A Phase I Study to Evaluate the Effects of Vorinostat and HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC) on Persistent HIV-1 Infection in HIV-Infected Individuals Started on Antiretroviral Therapy

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Vorinostat and HIV-1 multi-antigen, expanded specific T-cell Therapy (HXTC Therapy)

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LIST OF ABBREVIATIONS

2 LTR	2-long terminal repeat
AE	Adverse Event/Adverse Experience
AHI	acute HIV infection
ALK PHOS	alkaline Phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	antigen-presenting cell
ART	antiretroviral therapy
ATC	autologous T cell APCs
AST	aspartate transaminase
AUC	area under the curve
BID	twice a day
BMT	bone marrow transplant
ca-RNA	cell associated RNA
CB	cord blood
CCIR	Center for Cancer and Immunology Research
CETI	Program for Cell Enhancement and Technologies for Immunotherapy
CFR	Code of Federal Regulations
CHI	chronic HIV-1 infection
CRF	case report form
CMV	Cytomegalovirus
CNH	Children's National Hospital
CTLs	cytotoxic T cell lymphocytes
CTRC	Clinical and Translational Research Center
DCs	dendritic cells
DHHS	Department of Health and Human Services
DSMP	Data Safety and Monitoring Plan
EBV	Epstein-Barr virus
EBNA1	Epstein-Barr virus nuclear antigen 1
EBV-LCL	Epstein-Barr virus-transformed lymphoblastoid cell lines
FDA	Food and Drug Administration
GM-CSF	granulocyte macrophage colony-stimulating factor
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

GVHD	graft versus host disease
HBV	hepatitis B virus
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HDAC	histone deacetylase
HL	hodgkins lymphoma
HLA	human leukocyte antigen
HPC	hematopoietic progenitor cell
HPLC	high-performance liquid chromatography
HXTC	HIV-1 antigen expanded specific T-cell
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IFN-γ	interferon- gamma
IND	Investigational New Drug Application
IL-1β	interleukin 1, beta
IL-2	interleukin-2
IL-4	interleukin-4
IL-6	interleukin-6
IL-7	interleukin-7
IL-12	interleukin-12
IL-15	interleukin-15
IR	immune response
IRB	Institutional Review Board
IUPM	infectious units per million
IM	intramuscular
IV	intravenous
Leuk	leukapheresis procedure
LLN	lower limit of normal
LMP	latent membrane protein
LMP1	latent membrane protein 1
LMP2	latent membrane protein 2
LRA	latency-reversing agent
MS	mass spectroscopy
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NHL	non-hodgkin’s lymphoma

NNRTI	non-nucleoside reverse transcriptase inhibitor
NPC	nasopharyngeal carcinoma
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PACT	Production Assistance for Cellular Therapies
PBMC	peripheral blood mononuclear cell
PGE1	prostaglandin E1
PHA	phytohemagglutinin
PI	protease inhibitor
PLWH	People Living With HIV
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disorder
QVOA	quantitative viral outgrowth assay
rca-RNA	resting cell associated RNA
RCI	resting cell infection
SAE	Serious Adverse Event/Serious Adverse Experience
SCA	single copy assay
SFC	spot forming cell
SOE	schedule of events
SIV	simian immunodeficiency virus
SMC	safety monitoring committee
T-APC	T-antigen-presenting cells
TCR sequencing	T cell receptor sequencing
TEAE	treatment emergent adverse events
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
UNC	University of North Carolina
US	United States
VIA	viral inhibition assay
VST	virus-specific T-cell
VOR	vorinostat
WNL	within normal limits

