no information that could identify you, *t*here is a risk that someone could use information from genetic studies to trace your samples back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small but cannot promise that they will not occur.

Let your study doctor know of any questions you have about these possible risks. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. This study may help us learn things that may help people in the future.

The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, these studies could help find ways to prevent or improve treatments for HIV-related diseases and AIDS-related cancers.

Can I stop taking part in this study?

Yes, you may withdraw your samples from the ACSR at any time. You may contact your AMC study coordinator if you would like to withdraw your samples. The coordinator can ask in writing that your sample be removed from research use and that any identifiable sample and information still in their possession be destroyed. However, if any research has already been done using some of your samples, the data will be kept and analyzed as part of those studies.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There will be no cost to you for donating your samples to the ACSR. You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AMC will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to seek payment for injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Office for Human Research Protections and the National Cancer Institute in the U.S.

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Thus, information, including genetic information, that researchers may obtain in studies that use your samples may not be directly linked to you and will not be placed in your medical record. However, some clinical and basic information obtained confidentially from the AMC will be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

Where can I get more information?

You may visit the NCI Web site at **http://cancer.gov/** for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Please circle your answer to show whether or not you would like to take part in each option:

1) I agree to donate my blood to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

2) I agree to donate my blood to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

3) I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

4) I agree to donate some of my tissue biopsy material to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the optional study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX V: CONSENT FORM FOR GI BIOPSIES

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: A Pilot Project of Virologic, and Immunologic Correlates of Gastrointestinal-Associated Lymphoid Tissue Immune Reconstitution as a Part of Bone Marrow Transplant with Anti-HIV Gene Modified Stem Cells

INTRODUCTION

You are being asked if you want to take part in a research study. The main goal of a research study is to learn things to help patients in the future. No one can guarantee that a research study will help you.

Participating in research is voluntary. You have the right to know about the procedures, risks, and benefits of the research study. If you decide to take part, you can change your mind later and leave the study. To participate in this study, you will need to give your written consent by signing this form. Please take your time to make your decision and discuss it with your family, friends, and caregivers.

A minimum of seven people and a maximum of 18 people will take part in this study at University of California Davis and other AIDS Malignancy Consortium (AMC) sites.

WHY IS THIS STUDY BEING DONE?

We are asking that you take part in a research study of how the immune system in the small intestines improves after your bone marrow transplant with anti-Human Immunodeficiency Virus (HIV-1) gene treated stem cells. We do this by taking biopsies from the part of the intestines just below the stomach. A biopsy is a sampling of small snips of tissue. The samples will be studied in the laboratory.

The main purpose of this study is to measure any increase in the number of immune cells in the intestines to see if this number is related to the development of an immune system that is resistant to HIV-1 because of gene therapy.

We are asking you to take part in this study because you participated in the Stem Cell Gene Therapy for HIV-1 in AIDS Lymphoma Patients protocol.

You must be between the ages of 18 and 60. In order to participate in this study, it will be necessary to give your written consent.

Up to 18 people who have participated in the Stem Cell Gene Therapy for HIV-1 in AIDS Lymphoma Patients protocol will take part in this study. Ten volunteers will be HIV-1 negative and will only undergo a single set of procedures called upper endoscopy. This is when the doctor takes an endoscope to look into the intestines and take biopsies that can be taken to the laboratory for testing. Two sets of endoscopies (at approximately 6 months and 8 months after transplant) will be performed.

BEFORE YOU BEGIN THE STUDY

The only additional test you need for this study (above and beyond the tests and exams that you have done) is a short medical history and physical exam by the doctor that performs the study.

A blood draw (approximately 1/3 of tablespoon of blood) will also be done by inserting a needle into a vein in your arm to make sure that it is safe to do the endoscopy. We will measure the clotting factors in your blood.

If you decide to take part in this study, you will be asked to have the screening exams, tests or procedures mentioned above to show that you can continue to be in the study.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you decide to take part in this study, you will be asked to have a procedure called endoscopy. If you are an HIV-1 positive participant, you will be asked to have two sets of endoscopies: at 6 months after the transplant and at 8 months post-transplant.

You will also have blood drawn at the time of endoscopy. We will also review your medical records with respect to the HIV-1 infection you have and your treatment for it.

Endoscopy uses a small flexible rubber tube (about as big around as a pencil) connected to a video camera to examine the inside of your esophagus, stomach and small intestines. It is commonly used to diagnose and treat many conditions of the upper intestinal tract and we will use this tube to take biopsy samples by inserting a small device into the tube that can take a tiny piece of your gut.

All participants will undergo the procedure in the same manner as any other patient having endoscopy. You will receive an IV injection of a pain medication and/or sedative (Demerol or Versed) and be placed on your side. The back of your throat will be numbed using 2% lidocaine gel (like numbing medication used by dentists).

An experienced gastroenterologist (specialist in intestinal disease) will pass the flexible endoscope tube into your stomach and intestines. He/She will examine them by looking at the video camera image. He/She will collect biopsy samples (small pieces of tissue about the size of a grain of rice) from your small intestines in several places (up to 24 biopsies total). This tissue will be examined under a microscope and cells will be examined for certain chemicals that are thought to be important in HIV-1 infection. In addition, cells will be examined and counted for T-helper and other types of lymphocytes (the cells affected by HIV-1). Finally, the functions of the cells in your biopsy specimens will be measured and the amount of HIV-1 virus and HIV-1 medication in the specimen will be determined.

You must be fasting for 12 hours before the endoscopy procedures. You will be asked about your medications before the endoscopy, check with the study doctor or nurse to see if you may take your routine medications during the fasting period. Do not take aspirin, products, containing aspirin or anti-inflammatory agents like Motrin, Advil, or similar non-steroidal anti-inflammatory drugs (NSAID) medications (Tylenol/acetaminophen is permitted) for 7 days before and after the endoscopy procedures. Ask the study doctor what alternatives that you may take. The endoscopy procedure lasts about 30 minutes.

You are sedated during the procedure, so it is not uncomfortable.

You will be observed for any problems after the procedure and will be given an emergency phone number to call if you experience problems after you leave the endoscopy area. You will need to arrange for transportation to and from the endoscopy procedure so that you do not drive home after the procedure. Any medical observations of clinical importance will be discussed with you and forwarded, in writing, to your treating physician.

HOW LONG WILL I BE IN THE STUDY?

The study is limited to the 2 time points for endoscopy mentioned above. There are no additional studies scheduled after that point.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on this study. Everyone taking part in the study will be watched carefully for any side effects. However, the researcher may not know all the side effects or risks. Side effects may be mild or very serious. The researchers may give you medicines to help lessen side effects. Many side effects go away. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to the researchers about any side effects that you have while taking part in the study.

Risks and side effects related to the procedures we are studying are listed below:

Blood draw risks: You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein.

Endoscopy risks: The endoscopy is being performed as a part of a research project. The risks of endoscopy are remote, however, there can be pain, gagging, bleeding, infection, perforation (a hole through the bowel wall can occur) and rarely, death can occur.

Sedation risks: The risks of intravenous sedation (putting someone to sleep) include bleeding, bruising, pain, infection from intravenous catheter, low blood pressure, decreased breathing, and allergic reaction to the medicine.

Allergic reaction risks: Symptoms of allergic reaction may vary from individual to individual but often consists of generalized rash (red skin), itchiness, and a feeling of being excited or anxious.

Very rarely swelling of the throat and/or difficulty breathing can accompany these symptoms. Occasionally (rare), midazolam (also called versed, a drug used for sedation) may cause a state of over excitement. The risks for small bowl biopsy are perforation and bleeding. These events have occurred in some patients though not with these physicians. These risks will be explained to you again by in detail prior to the endoscopy procedure by the gastroenterologist.

Reproductive risks**:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

There may also be risks to your privacy. The researchers will store study records and other information about you in a secure location and will grant access only to those with a need to know. However, just like with other personal information kept by your health care providers, your banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands, it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.

For more information about risks and side effects, ask the researcher.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We do not expect that you personally benefit from participating in this study. However, we may learn more about how immune cells coming from stem cells treated with anti-HIV genes recover after transplant and how it reacts when challenged by HIV-1.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There is no charge for you to participate in this study. Neither you nor your insurance carrier will be charged for your taking part in the research. All costs associated with the study including medications and procedures will be paid by the research.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S.

If we access protected health information (for example your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A research record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

Designated University officials, including the Institutional Review Board, and the Food & Drug Administration have the authority to review research records.

If information from the study is published or presented at scientific meetings, your name and other personal information will not be used.

DO I HAVE TO PARTICIPATE AND CAN I STOP BEING IN THE STUDY?

Taking part in this study is your choice and completely voluntary. Participation or a decline in participation in this part of the study is independent of your participation in the stem cell gene therapy study.

If you decide to take part in this study, you can decide to stop at any time. Leaving the study will not affect your medical. Tell the researcher if you are thinking about stopping or decide to stop so any risks from the can be managed safely.

The researcher may withdraw you from this research if circumstances arise which warrant doing so even if you would like to continue.

We will tell you about new information or changes in the study that may affect your health or willingness to continue in the study.

WILL I BE COMPENSATED FOR BEING IN THIS STUDY?

For the optional intestinal biopsy (upper endoscopy), a fee of $300 for each procedure completed will be paid to you.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

If you have questions, please ask us. You can talk to the study doctor about any questions or concerns you have about this study.

Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will **not** offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, _____ *(insert name of center)* will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by _____ *(insert name of center)*, or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number)*.

My Signature Agreeing to Take Part in the Study

I have read the consent form or had it read to me and understand the information above. I have discussed it with the study doctor and my questions have been answered I understand that I will be given a signed and dated copy of this consent form. I agree to take part in the study. My signature below indicates that I understand my rights and want to take part in this study as a research participant.