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1 PROTOCOL SUMMARY

Title:	*A Phase I Study to Evaluate the Effects of* V*orinostat (VOR) and HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC) on Persistent HIV-1 Infection in HIV-Infected Individuals Maintained on Suppressive Antiretroviral Therapy (**XTRA study**)*
Hypothesis:	The combination of HXTC therapy and multiple doses of VOR will result in depletion of persistent, latent, replication-competent HIV infection.
Objectives:	Primary: 1. Evaluate the safety of serial administration of VOR followed by autologous ex vivo expanded HIV-1 specific T-cells (HXTC) therapy in participants maintained on suppressive combination antiretroviral therapy (ART). 2. Evaluate the association of serial VOR dosing and serial HXTC therapy on the frequency of resting CD4 T cell infection (IUPM) via quantitative viral outgrowth (QVOA) in participants who complete the leukapheresis procedure (#2) in Step 6, Visit 23. Secondary: 1. Explore the ability of combination VOR and HXTC therapy to increase HIV-1 specific immune responses in participants maintained on suppressive ART. Other Outcome Measures: 1. Explore the influence of HXTC therapy combined with serial VOR doses on low-level plasma viremia as measured by single copy assay (SCA) in participants who maintained suppression on ART. 2. Explore the impact of VOR and HXTC therapy on the ability of CD8 T cells to enhance clearance of latently infected cells as they emerge from latency in a latency clearance assay. 3. Explore the impact of VOR and HXTC therapy on integrated proviral DNA quantification. 4. Explore the impact of VOR and HXTC therapy on the presence and persistence of T cell escape variants within the latent reservoir
Population:	Men and women living with HIV, ≥ 18 and < 65 years of age, with durable viral suppression for ≥ 24 months as measured on standard HIV RNA assays. Eligible participants must be on stable ART and have a CD4 count ≥ 350 cells/mm^3.
Phase:	Phase 1
Number of Sites:	Single site – University of North Carolina at Chapel Hill
Description of Intervention:	In Step 1 and prior to initiating the two series of VOR and HXTC combined therapies, all participants will undergo study screening and enrollment where they will be required to:

1. Demonstrate a baseline measurement of the frequency of resting CD4 T cell infection ≥ 0.3 infected cells per million as determined by QVOA, as a further decrease from this low frequency of infection cannot be definitively measured given the QVOA assay threshold

Participants with an IUPM measurement ≥ 0.3 will provide whole blood cells for the manufacture of their HXTC product (Step 3). Successful manufacturing of the HIV-1 antigen expanded specific T cells will progress participants to combination treatment in Steps 4 and 5. In Steps 4 and Step 5, participants will receive two series of VOR dosing and HXTC infusions, for a total 20 doses of VOR 400 mg and 5 HXTC infusions.

In the first series (Step 4), participants will receive VOR 400 mg PO every 72 hours for 10 doses and 2 infusions of HXTC. The first HXTC infusion will be administered six hours after the first dose of VOR (HXTC #1) and the 2nd HXTC infusion (HXTC #2) will occur 6 hours after the 6th dose of VOR.

In the second series in Step 5, participants will receive an additional 10 doses of VOR 400 mg PO every 72 hours and 3 HXTC infusions. The first HXTC infusion in Step 5 (HXTC #3) will occur 6 hours after the 11th dose of VOR (1st dose in Step 5), the 2nd HXTC infusion (HXTC #4) will occur 6 hours after the 16th dose of VOR, and the 3rd HXTC infusion (HXTC #5) will occur 1 – 3 days after the 20th dose of VOR.

If there are insufficient cells manufactured to allow 5 infusions at 1 x 10^8 cells/m^2 dose, the dose will be adjusted to allow 5 infusions at a dose ≥ 5 x 10^7 cells/m^2 but < 1 x 10^8 cells/m^2 dose.

Study Duration:	48 months
Subject Participation Duration:	Up to 12 people living with HIV (PLWH) on ART will be followed for approximately 52 weeks after the last HXTC infusion. Up to 6 of these participants will have started ART during acute HIV infection.
Estimated Time to Complete Enrollment:	36 months

NOTE: THE PROTOCOL AMENDMENT FOR VERSION 3.0, DATED 20 DECEMBER 2019 ELIMINATED STEP 2 OF THE PROTOCOL. IN ADDITION, THE PROTOCOL AMENDMENT FOR VERSION 4.0 DATED 31 JANUARY 2022 ELIMINATED VISITS 22, 25, AND 26. TO AVOID DATA AND PROTOCOL IMPLEMENTATION ISSUES RELATED TO RENUMBERING ALL STUDY VISITS AND STEPS, WE OPTED TO REMOVE STEP 2 AND VISIT NUMBERS 3, 4, 22, 25, AND 26 FROM THE PROTOCOL.