Signature of Participant _____ Date_____

Print Name of Participant _____

Signature of person(s) obtaining consent_____ Date_____

Print Name of Person Obtaining Consent_____

APPENDIX VI: AMC DATA AND SAFETY MONITORING PLAN

(Version 9.0 • 06OCT2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND sponsor (AMC investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a clinical investigator for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S., all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND sponsor or its designee will issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and

unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND, in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the sponsor or sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC investigators or industry sponsors.

Expedited reporting to the Institutional Review Board (IRB)

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S. sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that IRB, in accordance with its standards of procedure.

To comply with investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all investigators upon receipt from the sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S. trials subject to single IRB review/CTEP IND agents). The site clinical investigator responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for monitoring trial progress and pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC investigators and their staff It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board (DSMB) review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The group chair or designee is then responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair, DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC investigators and staff. It is each site principal investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

Cohort trial reviews not subject to DSMB review

For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration, and also for AMC IND studies sponsored by AMC investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials

monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC investigators, the AMC DSMB will be notified of the suspension and the reason. For phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site principal investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX VII: CORRELATIVE STUDY SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

DNA and Immunological Monitoring studies for Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-selected CD34+ Cells in AIDS-lymphoma participants

Biomarker Name, Laboratory Conducting Assay and Laboratory Director	**Assay (CLIA: Y/N)**	**Use and Purpose**	**Tissue/Body Fluid Tested and Timing of Assay**	**Tube Type, Blood Component Needed, Whole Blood Collection Volume, and Aliquot Volume**	**Timing of Analysis, (conducted during the trial or after the trial)**	**Funding Source(s)**
Study T Lymphocytes and their subsets Pollard, UC Davis	Flow Cytometry CLIA: N	Exploratory To evaluate the development of normal T cell subsets	Blood Baseline, 3, 6, 12, 24 months post-transplant, Early Disc., and Off-Study Disc.	White blood cell component EDTA whole blood, 2-mL, purple top, and (PBMCs), from 18-mL EDTA, purple top	Analyses will be performed during the trial. Samples should be shipped to the Pollard lab upon collection.	CIRM
Cytokine studies using stored plasma and serum, Pollard, UC Davis	ELISA CLIA: N	Exploratory to evaluate the level of cytokines related to a chronic inflammatory status	Blood Baseline, 3, 6, 12, 24 months post-transplant, Early Disc., and Off-Study Disc.	Serum from 5 mL Red top, stored as 0.5 mL aliquots 10 mL Plasma (from EDTA blood), stored as 1 mL aliquots	Plasma and Serum samples will be aliquoted and stored for delayed analysis	CIRM
Functional Responses Upon Reconstitution of T Cell Immunity Pollard, UC Davis	Flow cytometry, assessment of response to antigen CLIA: N	Exploratory To evaluate the development of functional immune cells	Blood Baseline, 3, 6, 12, 24 months post-transplant, Early Disc., and Off-Study Disc.	White blood cell component (PBMCs), EDTA, purple top, from 20 mL aliquot	Analyses will be performed during the trial. Samples should be shipped to the Pollard lab upon collection.	CIRM
Monitoring for Insertional Oncogenesis and Clonality of Hematopoiesis after Gene Therapy Anderson, UC Davis	LAM-PCR CLIA: N	Exploratory To determine if clones of transduced cells have developed	Blood 1, 2, 4, 6, 8, 10, 12, 18, 24 months post-transplant, Early Disc., and Off-Study Disc.	White blood cell component (PBMCs), EDTA, purple top, 10 mL aliquot	Analyses will be performed during the trial. Samples should be shipped to the Pollard lab upon collection and will be transferred to the Anderson lab for analysis.	CIRM

Biomarker Name, Laboratory Conducting Assay and Laboratory Director	Assay (CLIA: Y/N)	Use and Purpose	Tissue/Body Fluid Tested and Timing of Assay	Tube Type, Blood Component Needed, Whole Blood Collection Volume, and Aliquot Volume	Timing of Analysis, (conducted during the trial or after the trial)	Funding Source(s)
DNA monitoring studies Anderson, UC Davis	PCR, qPCR, sequencing CLIA: N	Exploratory To evaluate in vivo gene marking, anti-HIV gene expression, sequence analysis, vector stability analysis	Blood Baseline, 1, 2, 4, 6, 8, 10, 12, 18, 24 months post-transplant, Early Disc., and Off-Study Disc.	White blood cell component (PBMCs), EDTA, purple top, 5 mL aliquot	Analyses will be performed during the trial. Samples should be shipped to the Pollard lab upon collection and will be transferred to the Anderson lab for analysis.	CIRM
Monitoring for immune response to TRIM5α Anderson, UC Davis	ELISA CLIA: N	Exploratory To evaluate whether any immune response is occurring with the expression of the chimeric TRIM5α protein	Blood 1, 2, 6, 12, 18, 24 months post-transplant, Early Disc., and Off-Study Disc.	White blood cell component (PBMCs), EDTA, purple top, 10 mL aliquot	Analyses will be performed during the trial. Samples should be shipped to the Pollard lab upon collection and will be transferred to the Anderson lab for analysis.	CIRM
Monitoring of changes in the HIV reservoir and viral diversity Henrich, UC San Francisco	Peripheral blood and leukapher-esis cells/plasma CLIA: N	Exploratory To characterize changes in HIV reservoir/diversity	Blood; baseline, 2 and 10 weeks then 6, 12- and 24-months post-transplant	Double spun plasma and EDTA PBMC (2×10^7)	Analysis during study, shipped to the Henrich Lab at UC San Francisco	Dr. Henrich Lab Internal Funding
Monitoring of mixed lymphocyte reactions Henrich, UC San Francisco	Peripheral blood and Leukapher-esis CD34+ depleted cells; PBMC CLIA: N	Exploratory To monitor for reaction to transformed cells	Blood baseline, 2 and 10 weeks then 6, 12- and 24-months post-transplant	CD34+ depleted leukapheresis cells EDTA PBMC (2×10^7)	Analysis during study, shipped to the Henrich Lab at UC San Francisco	Dr. Henrich Lab Internal Funding

Biomarker Name, Laboratory Conducting Assay and Laboratory Director	Assay (CLIA: Y/N)	Use and Purpose	Tissue/Body Fluid Tested and Timing of Assay	Tube Type, Blood Component Needed, Whole Blood Collection Volume, and Aliquot Volume	Timing of Analysis, (conducted during the trial or after the trial)	Funding Source(s)
GI Biopsy	IFA, PCR and RT-PCR and FACS, IHC	Exploratory to evaluate the response of immune system following reconstitution of new anti-HIV hematopoietic cells. To evaluate the persistence of HIV in HIV dormant reservoirs following transplant	Endoscopy biopsy samples will be obtained at 6 months post-transplant for the group that will not undergo ART withdrawal or any time before ART withdrawal and at 8 weeks later.	Separate samples will be obtained for IHC, snap freezing or to put on RNA later for DNA and RNA analysis	Fresh samples will be run immediately after receiving the samples by courier. Frozen samples will be stored at UC Davis for future tests.	CIRM
Bone Marrow Aspirate	CFU assay, DNA extraction, quantitative PCR CLIA:N	To evaluate the in vivo gene marking of human CD34+ cells	Residual Samples of Bone marrow aspirate	Two 10.0 ml EDTA / (Purple top tubes)	3- and 12-months post-transplant, treatment discontinuation	CIRM

SPECIMEN COLLECTION AND PROCESSING INSTRUCTIONS

The correlative studies can be divided into immunological and HIV studies, DNA monitoring studies, and monitoring for oncogenesis and hematopoietic clonality. The immunological studies will be done in 2 compartments: peripheral blood samples and endoscopy (gut mucosa) samples.

1. Blood Samples

Samples will be collected via blood draws from participants (Maximum of 65 mL of blood collected).

Blood samples for immunological studies

A total of 45 mL of blood will be collected for immunological studies:

- 40 mL EDTA anti-coagulated whole blood specimens and divided into four 10 mL tubes. Whole blood (for PBMCs) is required from each participant at each time point described in the clinical protocol.
- 5mL of non-anticoagulated blood (processed for ~ 3 mL of serum) in one 5 mL tube red top tube

Processing procedures red top tube serum

- Collect 5 mLs of whole blood in a 5 mL red top tube.
- After blood is drawn, invert collection tube 5 times and allow the blood to clot 60 minutes, leaving the tube in an upright position during the clotting process for immediate processing. If multiple samples are collected in one day, and the site would like to hold the sample for processing later the same day, store the sample between 2-8^{o}c until ready to invert the tube and clot the sample.

  Once clotted, the collection tube should not be allowed to sit at room temperature for more than 1 hour prior to centrifugation and separation of the serum from the clot.

  Centrifuge the collection tube for 10 minutes at 1000 g. After separation, the serum should be clear and free from all blood cells. Aliquot the serum in the 3 mL cryovial.
- Separated sera aliquots must be stored refrigerated until ready for shipment to UC Davis on next available business day (specimens should be shipped **MONDAY** through **THURSDAY)**.

Each sample tube should be labeled with GlobalTrace^{SM} specimen labels using a Sharpie pen to include the following information:

- 11-digit Participant #
- Date and time of collection
- Specimen type: (i.e., WB=Whole Blood, S=Serum)
- Specimen purpose: (i.e., Immunological Studies)

Blood samples for DNA monitoring studies

A total of 20 mL of blood will be collected for DNA monitoring studies (see Section 2.5.4 for analyses to be performed):

- 20 mL of EDTA anti-coagulated whole blood specimens in two 10 mL tubes will be collected.