2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. BACKGROUND INFORMATION

HIV INFECTION AND THE NEED FOR ALTERNATIVE THERAPIES: There are still over 37 million PLWH worldwide, 1 million of which reside in the United States (US). Despite educational and medical resources, the number of new infections far outpaces the number of

those starting on combination antiretroviral therapy (ART) [1]. Over 50% of the affected individuals in the US are minorities, with the African American population most affected. Despite the success of ART in suppressing HIV viral load, it cannot eradicate established HIV infection due to the presence of persistent HIV infection in the form of latent, transcriptionally silent but inducible replication-competent virus that is impervious to ART, which only blocks spread of actively replicating virus [2-4]. Latent HIV infection can, however, reactivate, necessitating lifelong ART adherence to prevent viral rebound and, in some cases, the emergence of drug resistance. However, treatment of HIV-1 infection remains a significant financial burden in the US, at an estimated $379,668 life time cost/patient [5], and daily ART adherence is challenging. The Center for Disease Control estimates that only 28 out of every 100 HIV-infected individuals in the US are engaged in care and adherent with ART [6]. Even for those who do successfully adhere to ART, the long-term use of ART has side effects and does not completely eliminate the effects of persistent low level inflammation, reflected by an increased risk of neurologic and cardiovascular disease as well as malignancies [6-8]. Innovative therapies to purge the latent reservoir, thereby eradicating HIV-1 infection, are urgently needed [4, 9].

ELIMINATING THE LATENT RESERVOIR: ***Induction of Viral Expression.***

Eradication of HIV will require elimination of the latent reservoir. Resting CD4+ T cells are the most well characterized contributor to the latent HIV reservoir [4]. Host cell molecular mechanisms maintain the quiescence of HIV gene expression in infected resting CD4+ lymphocytes, and could therefore serve as therapeutic targets for disrupting latency. One well defined mechanism contributing to maintenance of latency is the recruitment of histone deacetylases (HDACs) to the HIV long terminal repeat (LTR) promoter, mediating the formation of a repressive chromatin environment that inhibits LTR expression and viral production [10-13]. The relevance of this mechanism has been validated in the resting CD4+ T cells of ART-treated, aviremic, PLWH [11, 12, 14], and extended by several research groups [15-18]. Our group has attempted to translate these discoveries into anti-latency therapy, and while the task has been challenging we have made steady progress. An initial study demonstrated a depletion of resting cell infection (RCI) in three of four ART-treated PLWH receiving intensified ART and the weak HDAC inhibitor (HDACi), valproic acid (VPA) [19]. However, further studies by our group and others found infrequent or modest depletion of RCI in participants treated with VPA [20-23].

In pre-clinical studies, we and others found that the more potent HDACi, Vorinostat (VOR), which is already licensed for use in patients with cancer, induces HIV chromatin acetylation and promoter expression in cell lines, and virus production ex vivo from the resting CD4+ T cells of PLWH on suppressive ART [24, 25]. This effect was achieved without upregulation of cell surface markers of activation, HIV co-receptors, or de novo HIV infection. We then demonstrated a significant increase in cell-associated RNA production following in vivo administration of VOR to ART suppressed individuals, the first direct proof-of-concept of latency reversal [10].

However, administration of a latency reversing agent (LRA) alone would not be expected to deplete the latent reservoir, as viral cytopathic effects do not appear prominent in the absence of full T cell activation and high-level virus production [26]. An effective HIV-specific immune response will be necessary to clear latently infected cells following induction of viral expression [4, 26-28]. Further, it is not yet clear that the induction of cell-associated HIV RNA expression observed in several studies leads to the expression of viral antigens that could mark the infected cell for clearance. By combining the most well characterized latency reactivating agent, VOR, with a powerful and precisely controlled immune augmenting tool, this study may provide definitive evidence that a latency reversing agent can induce clinically relevant HIV antigen expression, and allow depletion of the latent reservoir.

ELIMINATING THE LATENT RESERVOIR: ***Enhancing the HIV-specific T cell Response.***
Recent work suggests that in most individuals the existing low frequency CD8+ T cell responses are insufficient to clear the latent reservoir [26], in part because of CD8+ T cell escape mutations which arise within weeks of HIV-1 infection and are archived in the latent reservoir [28-31]. Strategies to eliminate the need for ART by strengthening HIV-specific T cell immune responses using a therapeutic vaccine have been attempted, but with disappointing results [27, 32-34]. Most notably, only a small number of vaccine trials have reported the impact of vaccines on the size of the latent reservoir; finding either no sustained impact [35] or, at best, a small, transient decline in the frequency of replication competent latent infection [52] that was below the threshold of what our group has found to be significant [36]. These failures in part can be attributed to the poor immunogenicity of vaccine regimens employed that failed to produce sustained expansion of HIV-specific CD8+ T cells in the time frame studied, as well as due to a lack of viral expression in latently infected cells [4].