Each sample tube should be labeled with GlobalTrace[SM] specimen labels using a Sharpie pen to include the following information:

- 11-digit Participant #
- Date and time of collection
- Specimen type: (i.e., WB=Whole Blood)
- Specimen purpose: (i.e., DNA Monitoring Studies)

Blood samples for safety monitoring studies

A total of 30 mL of blood may be collected for safety monitoring studies, as determined with the protocol chair per Section 2.5.8. If determined to be required, 30 mL of EDTA anti-coagulated whole blood specimens in three 10 mL tubes will be collected and shipped to the Pollard lab as noted below for blood samples.

Each sample tube should be labeled with GlobalTrace[SM] specimen labels using a Sharpie pen to include the following information:

- 11-digit Participant #
- Date and time of collection
- Specimen type: (i.e., WB=Whole Blood)
- Specimen purpose: (i.e., Safety Monitoring Studies)

Blood specimen shipment

All **Blood Samples** should be shipped by priority overnight express on **MONDAY** through **Thursday** to the UC Davis correlative study laboratory.

Refrigerated Blood Specimen Protocol

- Apply a strip of Parafilm, around all vials, where the cap meets the tube.
- Wrap all blood tubes individually with bubble wrap.
- Place all specimens in the clear plastic biohazard bag with an absorbent pad and seal.
- Place the clear plastic biohazard bag in the white Tyvek biohazard bag and seal.
- Place the sealed white Tyvek biohazard bag in the inner cardboard box of the shipper.
- Place the inner cardboard box in the Styrofoam cutout, put the notched flap down first, and fold across. Remove your gloves.
- Place four frozen cold packs in the Styrofoam box, one on each side of the inner cardboard box. Thermal protective gloves are recommended.
- Place the lid on the Styrofoam box and put the Styrofoam box in the outer cardboard shipper.
- Place the shipping manifest on the top of the closed Styrofoam box.

- Close and tape the box along the center break and on the sides. Secure the shipping label to the top of the box.

NOTE: FedEx's "Priority Overnight" is required shipping method.

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site).
- Use a federally approved shipper for biological substance shipment (Category B). Label the shipper with the "Infectious substance" diamond shaped label. On one side, in black marker write "Biological Substance, Category B, UN 3373", your name or name of responsible person, date of collection and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.
- A Shipper's Declaration for Dangerous Goods is not required.

Please Note: The shipper will be mailed back to the AMC site. The STP-100 SAF-T-PAK shipper (VWR Cat # 11217-082) is a complete kit (bubble wrap, absorbent paper, labels, etc.) for specimen shipment. To reuse the shipper, you will need new labels, wrap, etc. There is a refurbishment kit with extra bubble wrap and absorbent material (Fisher Scientific Cat # 19-038-301E).

Sample receipt and processing are performed Tuesday through Friday, unless other arrangements have been made for with the lab. Avoid collecting specimens for shipment on Fridays, and on days before an observed UC Davis holiday. All specimens should be shipped to:

Dr. Joseph Anderson

University of California Davis

2921 Stockton Blvd., Room 1300

Sacramento, CA 95817

Tel: (916) 703-9300

Email: jsanderson@ucdavis.edu

2. Blood, plasma and leukapheresis for mixed-lymphocyte reaction analysis and HIV reservoir characterization.

Samples will be sent same day by special courier by arrangement of Dr. Henrich and sent to:

Henrich Laboratory

University of California, San Francisco

1001Potrero Ave., Bldg. 3, Rm 603

San Francisco, CA 94110
Email: Timothy.Henrich@ucsf.edu

3. Endoscopy Samples

Participants will have upper endoscopy performed in Gastrointestinal Suites according to standard clinical procedures:

Participants are sedated with IV Benadryl, versed, and Demerol to achieve conscious sedation while being monitored for vital signs and comfort levels (heart rate and rhythm, blood pressure, O2 saturation). When participants are adequately sedated, an Olympus upper endoscope is passed to the small intestines where 24 biopsies are obtained using Boston Scientific biopsy forceps (large 2.8 mm). This typically requires 12 passes to acquire adequate samples for subsequent studies.

Sample disposition during the procedure is as follows:

A total of 24 endoscopy (gut mucosa) samples will be collected.

Endoscopy samples for RNA & DNA analysis

- A total of 8 biopsy specimens should be collected and **snap frozen**:
  - **Six** of the eight biopsy specimen should be transferred overnight on dry ice to UC Davis.
  - **Two** of the eight biopsy specimen should be placed in 1 mL of RNAlater Qiagen and sent over night to UC Davis with chilled packaging.

Endoscopy samples for IHC and in situ staining

- A total of 3 biopsies should be collected and placed in formalin per clinical practice.
- These are transported to the Pathology laboratory for paraffin embedding per clinical practice.

Endoscopy samples for vector frequency, immunologic flow cytometry analysis, and cellular HIV DNA measurement

- A total of 13 biopsies are collected and placed in chilled 30 mL of RPMI media and transported overnight with chilled packaging to UC Davis.
- These are transported to the UC Davis immunology laboratory for collagenase digestion and single cell suspension.

Each sample tube should be labeled with GlobalTrace^{SM} specimen labels using a Sharpie pen to include the following information:

- 9-digit Participant #
- Date and time of collection
- Specimen type: (i.e., WB=Whole Blood)
- Specimen purpose: (i.e., DNA Monitoring Studies)

Participants are monitored in the Endoscopy Suites recovery area and are released to a companion for transport home with specific instructions about who to contact from the study team should any concerns or side effects arise.

Endoscopy Samples obtained at UC Davis Medical Center will be transported directly from the endoscopy suite to the laboratory. Samples from UC San Francisco will be transported by special courier as has been performed by previous clinical protocols. This is achieved by car from San Francisco and air from San Diego.

ENDOSCOPY SPECIMEN SHIPMENT

Frozen endoscopy specimen protocol

- Apply a strip of Parafilm, around all vials, where the cap meets the tube.
- Place all specimens in the inner plastic biohazard bag with an absorbent pad and seal.
- Place the clear plastic inner biohazard bag in the white Tyvek biohazard bag and seal.
- Place the sealed white Tyvek biohazard bag in the inner cardboard box of the shipper.
- Place the inner cardboard box in the Styrofoam cutout, put the notched flap down first, and fold across. Remove your gloves.
- Using thermal protective gloves place the dry ice in the Styrofoam box and spread it evenly around each side of the inner cardboard box.
- Place the lid on the Styrofoam box and put the Styrofoam box in the outer cardboard shipper.
- Place the shipping manifest on the top of the closed Styrofoam box.

Close and tape the box along the center break and on the sides. Secure the shipping label to the top of the box.

NOTE: FedEx's "Priority Overnight" is required shipping method

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site).
- Use a federally approved shipper for biological substance shipment (Category B). Label the shipper with the "Infectious substance" diamond shaped label. On one side, in black marker write "Biological Substance, Category B, UN 3373," your name or name of responsible person, date of collection and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.
- A Shipper's Declaration for Dangerous Goods is not required. However, for all dry ice shipments, the following information must be shown in sequence on the airway bill in the "Nature and Quality of Goods" box: Dry Ice, 9, UN1845, number of boxes being shipped, net weight of dry ice per box.

  Please Note: The shipper will be mailed back to the AMC site. The STP-100 SAF-T-PAK shipper (VWR Cat # 11217-082) is a complete kit (bubble wrap, absorbent paper, labels, etc.) for specimen shipment. To reuse the shipper, you will need new labels, wrap, etc. There is a refurbishment kit with extra bubble wrap and absorbent material (Fisher Scientific Cat # 19-038-301E).

Sample receipt and processing are performed Tuesday through Friday, unless other arrangements have been made for with the lab. Avoid collecting specimens for shipment on Fridays, and on days before an observed UC Davis holiday. All specimens should be shipped to:

Dr. Joseph Anderson

University of California Davis

2921 Stockton Blvd., Room 1300

Sacramento, CA 95817

Tel: (916) 703-9300

Email: jsanderson@ucdavis.edu

Billing

Bill the FedEx # available on the AMC member's only website. This number is supplied by the AMC Operations and Data Management Center. It is only to be used for billing shipment of specimens to the lab where the sample is processed and/or stored.

Record of Blood and Endoscopy Specimens

This study will track specimens via GlobalTrace[SM], a component of the AMC AdvantageEDC[SM] system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

Technical Questions

Study Team

University of California, Davis

Comprehensive Cancer Center

4501 X Street, Suite 3016

Sacramento, CA 95817

Tel: 916-703-9118

Fax: 916-734-1895

Email: HS-CELLULARTHERAPYRESEARCH@UCDAVIS.EDU

4. Bone Marrow Aspirate samples for RNA & DNA analysis

Processing procedures

- Two 10.0 ml EDTA / Purple top tubes
- Collect specimen per site's institutional SOP
- Immediately transfer and if possible, completely fill two 10 ml EDTA (purple top tubes) with the bone marrow aspirate.

- Gently invert tubes 8-10 times.

Each sample tube should be labeled with GlobalTrace[SM] specimen labels using a Sharpie pen to include the following information:

- 9-digit Participant #
- Date and time of collection
- Specimen type: (i.e., BMA "Bone Marrow Aspirate")
- Specimen purpose: (i.e., DNA Studies)

All **Bone Marrow Aspirate Samples** should be shipped by priority overnight express on **MONDAY** through **Thursday** to the UC Davis correlative study laboratory.