Adoptive T cell therapy has proved very successful in certain oncology settings [37-39]. In this strategy, T cells are isolated from patients, expanded, and then reinfused into the patient. The Bollard group has successfully employed this strategy against reactivated EBV, CMV, and adenovirus in hematopoietic stem cell transplant recipients [37, 39, 40], as well as against EBV mediated malignancies [38, 41, 42]. The infused T cells are highly potent, including, in the cancer setting, inducing sustained complete responses in >50% of patients with high risk or multiply relapsed EBV related lymphoma [38]. Further, gene marking studies have confirmed that adoptively transferred donor-derived EBV specific T cells can be detected at least as far out as ten years post infusion [38]. The benefit to cost ratio is quite favorable, with a cost of about $6,000 per patient to manufacture and infuse virus specific T cells once a program is established [42]. This is in contrast to the estimated annual cost of HIV care of $23,000 (in 2010 dollars) [5, 43].

Adoptive T cell therapy for PLWH was first tested over a decade ago (reviewed in [44]). While these studies established the safety of adoptive transfer of HIV-specific T cells, antiviral efficacy was transient [45, 46]. This was due in part to a reliance on monoclonal T cells, extensive in vitro expansion resulting in a potentially exhausted phenotype, and the infusion of T cells into actively viremic, untreated patients [44]. More recently, HIV-specific T cell therapy was applied in the setting of ART suppression; these T cells persisted in blood and

were capable of homing to rectal tissue following infusion, but virologic outcomes were not reported [47]. Previous studies have also examined the utility of infusing T cells specific for a single HLA-restricted epitope, either by clonal selection or introducing an artificial, high-affinity T cell receptor for the HLA-A2 gag epitope SL9 [48]. Infused T cell clones showed little persistence and no clear long-term reduction in viral load. While high-affinity T cell receptor technology has promising preclinical data, it is not currently feasible to rapidly generate such T cell receptors against a well-conserved epitope for every patient's HLA-type.

In contrast, the advanced manufacturing approach the Bollard group has developed for cancer immunotherapy is more feasible than prior techniques used to generate a Good Manufacturing Practice (GMP) grade T cell product. Within one month it provides a product for any participant, independent of HLA type. We adopted this strategy to the HIV setting, and validated the generation of HIV-1 antigen-specific T-cells in a GMP compliant manner [49]. The advantage of this novel approach for HIV is that T cells may be primed against epitopes that are not immunodominant in vivo [44], thus expanding the breadth of the T cell responses to potentially include putative beneficial, subdominant responses [28, 50]. T cells were stimulated ex vivo with autologous dendritic cells pulsed with overlapping peptides (Pepmixes) spanning both early and late HIV proteins, Gag, Pol, and Nef to elicit a range of HIV-1 specific T cells that detect HIV-1 infected cells at different stages of the virus life cycle and have been associated with delayed disease progression and in vivo viral control [51-56].

The HXTCs generated detect endogenously processed and presented HIV-1 epitopes as demonstrated by specific inhibition of HIV-infected CD4 T cells, are not restricted to a single T cell receptor clonotype (are polyclonal), elicit multiple anti-viral cytokines and lytic molecules (polyfunctional), and can clear HIV latently infected cells following ex vivo exposure to VOR [49, 57]. This study aims to establish that *HIV-1 antigen-specific expanded T-cells (HXTC)* activated and expanded ex vivo can produce improved in vivo HIV-1 specific T cell responses in PLWH who remain on suppressive ART, and combine HXTCs with VOR to achieve clearance of the latent reservoir in vivo. HXTCs are an attractive tool for this proof-of-concept study, as their dose and time of administration can be controlled, allowing the precise delivery of immune effectors following the administration and clearance of VOR.

Dose Rationale

In versions 1 and 2 of this protocol, we infused $2x10^7$ cells/m^2 of HXTC based on doses of T cell therapy that had been effective in the treatment of EBV-related lymphoma. However, higher doses of CTL therapy for lymphoma have subsequently been found to be well-tolerated and feasible from a production standpoint. The experience treating oncology patients with up to twelve doses of up to 1.5×10^8 cells/m^2 per dose suggests that this increase will be safe and rational [80-82]. Given the need to target the rare T cell population with latent HIV infection as compared to tumor cells expressing EBV-related proteins, we propose to increase the dose of HXTCs infused in version 3.

As of 01 December 2019, we have studied individuals under Version 2 of the protocol for this pilot study, with the administration of Vorinostat and five infusions of 2×10^7 cells/m^2 of HXTCs.

There have been no study treatment-related AEs. All observed AEs have been ≤ Grade 1, transient, and judged to be related to the apheresis procedure. However, no significant decline in the primary endpoint of the frequency of persistent HIV infection within circulating resting CD4+ T cells has yet been observed. Two additional individuals will receive HXTCs under Version 2. If no unexpected AEs are observed, under Version 3 of this protocol we will administer an increased number of HXTCs with 5 infusions up to 1.0 x 10^8 cells/m^2 per dose, to an additional six participants.

Rationale: Elimination of latent HIV infection will require 1) induction of viral expression by a LRA and 2) enhancement of the existing HIV-specific immune response to clear the infected cells as they emerge from latency.

We hypothesize that induction of viral antigen expression by administration of VOR to PLWH while maintaining suppressive ART followed by HXTC therapy to recognize and clear the infected cells as they emerge from latency will be 1) safe, 2) increase in vivo, HIV-1 antigen specific T-cell immune responses that circumvent archived viral escape variants and 3) decrease resting cell infection.

2.2. VORINOSTAT (VOR)

VOR is a potent inhibitor of HDAC activity and binds directly to the catalytic pocket of HDAC enzymes. VOR, at low nanomolar concentrations, inhibits the enzymatic activity of HDAC1, HDAC2, and HDAC3 (Class I) and HDAC6 (Class II) [58-60]. Concentrations of VOR that cause the accumulation of acetylated histones also induce cell cycle arrest, differentiation, or apoptosis of transformed cells [59].

VOR induces apoptosis in a wide variety of transformed cells in culture, including cutaneous T-cell lymphoma (CTCL) cell lines, circulating atypical T-cells derived from patients with CTCL, human lymphoma cell lines and murine erythroleukemia (MEL) cells. VOR also inhibits proliferation of cultured transformed human cells derived from leukemias, non-small cell lung carcinomas, colon carcinomas, central nervous system tumors, melanomas, ovarian carcinomas, renal cell carcinomas, prostate and breast cancers. In cultured human transformed cell lines, VOR has synergistic or additive activity in combination with other cancer therapies, including radiation, kinase inhibitors, cytotoxic agents, and differentiating agents [58, 59, 61-68]. In vivo, VOR demonstrates anti-neoplastic activity in a variety of rodent tumor models including xenograft models of human prostate, breast, and colon carcinoma.

While it has been assumed that the effects of VOR on histone acetylation underpin its biological activities, a number of other proteins are regulated by histone acetyltransferases (HATs) and HDACs and may be targeted by VOR [69]. Several non-histone proteins, (e.g., tubulin, Hsp90, and p53) are known to be reversibly acetylated on lysine residues and undergo hyperacetylation following exposure to VOR [70-72]. Acetylation of these proteins may also contribute to the antitumor activity of VOR. Please refer to the VOR Clinical Investigator's Brochure (CIB), edition 8, 8/1/2013, for detailed information.

VOR and HIV

The U.S. Food and Drug Administration has approved Vorinostat (VOR) for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or following two systemic therapies. Due to its potency as an HDAC inhibitor, its effect on HIV infection within resting CD4+ T cells might be more profound than VPA.

The effect of VOR was compared to VPA in J89, a Jurkat T cell line infected with a single HIV genome encoding the enhanced green fluorescence protein (EGFP) within the HIV genome. Histone acetylation at nucleosome 1 of the HIV promoter was assayed by chromatin immunoprecipitation. EGFP mRNA expression was monitored by flow cytometry and RT-PCR, and p24 antigen production by ELISA. Both VPA and VOR induced chromatin remodeling at nucleosome 1, HIV transcription, and virus production in the J89 cell line [25].

Limiting-dilution outgrowth assays compared the ability of VOR, VPA, and maximal mitogen stimulation to induce virus expression from the resting CD4+ T cells obtained at four occasions from three aviremic, ART-treated HIV-infected participants. HIV p24 capsid antigen was measured by ELISA, and infectious units per billion (IUPB) calculated by a maximum likelihood method. Comparable and clinically relevant concentrations of both compounds also induced virus outgrowth ex vivo from participants' cells at similar frequencies.

2.2.1. Nonclinical Pharmacology of VOR

VOR is approximately 71% bound to human plasma proteins over the range of concentrations 0.5 to 50 µg/mL.

VOR has a low propensity to cause or be affected by drug-drug interactions. In animal models and in vitro human systems, the major pathways of metabolism of VOR involve glucuronidation and hydrolysis followed by β-oxidation. Additionally, the glucuronidation of VOR is mediated by multiple uridine diphosphate glucuronosyltransferase isozymes (UGTs), making it less susceptible to drug interactions through modulation of UGTs. VOR is not recovered intact in urine to any appreciable extent. Therefore, compounds known to affect renal elimination are not expected to affect the pharmacokinetics of VOR.