Cool Bone Marrow Aspirate Specimen Process and Shipping

- Apply a strip of Parafilm, around all vials, where the cap meets the tube.
- Wrap all tubes individually with bubble wrap.
- Place all specimens in the clear plastic biohazard bag with an absorbent pad and seal.
- Place the clear plastic biohazard bag in the white Tyvek biohazard bag and seal.
- Place the sealed white Tyvek biohazard bag in the inner cardboard box of the shipper.
- Place the inner cardboard box in the Styrofoam cutout, put the notched flap down first, and fold across. Remove your gloves.
- Place four cool gel packs in the Styrofoam box, one on each side of the inner cardboard box.
- Place the lid on the Styrofoam box and put the Styrofoam box in the outer cardboard shipper.
- Place the shipping manifest on the top of the closed Styrofoam box.
- Close and tape the box along the center break and on the sides. Secure the shipping label to the top of the box.

NOTE: FedEx's "Priority Overnight" is required shipping method.

- It is the responsibility of the Primary Investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations (IATA Packing Instruction 650) relating to the handling and shipping of hazardous goods. (IATA Packing Instruction 650 is located on the AMC web site).
- Use a federally approved shipper for biological substance shipment (Category B).

Label the shipper with the "Infectious substance" diamond shaped label. On one side, in black marker write “Biological Substance, Category B, UN 3373”, your name or name of responsible person, date of collection and phone number of the person responsible for the package. Package and label the shipment in accordance with the instructions provided for that specific shipper.

- A Shipper’s Declaration for Dangerous Goods is not required.

Please Note: The shipper will be mailed back to the AMC site. The STP-100 SAF-T-PAK shipper (VWR Cat # 11217-082) is a complete kit (bubble wrap, absorbent paper, labels, etc.) for specimen shipment. To reuse the shipper, you will need new labels, wrap, etc. There is a refurbishment kit with extra bubble wrap and absorbent material (Fisher Scientific Cat # 19-038-301E).

Sample receipt and processing are performed Tuesday through Friday, unless other arrangements have been made for with the lab. Avoid collecting specimens for shipment on Fridays, and on days before an observed UC Davis holiday. All specimens should be shipped to:

Dr. Joseph Anderson

University of California Davis

2921 Stockton Blvd., Room 1300

Sacramento, CA 95817

Tel: (916) 703-9300

APPENDIX VIII: INTERNATIONAL PROGNOSTIC INDEX (AGE-ADJUSTED)

Characteristic	Prognostic Factor (1 point for each)
Ann Arbor Stage	Stage III or IV
Serum LDH level	Elevated
ECOG performance status	2, 3 or 4 (patients with PS 3 or 4 are not eligible)

APPENDIX IX: CCR5-TROPISM ASSAY

1. Monogram Biosciences Assays:

   GenoSure Archive^{SM} DNA Sequencing – Test Code: R6000

   Trofile® DNA – Test Code: E3600
2. This sample is to be collected within 8 weeks prior to study enrollment.
3. Draw 4mL of whole blood in 1 lavender top EDTA tube.
4. **DO NOT CENTRIFUGE.**
5. Freeze *immediately* at -20°C. Sample needs to be FULLY frozen before shipping.
6. Call Monogram Biosciences Client Services to schedule specimen pick-up at 800-777-0171 by 1:00 p.m. to ensure next day delivery.
7. Upon arrival of courier, please place frozen specimen tube into the secondary container offered by the courier.
8. Ensure there is enough bubble wrap and absorbency sheets inside to contain any spills.
9. Close container and give back to the courier for shipment to Monogram Biosciences.

APPENDIX X: RISK LIST FOR BEAM

COMMON	
CTCAE Term	**Grade**
BEAM	
Neutrophil count decreased	1-2
Platelet count decreased	1-2
Lymphocyte count decreased	1-2
Febrile Neutropenia	3
Nausea	1-2
Vomiting	1-2
Mucositis oral,	1-2
Esophageal ulcer, esophagitis	1-2
Abdominal pain	1-2
Diarrhea	1-2
Anorexia, dysphagia	1-2
Alopecia	1-2
Fatigue	1-2
Infusion of Unmodified Cells	
Presyncope, dizziness	1-2
Syncope	3
Hypoxia	2
Fever	1-2
OCCASIONAL	
BEAM	
Blood Bilirubin increased	1-2
Alanine aminotransferase (ALT) increased	1-2
Aspartate aminotransferase (AST) increased	1-2
Pneumonitis	1-2
Hypotension	1-2
Hyperuricemia	1-2
Maculopapular Rash	1-2
Chills	1-2
Infusion of Unmodified Cells	

Sinus Tachycardia	1-2

APPENDIX XI: ATI RISK MITIGATION COUSENLING FORMS:

Participant ID Number: ¦__¦__¦__¦__¦__¦ Date ¦__¦__¦/|__|__|__|/|__|__|__|__| (DD/MMM/YYYY)
Visit Type: ¦__¦__¦__¦__¦__¦

Pre-ATI Risk Mitigation Counseling

Procedure	Initials	Comments
Partner assessment: Ask whether the volunteer has regular sex partner(s), casual partner(s), or both, and the gender of their sex partner(s): including but not limited to: cisgender male and/or female, and/or transgender partners		
Assess whether HIV status of partner(s) is known		
Assess the volunteer's current understanding of HIV transmission risk to partner(s)		
Assess if the volunteer has other risk factors for transmitting HIV, such as sharing needles		
Describe the expected viral rebound during the ATI and the rationale for HIV-negative partners to use condoms and/or PrEP		
Ask whether the volunteer has heard of PrEP		
Describe PrEP and its potential benefits		
Provide and review the **HIV Treatment Interruption Study Participation Disclosure Sheet**		
Provide the **PrEP for Partners** information sheet		
If cisgender female partners are involved, provide **PrEP for Cisgender Female Partners** supplement		
Review the resources for accessing PrEP provided on the information sheets		
Offer to follow up with the volunteer and/or their partner(s) if requested		

Participant ID Number: ¦__¦__¦__¦__¦__¦ Date ¦__¦__¦/|__|__|__|/|__|__|__|__| (DD/MMM/YYYY)
Visit Type: ¦__¦__¦__¦__¦__¦

Ongoing Risk Mitigation Counseling

Procedure	Initials	Comments
Has volunteer previously reported any sex partners on study? Yes No		
Is there a protection plan for partners? Yes No If no, offer shared study visit and navigation assistance.		
Has volunteer had new sex partners since last visit and/or anticipate change in sex partners: No Yes, new partner(s) Yes, anticipate change		
If Yes, describe type of partners (cis/trans male/female), context (travel, event/party, sex work, etc.), and plans for protecting partners. Offer shared study visit and navigation assistance.		
Review that viral rebound can occur at any time during the treatment interruption and may occur without any symptoms		
Review the risk that viral rebound poses to sexual partners		
Ask whether the participant wants to leave with condoms		
Ask whether the participant or their partners want to discuss PrEP with a study team member		
If PrEP has been discussed previously, follow up on whether action has been taken by the partner(s) and whether navigation assistance is needed		
Offer the **HIV Treatment Interruption Study Participation Disclosure Sheet, PrEP for Partners, and PrEP for Cisgender Female Partners**, as applicable		

APPENDIX XII: HIV TREATMENT INTERRUPTION PARTICIPANT DISCLOSURE FORM:

HIV Treatment Interruption Study Participation Disclosure Sheet

This document can help you talk with your partner(s) about the HIV treatment interruption study in which you are participating. You should take your time to decide if and who you want to tell. Telling others about your participation is a personal choice. You will need to find the right time and place to tell your partner(s). Below are a few points you can discuss with your partner(s).

"Undetectable means Untransmittable" (U = U)

- ❑ I am a person living with HIV. I have been taking HIV medications. My virus has been undetectable for some time.
- ❑ People who have taken their HIV medications and maintained an undetectable viral load for at least six months have no risk of sexually transmitting the virus to an HIV-negative partner according to the Centers for Diseases Control and Prevention (CDC).

Participation in an HIV Treatment Interruption Study

- ❑ I am participating in a research study.
- ❑ Part of the study requires that I pause my HIV medications.
- ❑ Stopping my HIV medications means that my virus could come back (rebound) at any time.
- ❑ After pausing my medications, I will be tested frequently to see when my HIV comes back.
- ❑ I may be off my HIV medications for as long as 12 weeks or more. During this time, I may no longer be "undetectable." I will restart my HIV medications if my virus remains detectable at high levels for weeks, months, if my CD4 count becomes too low, or if I develop symptoms or health problems.

PrEP, HIV Testing and Counseling Information to Relay to Your Partners

- ❑ While I'm off my HIV medications, there is a risk of transmitting HIV to my partner(s).
- ❑ The study staff can provide counseling about how to protect my partners against HIV transmission.
- ❑ If you are HIV-negative, you should consider using PrEP to prevent HIV. The study team can provide a list of PrEP resources available in the area. PleasePrEPme.org can also help you find a PrEP provider.
- ❑ Using a condom may decrease the risk of transmitting HIV and other STIs during the treatment interruption period.
- ❑ We do have the choice of not having sex during the HIV treatment interruption period, until I restart HIV medications.
- ❑ If you think you have been exposed to HIV, you should contact the study staff immediately. The research team can link you with HIV testing services that provide post-exposure prophylaxis (PEP) which may also prevent HIV transmission. You should do this within 72 hours of being exposed to HIV. If you can't reach the study staff or don't want to call them, you should go to an Emergency Department within the 72 hour period.

You should give your partner(s) time to process the information to ask questions.