VOR is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state Cmax of the 400 mg dose (Cmax of 1.2 µM vs. IC50 of >75 µM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by VOR at concentrations higher (≥ 10 µM) than pharmacologically relevant. Thus, VOR is not expected to affect the pharmacokinetics of other agents metabolized by CYP enzymes. As VOR is not eliminated via the CYP pathways, it is anticipated that VOR will not be subject to

drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with VOR.

2.2.2. **Nonclinical Toxicology of VOR**

VOR has been investigated in nonclinical acute and oral repeated-dose toxicity studies, reproductive, developmental toxicity studies, and genetic toxicity studies to support oral administration of this compound to humans.

The main toxicities observed in animal models were weight loss and loss of appetite, apparent hemolytic anemia (rats only at 3.8 times the equivalent 400 mg human dose), leukopenia (rats only at 1.3 times the equivalent 400 mg human dose), thrombocytopenia (male rats only, statistically significant change at 0.5 times the equivalent 400 mg clinically effective human dose, but within normal range at all doses), and gastrointestinal tract irritation (dogs only, at 8.5 times the equivalent 400 mg human dose). Although statistically significant and dose-dependent, many of the clinical pathology findings were within normal historical ranges indicating that they should not have major toxicological consequences. The toxicities appeared to be rapidly reversible within 12 to 14 days. There has been no evidence of cardiac toxicity based on electrocardiogram (ECG, dogs only), blood pressure (dogs only), heart rate (dogs only), creatinine kinase, organ weight, gross pathology, or histopathology assessments in studies up to one month duration. No serious, irreversible damage to any vital organ has been observed. Importantly, toxicities in rats and dogs were predictive of adverse effects in humans (anorexia, weight loss, fatigue). Toxicities present in animals would be manageable in the clinic, and the onset of serious toxicity is readily forecasted by prodromal symptoms. The nonclinical toxicity profile of VOR is acceptable for an oncology drug.

2.2.3. **Clinical Pharmacokinetics of VOR**

The pharmacokinetics of VOR following 400 mg single-dose in a fasted state; and 400 mg single- and multiple-doses in a fed (high-fat meal) state were evaluated in 23 participants in a Phase I study with relapsed or refractory advanced cancer using a validated assay. VOR is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of VOR. Recovery of two pharmacologically inactive metabolites, O glucuronide of VOR (OG-V) and 4 anilino-4 oxobutanoic acid (4A4OA), in urine was more substantial.

A population pharmacokinetic model using nonlinear mixed effects (NONMEM, ICON plc) demonstrated that a first-order, transit-compartment absorption and linear elimination best described VOR concentration data. The structural model was: (1) $dXa/dt = -Ka \times Xa$, (2) $dXb/dt = Ka \times Xa - Kt \times Xb$, (3) $dXc = Kt \times Xb - (CLt/Vc \times Xc)$.

Fixed effects: CLt (731 L/h), Vc (5.21 L), Ka (1.35 1/h), Kt (0.7 1/h). Random effects: CLt (26% CV), Vc (76.8%), Ka (73%). Residual error was: 0.0001 ng/mL (additive), 73.6% (proportional). An exponential model was used for inter-individual variability; and a heteroscedastic model was used for residual variability. Weight (power model, Vctyp=Vcwt x Weight (kg)$^{\theta}$, θ=1.17) was found to be a significant covariate on Vc.

2.2.4. **Summary of Clinical Experience with VOR**

VOR has been studied in Merck Research Labs (MRL) sponsored studies, Investigator Initiated Study Protocols (IISP) and National Cancer Institute (NCI) sponsored studies. VOR has been orally administered in Phase I, Phase II, and Phase III clinical studies in participants with advanced solid tumors and hematologic malignancies. VOR has been studied both alone and in combination with other chemotherapy agents. As of 02-Jul-2012, over 5,000 participants have received at least one dose of VOR in studies sponsored by Merck and Co., Inc., the NCI, or independent Investigators.

2.2.5. **Risks Associated with VOR**

The types of adverse experiences observed in clinical trials of VOR in the oncology setting were those usually associated with chemotherapy, such as nausea, fatigue, diarrhea, constipation, and cytopenias. The three major clinical categories of adverse experiences attributable to VOR include a constellation of gastrointestinal symptoms, constitutional complaints, and cytopenias. All adverse experiences were manageable using conventional supportive care for chemotherapy. On the whole, treatment with oral VOR was well tolerated for use in the outpatient setting.