You should also be familiar with the partner-notification laws in your state. You can check with your state's Department of Health to find out more about the laws in your area. For the state of California, you can consult:

- California HIV Laws (2019): http://www.californiaaidsresearch.org/topic-areas/hiv-laws_final.pdf

If your partner(s) have any questions about the study, we are happy to discuss these issues with them. S/he/they should feel free to contact:

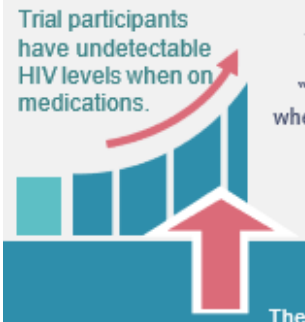
- Name: _____
  Address: _____
  Phone: _____

APPENDIX XIII: PREP INFORMATION SHEET FOR PARTICIPANTS

PrEP for Partners

What is PrEP (Pre-Exposure Prophylaxis)?

PrEP is a medicine that prevents HIV.



PrEP is a medicine that prevents HIV. We recommend that participants in our trial talk with their HIV-negative sexual partner(s) about PrEP. This is because volunteers may no longer have "undetectable" HIV when they stop taking HIV medications during part of the trial. They may be able to transmit HIV to partner(s) during this period.

We recommend that trial participants talk with their HIV-negative sexual partner(s) about PrEP, because PrEP can reduce the risk of transmission.

How can partners of study participants access PrEP?

There are several different ways to access PrEP. The best way will depend on a partner's insurance and where they receive medical care. We can help figure out the best way to get PrEP.

Partners should start by seeing whether their primary care doctor can prescribe PrEP.

How can my partners and I learn more about PrEP?

The study team can provide information to help you or your partner(s) learn more about PrEP. If you or your partner(s) want more information, please ask!

Where else can my partner access PrEP?

- **www.PleasePrEPMe.org** is a searchable online resource that can help find a PrEP provider according to specific geographic or insurance needs.
- PrEP can be accessed via telehealth through **Nurx.com** and **PlushCare.com**

PrEP for Cisgender Women

What is PrEP (Pre-Exposure Prophylaxis)?

Truvada for PrEP is a tool woman can use to take active control of their sexual health to prevent HIV without requiring their partner's cooperation!

Truvada is a daily oral medication that when taken regularly is more than 99% effective at preventing HIV. For women, Truvada for PrEP works best when taken every day.

Is it safe to use?

Research studies have shown that Truvada for PrEP is safe to use in women. It does not interfere with hormonal contraceptives. It is safe to use if you think you might become pregnant or are breastfeeding.

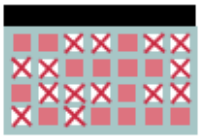
Is PrEP for you?

Truvada for PrEP may be for you if you:

Want to take it

Have sex without using condoms

Are unsure of your partner's HIV status



If a partner with HIV is not regularly taking their HIV medication

Recently had a sexually transmitted infection

Inject drugs

Are worried about your risk for HIV

How can I get Truvada for PrEP?

Truvada for PrEP resources are available online at

- www.pleaseprepme.org/women
- NURX (www.nurx.com)

We are happy to answer any questions you may have!

SUMMARY OF CHANGES

A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells

Version 9.0

NCI Protocol #: AMC-097
Local Protocol #: AMC-097

NCI Version Date: 07FEB2022
Protocol Date: 07FEB2022

I. Scientific and Substantive Changes

#	Section	Description of Change
1.	How long will I be in this study	During years 3-15, participants will be contacted by a person from the clinic rather than a person from the protocol team to collect information about their health.
2.	During the Study	The conditioning regimen prior to transplant has been revised to indicate that agents proven that have the same effects as rituximab (biosimilars) may be used instead of ritixumab for participants with B cell lymphoma. Participants will be informed of whether they will receive rituximab or a similar agent. In addition, the duration that each chemotherapy agent will be given has been removed. Both of these changes are because instiutions are permitted to administer conditioning regimens in accordance to their local guidelines and for consistency with the protocol. In addition, allowing administration of agents similar to ritiumab will give participating centers an alternative option for treatment if there is a supply shortage of rituximab.
3.	Use of HIV-1 Medications During the Study Risk Considerations related to COVID-19 Attachment 2	Additional information on the effects and risks of stopping HIV medications have been added. In addition recommendations and requirements to help reduce these risks have been added. Participants will be informed that HIV levels will increase while immune function may decrease and that it may take over 4-6 weeks for these levels to return to baseline, increasing the risk of developing symptoms. Additional risks include: • Symptoms similar to those experienced upon initial HIV infection • Inflammation / heart problems • Resistence to HIV medications, increased risk of spreading HIV • Increased risk of infection of another strain of HIV

#	Section	Description of Change
		• Risks related to COVID-19 have been added. Participants will be counseled on the risks of stopping HIV medications, and if sexually active, advised to use condoms and to refer their partners for HIV testing and post-exposure treatment. Participants will now be required to be tested for COVID-19 before stopping HIV medications. In addition, participants will restart their HIV medications if they development symptoms believed to be related to increased levels of HIV, have been exposed to HIV infection, or become pregnant. A calendar was added in Attachment 2 that outlines required assessment required after stopping and restarting HIV medications.
4.	Use of HIV-1 Medications During the Study Attachment 2	The duration that HIV medications may be stopped post transplant has been updated from 12 weeks to until the onset of criterion for resumption to allow for additional assessment on the survival of the anti-HIV gene. This is considered a safe duration as participants will be closely monitored and HIV medications will be restarted if symptoms develop.
5.	Use of HIV-1 Medications During the Study	Requirements during the conditioning regimen were revised to indicate that HIV medication may be held and that participants will be informed by their study doctor whether holding HIV medications is necessary. This change is consistent with the protocol requirements.
6.	Optional Sample Collections Attachment 2	The consent has been revised to include information on the SCOPE study being conducted by University of Califnornia San Franscico. The SCOPE study includes optional GI biopsies at the same timepoints as the optional GI biopsies in this study. Participants that join this study and the SCOPE study at the same time and consent to optional studies may have biopsy results from the SCOPE study used for this study. This will minimize the number of biopsies taken for participants planning to participate in both studies and that consent to optional GI biopsies. GI biopsies were added to the study calendar to clarify timepoints and collection.
7.	How long will I be in this study Optional Bone Marrow Biospies Optional Sample	Optional bone marrow collections have been added for research to study the effects of the vector on participants' genetics and immune system. Participants that consent to optional bone marrow biopsies will have about 2 tablespoons (20mL) of bone marrow collected at 3, months, 12 months, and at study discontinuation. Risks of participating in optional bone marrow collection include discomfort, pain, bleeding, scarring or infection at the site of the aspirate/biopsy and chance of allergic reaction to the numbing medicine.

#	Section	Description of Change
	Collections What is Involved? Risks of bone marrow biopsies Samples for Future Research Studies Attachment 2	
8.	How long will I be in this study Optional Blood Sample Collections Optional Sample Collections What is Involved? Risk of blood collections Samples for Future Research Studies Attachment 2	Optional blood sample collections have been added to monitor HIV levels and the vector. Participants that consent to optional blood collections will have about 3 tablespoons (30mL) of blood collected every 12 months for years 3-15 on study. Risks of bloow draws include pain, a bruise or lump at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.
9.	Attachment 2	Required bone marrow biopsies to assess disease for staging were added for consistency with the protocol

II. Administrative and Editorial Changes

#	Section	Description of Change
10.	Global	The protocol version was changed to 9.0 and the date to 07FEB2022
11.	Attachment 2	Optional GI biopsy collections were added to attachment 2 for consistency with the optional study collections sections of the consent form.

AMC-097 MODEL INFORMED CONSENT FORM

Study Title for Study Participants: **Stem Cell Gene Therapy for HIV-1 in AIDS Lymphoma Participants**

Official Study Title for Internet Search on **http://www.ClinicalTrials.gov: A Phase I Study of Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-selected CD34+ Cells**

A Clinical Trial of the AIDS Malignancy Consortium (AMC)

INTRODUCTION

You are being asked if you want to take part in a research study. The main goal of a research study is to learn things to help participants in the future. No one can guarantee that a research study will help you.

Participating in research is voluntary. You have the right to know about the procedures, risks, and benefits of the research study. To participate in this study, you will need to give your written consent by signing this form. Please take your time to make your decision and discuss it with your family, friends, and caregivers.

This study is being led by Mehrdad Abedi, MD from the Department of Hematology/Oncology at the University of California Davis, with AIDS Malignancy Consortium (AMC) sites at medical centers across the U.S.

WHAT IS THE USUAL APPROACH TO TREAT MY LYMPHOMA?

You are being asked to take part in this study because you have human immunodeficiency virus (HIV) infection and a type of blood cancer called lymphoma. You have already been treated with chemotherapy and your disease is now growing. People who are not in a study are usually treated with an autologous peripheral blood stem cell transplant with high dose chemotherapy (for example BEAM, described below). An autologous peripheral blood stem cell transplant is when your own stem cells are collected from your blood, frozen, and then given back to you after you receive high dose chemotherapy. This transplant with high dose chemotherapy is intended to prevent your disease from coming back in the future.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above.
- You may choose to take part in a different study, if one is available.
- You may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms. Comfort care, or palliative care, helps reduce pain, tiredness, appetite problems, and other issues caused by your disease. It does not treat the disease directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the safety of combining the autologous stem cell therapy with gene therapy to treat your lymphoma. For gene therapy, researchers in a laboratory will add small

stretches of DNA called “anti-HIV genes” into your stem cells to make the gene therapy product used in this study. The type of anti-HIV genes and therapy in this study might make your immune cells more resistant to HIV.

The goal of the study is to develop an immune system that can actively prevent new immune cells from getting infected with HIV, while the older cells die due to HIV. This new immune system might be able to fight the spread of HIV even without HIV medications.