Merck & Co., Inc. sponsored VOR clinical studies showed that adverse experiences considered by the Investigators to be at least possibly related to VOR in ≥10 % of participants included (in descending frequency): nausea, fatigue, diarrhea, anorexia, vomiting, thrombocytopenia, anemia, weight decreased, blood creatinine increased, dysgeusia, hyperglycemia, neutropenia, constipation. The total daily doses studied ranged from 200 mg to 900 mg. The tolerability of oral VOR appears to be determined by total daily dose and the length of consecutive days of dosing. The maximum tolerated dose (MTD) for continuous daily dosing without a rest period is 400 mg daily or 200 mg BID. The MTD for intermittent dosing is 300 mg BID x 3 consecutive days per week, or 250 mg TID x 14 consecutive days followed by a 7-day rest. Dose-limiting toxicities (DLTs) of single agent VOR were mainly non-hematologic (anorexia, dehydration, diarrhea, and fatigue); hematologic toxicities are primarily anemia and thrombocytopenia, most of which were mild to moderate. The majority of these DLTs occurred within the first month on oral VOR. The DLTs were manageable because the toxicities resolved quickly after drug administration was interrupted.

Dose-limiting toxicities (DLTs) have been mainly non-hematologic. The majority of these DLTs occurred within the first month on VOR. At continuous daily dosing of 600 mg QD, 300 mg BID, and 400 mg BID, doses that exceeded the established MTD, the pattern and severity of DLTs were similar. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted. Hematologic events were primarily anemia, leukopenia, and thrombocytopenia. Generally, these events were rapidly reversible after study drug interruption.

Clinical serious adverse experiences (SAEs) regardless of causality have been reported in approximately 39% of the first 350 participants treated with VOR in Merck & Co., Inc. sponsored studies. This overall high incidence may reflect the underlying conditions of participants in this group. Of the participants who had a serious adverse experience, approximately 16% were considered by the Investigator to be related to study medication. Serious laboratory adverse experiences were uncommon, occurring in 3% or fewer of patients in the various populations. By contrast to patients with solid tumors, the incidence of SAEs was higher in patients with hematologic malignancies. Pulmonary embolism and deep vein thrombosis have been reported.

In prior studies, we assessed the intermittent administration of VOR to PLWH suppressed on ART. Thirty-two individuals received at least one 400 mg dose and thirteen received at least 10 doses of 400 mg (with up to 11 doses in one month), and we observed minimal side effects attributed to VOR. We observed no adverse events (AEs) exceeding Grade 1, but for a single episode of Grade 2 fatigue in one participant that resolved after 24 hours without intervention. No AEs led to the interruption of VOR dosing. We observed no new or unique AEs other than those commonly reported. Participants completing the combination VOR and HIV-specific ex vivo expanded T cells (HXTC) protocol will receive no more than a total of 4000 mg (2 cycles of 10 doses) of VOR. For reference, participants who completed our prior multi-dose studies under NIH U01 AI095052 received a total of 10,000 mg and 5200 mg of Vorinostat, respectively, without clear evidence of any durable drug-associated toxicity, and no AE greater than Grade 1.

In this proposed study, participants will receive 10 doses of 400 mg VOR over a 30 day period, then no VOR for 4 weeks. They will then receive a second cycle of 10 doses of 400mg VOR over another 30 day period, for a total of 20 doses. Each participant will receive a total of 5 HXTC infusions; 2 infusions will be administered in the first 4 week cycle and 3 administered in the second 4 week cycle. In our previous study with VOR, most participants exhibited a 15%–35% transient decline in platelet count after 4 weeks of 3 daily doses each week. However, only one participant's platelet count reached grade 1 toxicity level. No other clinical events or drug-related AEs were observed. Given we now propose to administer fewer doses, over a shorter time (20 doses over 3 months), significant toxicity seems unlikely.

2.2.6. **Risk Associated with "unmasking" HIV**

The HDAC inhibitors that "unmask" HIV in latent cells could cause other cells to become infected. However, we have not detected any evidence of this in the participants who received VOR thus far [73, 74]. We have observed a rare "blip" of low-level viremia; however, we have not observed any drug-resistance and/or failure of ongoing ART. Should we observe any instances of detectable HIV-1 RNA (> 50 copies/mL), we would repeat testing to confirm the result and inform all participants of the reason for re-testing. For those with confirmed viremia, we would notify the participant and their primary care provider for management per standard of care. If clinically indicated, blood samples would be obtained to measure antiretroviral serum drug levels and/or HIV phenotype and genotype to measure for the development of resistance. Participants with confirmed viremia > 150 copies/mL will be discontinued from the study.