The gene therapy product in combination with your clinically indicated stem cell transplant in this study is considered experimental, because it has not been used in human clinical trials in the setting of an autologous transplant, and has not been approved by the Food and Drug Administration (FDA) for treatment of HIV. A similar gene therapy product has been used in other human clinical trials with stem cell therapy. Up to 18 people will take part in this study.

WHAT ARE THE STUDY GROUPS?

Study participants will get increasing amounts of stem cells with anti-HIV genes with autologous stem cell transplant.

- The first group of study participants will receive equal amounts of the stem cells with anti-HIV genes and stem cells without anti-HIV genes.
- If gene therapy does not cause serious side effects, it will be given to the second group of study participants. The second group will receive more stem cells with anti-HIV genes and fewer stem cells without anti-HIV genes.
- If the second group does not have serious side effects, the third group of participants will receive only stem cells with anti-HIV genes.
- If there are issues with cells engrafting in the third group of participants, a fourth group will receive only stem cells with anti-HIV genes, but at a higher amount than the third group received.

If you are among the participants that receive only stem cells with anti-HIV-1 genes, some of the stem cells without anti-HIV genes will be stored and will only be used as a safety back up if you need them. This means that the backup cells would be used if the stem cells with the anti-HIV genes do not allow for recovery of your blood cells quickly enough.

HOW LONG WILL I BE IN THIS STUDY?

You will receive a one-time infusion of stem cells with anti-HIV genes. The infusion goes into your vein like a blood transfusion over less than an hour. This is called an autologous transplant.

You will have clinic visits to follow up on your transplant on this clinical trial for two years after your stem cell transplant. However, we would like to keep track of your medical condition for at least 15 years and maybe for the rest of your life. Additionally, every 12 months for years 3-15 we will request optional lab studies to monitor your HIV levels and to see how the vector is working in your body. A member of the research team at the clinic will contact you by phone or mail once a year for a short conversation and to ask if any new changes have occurred in your health.

Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study and the process of transplantation in general. Many transplant centers include this type of long-term follow-up as part of their regular medical care.

WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra exams, tests, and/or procedures that you will need to have if you take part in this study.

Before You Begin the Study:

Your study doctor will review your past medical history to determine if you are eligible to participate. If you are eligible, you will have an opportunity to ask questions and review the study completely. If you agree to participate, you will sign the consent form. You will also be required to have certain tests performed prior to the start of the study to make sure you are eligible for this study. Most of these tests are standard of care for autologous transplant.

You will have:

- A review of your HIV status, which includes asking questions about behaviors related to risk factors for HIV,
- A physical examination,
- A chest x-ray,
- Pregnancy test for females who could become pregnant,
- An EKG (basic heart test),
- An echocardiogram (heart ultrasound) that assesses the heart function and heart valves,
- A pulmonary function test to determine how well your lungs are working and how well you are breathing,
- Blood tests (several tablespoons will be taken from a vein in your arm).

If you recently had any of these tests, your doctor may decide it is not necessary to repeat them.

You may be required to have:

- A cardiac stress test that assess heart function when you are exercising for about 20 minutes,
- An imaging scan of your body called CT scan, to look at the location and size of your cancer and any possible source for infection,
- A bone scan if clinically indicated, and/or a bone marrow biopsy.

During the Study:

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, you will be admitted to the hospital as an inpatient only to give you the experimental stem cell therapy. If you experience sudden side effects or your lymphoma worsens during the study, an additional blood sample (about two tablespoons) may be drawn to study the causes.

The three parts of the experimental stem cell therapy include:

Part 1: Taking Blood for Stem Cells

To collect your stem cells, you will get standard drugs to move stem cells from your bone marrow into your blood. This process is called stem cell mobilization. The treatment required for stem cell mobilization is called the mobilization regimen. This is a standard of care

procedure for all patients undergoing autologous transplant. Your transplant doctor will discuss the procedure with you.

After the stem cells are in your blood, you will have a procedure called leukopheresis. This is where your blood is run through a machine to collect the stem cells. Leukopheresis will take about 4 hours for most people. You will have this procedure to collect stem cells each day until there are enough stem cells for a safe transplant.

The stem cells that are collected will be split into two parts:

- The first part will be used for stem cells with the anti-HIV genes. In a very clean laboratory, the anti-HIV genes will be put into your stem cells. Once the anti-HIV genes are in the stem cells, they will be frozen and stored until you are ready to receive them.
- The second part of the stem cells will just be frozen and stored without the anti-HIV genes in them.

Part 2: Conditioning Regimen

Starting six days before your stem cell transplant, you will get a high dose chemotherapy conditioning regimen called BEAM or R-BEAM through a vein in your arm to kill the lymphoma cells in your body. BEAM and R-BEAM are a mixture of several chemotherapy drugs that stop the growth of cancer cells. These chemotherapy drugs are widely used to treat lymphoma and for stem cell transplants. The name of the chemotherapy drugs in BEAM and R-BEAM regimens are:

- BCNU (also called carmustine)
- Etoposide (also called VP-16)
- Ara-C (also called cytarabine)
- Melphalan
- If you have a type of lymphoma called B cell lymphoma, you may receive rituximab or a drug proven to have the same effect. Rituximab or similar drug will be given before the transplant, and again after the transplant on day 21 and day 28. The study doctor will let you know if you will be given rituximab or a biological similar agent.

Part 3: Reinfusion of Stem Cells (Transplantation)

One day after BEAM conditioning regimen is complete, the frozen stem cells that were previously collected from you will be thawed and re-infused into your veins through a catheter in your arm.

As mentioned before, depending on the study group you are in, you may receive only anti-HIV gene treated stem cells, or a combination of anti-HIV gene treated stem cells and stem cells without anti-HIV genes. The stem cells with or without anti-HIV genes are supposed to travel to your bone marrow where they will begin making healthy, new blood cells. This step is necessary because the high doses of chemotherapy given to you during the conditioning regimen will not only destroy lymphoma cells, but also healthy cells in your bone marrow. Until the new stem cells begin producing healthy blood cells, you will be at an increased risk of excessive bleeding or developing an infection.

You will stay in the hospital for about 3 to 4 weeks until your blood counts recover. The duration of hospital stay can be longer if any complication occurs or if your blood counts do not recover on time and you require additional stem cell infusion. During your transplant and

for about 6 months after transplant you will receive antibiotics to prevent some specific infections that can occur after transplant. Your transplant doctor will prescribe those medications for you based on the hospital's guidelines.

Use of HIV-1 Medications During the Study

You are expected to take your anti-HIV medications during this study except for two occasions:

1. The anti-HIV medications you are currently taking may be stopped during BEAM chemotherapy, and may be held immediately after that if you cannot tolerate taking oral medicines because of the side effects of BEAM chemotherapy. The anti-HIV medications will be resumed as soon as you are able to tolerate taking pills. The study doctor will let you know if any of your anti-HIV medications need to be stopped. In addition, some antiretroviral therapies may have effects on the bone marrow during its recovery (e.g., zidovudine) or may interact with BEAM chemotherapy causing side effects. The study doctor will let you know if any of your anti-HIV medications need to be changed.
2. At a minimum of 6 months after transplant and only when we document that your immune system has recovered from the transplant, you will be asked if you would agree to stop all anti-HIV medications until you meet criteria for resuming your medications. This is to give an opportunity for the immune cells that have anti-HIV genes in them to increase in number; the cells that do not have anti-HIV genes will be eliminated. We will check your level of HIV-1 in the blood and its impact on your blood cells and your general health weekly.Your doctor will restart your anti-HIV medications if you or your doctor decides this is necessary, or you feel uncomfortable at any time. The decision to stop the anti-HIV medications during that time is voluntary and will not affect your follow up in this study. Even if the approach works, your virus is expected to come back (rebound) for several weeks before it comes under control. If the regimen works, the viral rebound will be temporary, meaning that it should go up and then down, but this is not guaranteed. Different participants might have different "patterns" of rebound – quick versus slow, high levels versus low levels, short versus prolonged. During this time, the study doctor will monitor you very carefully. Your capacity to transmit HIV will increase during this time, particularly when the virus rebounds, so we will ask you to protect your sexual partner(s). The study doctor will give you information on HIV testing sites and HIV prevention programs and will counsel you about risks related to stopping your HIV medications.

If you choose to pause your HIV medications, you will be asked to get tested for the virus that causes COVID-19. If the test is positive, we will ask you to stay on your HIV medicines until you recover. During the period when you pause taking your HIV medications, if you experience COVID-19 symptoms you will be asked to get tested for the virus that causes COVID-19. If you test positive, you will need to resume your HIV medications.

The follow-up study visits will be in an outpatient clinic. Your study doctor or a nurse will see you in the clinic to assess your health status. You will be requested to have blood tests on a periodic basis after you finish receiving the experimental treatment. These blood tests include:

- About three and a half tablespoons of blood will be taken from a vein in your arm for the blood tests to test the status of your health, and
- Approximately 4 large tablespoons of blood (60 mL) will be taken from a vein in your arm at

several time points for studies of your immune system, genetic studies of the effect of introduced gene in your blood cells and HIV-1 studies.

Optional Intestinal Biopsies

With your consent, we will collect optional biopsies from your upper intestine to see if combining the autologous stem cell therapy with gene therapy works to treat your lymphoma. More information about this optional study will be explained to you in the Additional Studies Section of this consent.

Optional Blood Tests:

With your consent, we will ask you have to have blood tests to monitor the levels of HIV in your blood. More information about this optional study will be explained to you in the Additional Studies Section of this consent.

Optional Bone Marrow Biopises

With your consent, we will collect optional bone marrow biospies to study the effects of the introduced gene on your genetics and immune systems. You can find more information about this optional study in the Additional Studies Section of this consent.

A study calendar that shows how often these exams, tests, and procedures will be done is attached.

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

You may have side effects while on this study. Everyone taking part in the study will be watched carefully for any side effects. However, the study doctor may not know or be able to predict all the side effects or risks. Side effects may be mild or very serious. The study doctors may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. You should talk to the study doctor about any side effects that you have while taking part in the study.

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss.
- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The study doctor may adjust the study drugs to try to reduce side effects. The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

The side effects associated with this study can be divided into side effects associated with autologous transplant that is the standard of care for the treatment of your lymphoma, and the side effect associated with gene therapy that is specific to your participation in this clinical trial.

Potential Side Effects with Autologous Transplant with BEAM Chemotherapy Include (But Not Limited To):

COMMON, SOME MAY BE SERIOUS In 100 people receiving BEAM, more than 20 and up to 100 may have:
• Low blood counts • Nausea/vomiting • Mouth sores • Sores in esophagus • Abdominal pain/diarrhea • Difficulty eating • Hair loss • Fatigue

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BEAM, from 4 to 20 may have:
• Liver problems • Lung problems • Low blood pressure • High levels of uric acid • Skin rash • Chills

RARE, AND SERIOUS In 100 people receiving BEAM, 3 or fewer may have:
• Liver failure • Severe lung problems • Severe allergic reactions • Second cancers, including Myelodysplastic Syndromes (MDS) and leukemia • Life-threatening infection • Disease of the peripheral nervous system • Sterility

Potential Side Effects with Gene Therapy Include (But Not Limited To):

As with any procedure, new adverse effects resulting in injury may be discovered. However, a similar gene therapy clinical trial for HIV-1 with a similar product given to five previous participants in a different institution was well tolerated. In the laboratory, no side effects have been seen. However, the potential side effects are:

- Failure of the stem cells to "take" and thrive in the bone marrow after infusion (this is known as engraftment). Back up stem cells will be saved if you are in the third group, and can be given to you if this happens.
- Gene therapy could theoretically cause leukemia. This has not been seen with this gene therapy model in the laboratory in extensive testing and in limited human studies with a similar vector. Four instances of leukemia were reported in children who participated in an experimental gene therapy study conducted in France, not under the jurisdiction of the U.S. Food and Drug Administration (FDA). In that study, children were treated by gene therapy for a serious genetic disease.
- Allergic Reactions: Proteins made from large amounts of non-human (protein) can sometimes lead to future allergic reactions. There is a small amount of a modified protein in the modified cells for which there is a small chance of allergic reaction, but it is unlikely to be harmful to you even if it occurs. If an allergic reaction occurs, it is more likely that the modified cells will be destroyed. After you receive the stem cells, your blood will be tested for any reaction that could affect the use of these agents in the future, but this reaction would not be directly harmful to you. This reaction is estimated to happen in about 4 out of 100 people.
- Reproductive Risks: You should not get pregnant, breastfeed, or father a baby during stem cell transplant and for the first 3 months after the day of stem cell transplant. The stem cells with anti-HIV genes used in this study could be very damaging to an unborn baby.

  If you are a woman of childbearing age, you can only be admitted to the study if:

a) you are not breast feeding;

b) you are not pregnant (as determined by a pre-study blood test for pregnancy);

c) you have been surgically sterilized or are using effective birth control.

Since the effects of the proposed treatments on a fetus are unknown, any woman who becomes pregnant while on this study must immediately let the study doctor know and will be removed from the study. Another method of treatment will be suggested.

If you are a male participant, you must practice effective birth control. You must immediately let the study doctor know if your partner becomes pregnant, and advise your partner to contact her physician.

Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

- Unknown Risks: The experimental treatments may have side effects that no one knows about yet. In addition, there may be problems of gene therapy that are unexpected but which may occur. The special virus ("retroviral vector") that is used to modify your cells does not have the genes needed to reproduce itself, but it is possible in the future that it could combine with other genes in your body, or that it could activate an unknown virus in your body, to result in a known or unknown medical problem or disease, including the possibility of another cancer.

For more information about risks and side effects of the gene therapy transplant, ask your study doctor.

Potential Side Effects with Stem Cell Infusion Unrelated to the Gene Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving Gene Therapy, more than 20 and up to 100 may have:
• Low blood pressure • Lightheadedness • Fainting • Fever • Decrease in oxygen in the blood

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gene Therapy, from 4 to 20 may have:
• Rapid heart rate • Chills • Allergic reactions

RARE, AND SERIOUS In 100 people receiving Gene Therapy, 3 or fewer may have:
• Bronchospasm (asthma like symptoms) • Second cancers, including leukemia

Additionally, while the cells are infused you may experience a garlic-like taste and a scratchy throat sensation. This is caused by the chemical used to preserve the cells and is usually a mild and temporary discomfort.

Risk of Antiviral Therapy Withdrawal: Your doctor will ask if you would agree to stop taking your anti-HIV medications on at least two occasions as discussed above.

Each time you stop your anti-HIV medications, there is a potential risk that HIV-1 infection become reactivated and suppress your immune system and make you susceptible to severe and potentially life threatening infections. The study doctors, including your HIV-1 doctor, will closely watch your immune system and will restart your anti-HIV medications if HIV viral reactivation and suppression of immune system reaches certain levels. However, restarting the anti-HIV medications may not completely stop the risk of complications.

Your HIV viral load will increase several days to weeks after you stop your HIV medications. The viral load might increase to very high levels. If this happens, your CD4+ T cell counts will likely drop. It is important to realize that, in this study, the doctors will monitor you very closely and will restart your HIV medications as soon as it is clear that the viral load or T cell count puts you at high risk of developing any new clinical problems. Your viral load and immune function might take over 4-6 weeks to return back to levels comparable to where they were when you entered the study.

When your HIV medications are stopped, you might have symptoms similar to when you first were infected with HIV, such as fever, rash, swollen glands, headache, sore throat, nausea, or vomiting. Other serious inflammation related symptoms, like increased buildup of plaque on artery walls which could possibly result in future heart attacks could happen. If you develop these symptoms, the study team will examine you and may restart your HIV medications if they believe the symptoms are due to increased HIV levels.

Resistance to your HIV medications might occur once viral loads become detectable. However, because the study doctor will stop all of your HIV medications the same time, the risk of developing resistance to your HIV medications is lower.

While you are off your HIV medications, you are at increased risk of transmitting HIV to sexual partners. You may also be at increased risk of becoming infected with a different HIV strain (called "superinfection"). Therefore, you should use male or female condoms at all times after HIV medications are stopped. If you feel you may have exposed someone to HIV, you should immediately refer them for testing and post-exposure prophylaxis (PEP). You should also seriously consider referring your HIV- negative sexual partner(s) for pre-exposure prophylaxis (PrEP) if you will be sexually active during the treatment interruption period. If you feel you have been exposed to HIV while off your HIV medications you may restart your medication this is recommended by your primary care provider.

If you are a woman and become pregnant while not taking your HIV medications, the study team will ask you to restart your medications immediately because there is a chance that you could transmit HIV to your developing baby.

Considerations related to COVID-19

There are additional risks of participation in this study due to the SARS-CoV-2 pandemic. SARS-CoV-2 is the virus that causes COVID-19, which is an illness that affects each person differently. Some people have no symptoms at all, and some people have very severe symptoms that require hospitalization, oxygen, or support with a breathing machine. COVID-19 is a potentially deadly illness.

The effects of COVID-19 in people with HIV are not fully known. It is currently thought that people with HIV on HIV medications are at similar risk of getting severe COVID-19 as people without HIV. The risk in people with HIV who are not taking HIV medications is unknown, but may very well be higher. This is important during the portion of the study when you will be asked to pause your HIV medications. If you choose to pause your HIV medications, you will be asked to get tested for the virus that causes COVID-19. If the test is positive, we will ask you to stay on your HIV medicines until you recover. Once you pause your HIV medications, you will be offered testing periodically or if you develop symptoms. If a test for the virus that causes COVID-19 returns positive, you may be asked to restart HIV medications.

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

You may not personally benefit from participating in this study. This study may help us learn things that may help people in the future.

CAN I STOP TAKING PART IN THIS STUDY?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your samples or your medical information to the organization running the study. If you decide you no longer want your samples to be used, any sample that remains will be destroyed and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

WHAT ARE MY RIGHTS IN THIS STUDY?

Taking part in this study is your choice. No matter what decision you make, and even if your

decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

The gene modified anti-HIV stem cells will be supplied at no charge while you take part in this study. The cost of getting a regular stem cell transplant as a standard of care for your disease is not paid by the study sponsor, so you or your insurance company may have to pay for this usually before transplant.

You and/or your health plan/insurance company will need to pay for all the other costs of taking care of your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in the mandatory part of this study. For the optional intestinal biopsy (upper endoscopy), a fee of $300 for each procedure completed will be paid to you.

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will **not** offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

WHO WILL SEE MY MEDICAL INFORMATION?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.

- The Food and Drug Administration and the National Cancer Institute in the U.S.
- The drug manufacturers supporting the study (University of California Davis and University of Indiana).

WHERE CAN I GET MORE INFORMATION?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, but you or your study doctor will know the results if requested.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collections for Laboratory Studies and Donation of Leftover Tissue Samples to the Aids and Cancer Specimen Resource (ACSR)

Researchers are trying to learn more about cancer, HIV/AIDS, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect these specimen types:

- **Optional intestinal biopsy:** To obtain important information about the efficacy of this study, we would like to ask you to provide a biopsy sample from your upper intestine. Your doctor will discuss this with you 6 months after the transplant, or when your CD4 count is greater than 300 cells/ mm^3. The endoscopy would be repeated 2 months after the first biopsy. **If you agree to the intestinal biopsy 6 months and 8 months after the transplant, you will be asked to sign a separate consent at that time before those procedures.** Our study partner at The University of California San Francisco is conducting a cohort study called SCOPE. There is also optional intestinal biopsies in this study. If you chose to coenroll in the SCOPE study, we will use their intestinal biopsy results for both studies. SCOPE is a separate study and requires a separate consent form. Participation in SCOPE is not a requirement of this study. If you agree to participate, you will be asked to sign a separate SCOPE consent form. We will give you the contact information for the SCOPE team if you are interested in learning more.
- **Optional bone marrow biopsies (for participants that do not have bone marrow involvement at baseline):** If you agree to participate in the optional portion of the study, we will request a research bone marrow biopsy or aspirate performed for research studies at 3 months, 12 months after your stem cell infusion, and when you discontinue the study. These studies would normally be standard of care if there is lymphoma in your bone marrow. These samples will be used to monitor the effects of the introduced gene on your genetic and immune systems.
- **Optional blood collections:** If you choose to take part in this study we will request optional lab studies every 12 months for years 3-15 to monitor your HIV levels and to see how the vector is working in your body.
- **Donation of left over study specimens to the ACSR for all study participants:** If you choose to take part in this clinical trial, the researchers would like to collect unused blood and biopsy tissue left over after the study is done. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking." The Biobank is being run by the **AIDS and Cancer Specimen Resource** and is supported by the National Cancer Institute.

What is Involved?

If you agree to take part, here is what will happen next:

1) **Optional intestinal biopsy:** An endoscopy will be performed to obtain small GI tissue samples. An endoscope (a small flexible tube) will be inserted into your stomach and a small tissue sample will be collected from your upper intestine using forceps. We will attempt to collect 24 very small tissue samples during each endoscopy session from you.
2) **Optional bone marrow biopsies:** About 2 tablespoons (20mL) of your bone marrow will be collected. A bone marrow biopsy is performed using a hollow needle to remove a small sample of bone marrow. Before the biopsy, a local anesthetic is used to numb the area where the needle will be inserted.
3) **Optional blood sample collections:** We will ask you to have about 3 tablespoons (30 mL) of blood collected. You will be seated in the lab or clinic and blood will be drawn by putting a needle into a vein in your arm.
4) **Donation of left over study specimens to the ACSR for all study participants:** Your sample and some related health information will be stored in the ACSR Biobank, along with samples

and information from other people who take part. The samples will be kept until they are used up. Information from your medical record may be updated after the study is over.

Qualified researchers can submit a request to use the materials stored in the ACSR. A science committee at the ACSR will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.

Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

Optional bone marrow biopsies, intestinal biopsy, and blood samples collected may be stored for up to 15 years to address research questions related to the treatment or the disease under study.

What are the Possible Risks?

Risks of Participating in the Optional Intestinal Biopsy (Upper Endoscopy)

1) Endoscopy risks: The upper endoscopy is being performed as a part of a research project. The risks of endoscopy are remote, however, there can be pain, gagging, bleeding, infection, perforation (a hole through the bowel wall can occur) and rarely, death can occur.
2) Sedation risks: The risks of intravenous sedation (putting someone to sleep) include bleeding, bruising, pain, infection from intravenous catheter, low blood pressure, decreased breathing, and allergic reaction to the medicine.
3) Allergic reaction risks: Symptoms of allergic reaction may vary from individual to individual but often consists of generalized rash (red skin), itchiness, and a feeling of being excited or anxious.
4) Very rarely swelling of the throat and/or difficulty breathing can accompany these symptoms. Occasionally (rare), midazolam (also called versed, a drug used for sedation) may cause a state of over excitement. The risks for small bowl biopsy are perforation and bleeding. These events have occurred in some patients though not with these physicians. These risks will be explained to you again by in detail prior to the endoscopy procedure by the gastroenterologist.
5) Reproductive risks: You should not become pregnant or father a baby if having an upper endoscopy because the drugs used during the procedure can affect an unborn baby. Women should not breastfeed a baby if having an upper endoscopy. It is important to understand that you need to use birth control. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Risks of Participating in the Optional Bone Marrow Biopsies:

The procedure may cause discomfort, pain, bleeding, scarring or infection at the site of the aspirate/biopsy. There is also a small chance that you could have an allergic reaction to the numbing medicine. After your skin heals, you may have a small scar where we took the sample.

Risks of Participating in Optional Blood Sample Collections

The risks of taking blood include pain, a bruise or lump at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

Risks of Donation of Left Over Study Specimens to the ACSR

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How Will Information About Me be Kept Private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. The ACSR and AMC staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the ACSR and the AMC send your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the Possible Benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are There any Costs or Payments?

There are no additional costs to you or your insurance for these optional studies. You will not be paid for taking part in the mandatory part of this study. For the optional intestinal biopsy (upper endoscopy), a fee of $300 for each procedure completed will be paid to you. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I Change My Mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I Have More Questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

Samples for Future Research Studies:

I agree to have an optional intestinal biopsy and/or have biopsy results from the SCOPE study used for this study as described above.

☐ YES ☐ NO Participant Initials: ____

I agree to have to have bone marrow biopsies as described above

☐ YES ☐ NO Participant Initials: ____

I agree to have blood samples collected as described above.

☐ YES ☐ NO Participant Initials: ____

My samples and related information may be donated to ACSR Biobank for use in future health research.

☐ YES ☐ NO Participant Initials: ____

I agree to have my samples undergo genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

☐ YES ☐ NO Participant Initials: ____

This is the end of the section about optional studies

MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

I have read the consent form or had it read to me and understand the information above. I have discussed it with the study doctor and my questions have been answered I understand that I will be given a signed and dated copy of this consent form. I agree to take part in the main study and any additional studies where I circled 'yes.' My signature below indicates that I understand my rights and want to take part in this study as a research participant.

Participant's signature: _____

Date of signature: _____

Signature of person(s) conducting the informed consent discussion: _____

Date of signature: _____

ATTACHMENT 1: AMC CERTIFICATE OF CONFIDENTIALITY STATEMENT

The NIH has given the AMC a Certificate of Confidentiality. The Certificate does not mean that the NIH or the U.S. Government recommend that you take part in this study. This Certificate helps us keep your health information private.

Your records for this study will have information that may identify you. This Certificate lets us turn down legal demands for your study records. We can use the Certificate to turn down demands for records from a U.S. court. The Certificate can be used in any federal, state, or local legal matters. We will use the Certificate to turn down any demands for your study records. The cases where we cannot use the Certificate are explained below.

We cannot use the Certificate to turn down a demand from the U.S. Government for study records. This applies to audits or reviews of the AMC. This also applies to study records that we have to report to the FDA.

The Certificate does not stop you or your family members from sharing your health information. It does not stop you from talking about taking part in this study. You may give written permission for an insurer, employer, or other person to get copies of your study records. If you give permission, we cannot use the Certificate to say no to a request for your study records.

ATTACHMENT 2: STUDY CALENDAR

Prior to study enrollment and treatment, the following tests will be performed:

Required Studies/Testing	Within 8 weeks prior to enrollment (stem cell collection)	Within 1 week prior to admission for transplant	On the day of admission for transplant before start of chemotherapy
Medical history and physical examination	X	X	X
Infectious disease tests	X		
Chest X ray	X	X	
Heart strip	X		
Imaging for staging of your disease	X		
Lung function test	X		
Kidney function blood tests	X		
Bone marrow biopsy	X		
Tests for HIV-1	X	X	
Heart tests	X		
Review of your diagnosis slides	X		
Tests of your immune systems	X	X	X
Future research blood sample		X	
Pregnancy test for females of childbearing potential	X		X

After you receive your stem cell transplant, you will have the following tests and follow up visits:

Study Assessments/ Testing Post Transplant	Weeks after-HCT					Months After-HCT												Years After-HCT
	1	2	3	4	6	2	3	4	6	8	10	12	14	16,	18	20	22	24	3-15, once a year
Blood count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
History and physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging for staging of your disease							X		X			X						X	
Required bone marrow if you have bone							X					X							X

Study Assessments/ Testing Post Transplant	Weeks after-HCT					Months After-HCT													Years After-HCT
	1	2	3	4	6	2	3	4	6	8	10	12	14	16,	18	20	22	24	3-15, once a year
marrow involvement (for staging your disease)																			
Optional bone marrow biopsy (for research)							X					X							X
Optional GI biospy									X	X									
Tests of your immune system				X		X	X	X	X	X	X	X			X			X	X*
Tests for HIV-1 activity							X		X	X	X	X		X		X		X	X*
Genetic testing				X		X		X	X	X	X	X			X			X	X*
Telephone contact with you or your health care provider for the follow up of HIV status and development of any other cancer																			X

Most of the tests above involve standard medical care. Standard care is what is normally done to prevent, diagnose, or treat a certain condition or illness. Other parts of this study, namely administration of stem cells with anti-HIV gene in them is investigational. Furthermore, the follow up visits and test for assessment of the side effects and the evaluation of your immune system will be a part of the study, and out of the standard of care boundaries, and the follow up blood work may involve that are being tested for a certain condition or illness.

Assessments if you stop taking your HIV medicaitons:

Assessments	Within 1 Week prior to stopping HIV medications	After stopping your HIV medications (for about 12 weeks or more)	After you resume taking your HIV medications			
		Weekly	When you start	W4	W8	W24

			your HIV medications			
COVID Testing	X					
Stop taking ART medication		X				
Clinical Assessment		X	X	X	X	X
Tests on your immune system		X	X	X	X	X
HIV studies		X	X	X	X	X
Blood samples collected for research			X	X	X	X
Couseling about not taking your HIV medications	X	X				