2.2.7. **Reproductive Toxicity**

VOR rapidly crossed the placenta in both the rat and rabbit, following administration of a dose of 15 mg/kg/day and 150 mg/kg/day, respectively (<1 times the human exposure based on AUC0-24) and reached transplacental equilibrium within 30 minutes post-dose.

Reproductive toxicity studies were conducted in male and female rats to determine potential effects of dosing with VOR for more than 20 days, and up to 26 weeks, on fertility and reproduction. In male rats, there were no treatment-related effects on mating performance, fertility, embryonic/fetal survival, sperm count and motility, testicular weight, or testicular and epididymal histomorphology in any drug-treated group. The NOEL for effects on female fertility was ≥150 mg/kg/day (≥900 mg/m2/day). The NOEL for effects on female reproductive performance, however, as determined by increases in the number of corpora lutea, was <15 mg/kg/day (<90 mg/m2/day), which is below the equivalent human dose expressed on an equivalent surface area basis (250 mg/m2/day).

VOR was evaluated in a panel of genetic toxicity assays; in vitro assays were found to be positive. No human safety data for the use of VOR during pregnancy are available.

2.3. HIV-SPECIFIC EX VIVO EXPANDED T CELL THERAPY (HXTC)

2.3.1. **T cell Therapy in HIV-Infected Individuals**

Support for this phase I study is derived from studies demonstrating the feasibility and safety of infusing PLWH with ex vivo-expanded HIV-specific CTLs that were specific for 1-3 epitopes of Gag, Pol, or Nef [45-47, 75, 76]. The earliest study of

expanded HXTCs in actively viremic participants found that infusion with up to 10^{10} non-specifically activated, expanded autologous CD8+ T cells was safe and tolerable with no CTL related adverse events in 5 participants with AIDS, but enhancement of HIV specific cytotoxicity post-infusion was transient and no impact on virologic outcome was found [77, 78]. In another pilot study of actively viremic participants with CHI, autologous administration of CD8+ CTLs primed to express cytotoxicity against HIV-1 epitopes gp120, gag p17, p24m, and nef produced no toxicity or clinical deterioration over six months of follow-up [46]. Three of six participants showed improvements in plasma HIV RNA levels or CD4+ count at six months despite low enrollment CD4+ counts (100-400 c/mm^3). Two additional studies of one patient each who received an infusion of CTL clones against Gag and Nef, respectively, did not find any impact on viremia due to the short lived nature of the Gag clone and development of HIV escape variants to the Nef clone, but did find that the infusion was safe and well-tolerated [75, 79]. Another small study in three participants on ART but with low level viremia established the safety and tolerability of escalating doses of gag-specific CTL clones of up to 3.3 x $10^9/m^2$ [45]. Transferred HIV-specific CTLs migrated to lymph nodes where they co-localized with HIV RNA+ cells in the parafollicular regions. The presence of CTL clones in the peripheral blood correlated with a significant but transient reduction in the number of HIV-infected peripheral CD4+ T cells. In all of these studies, the only adverse event reported was mild and transient chills and rigors following infusion. These studies established the feasibility and safety of adoptive transfer of HIV-specific CTL clones, but showed only modest results. Notably, these studies were performed in actively viremic HIV-infected participants, and infused cells were generally monoclonal and had been expanded extensively in vitro, hence were likely highly differentiated. In a more recent study, HIV-specific CD8+ T cell clones derived from the central memory population of chronically HIV-infected participants on suppressive ART were expanded in vitro, and following autologous re-infusion could be detected for up to 84 days in blood and rectal tissue and retained or re-expressed memory markers (CD28+, CD62L+) and function (secretion of IL-2 and proliferation on cognate Ag exposure) [47]. Virologic outcomes were not assessed in this study, however. In contrast to the latter study, we will break new ground by generating polyclonal CD4+ and CD8+ T cells specific for multiple HIV epitopes in multiple antigens.

Among these studies and others with HIV-specific T cells, the only adverse events reported were mild and transient fever, arthralgias, myalgias, chills, and rigors following the infusions [45-47, 75-79]. Some of these events were associated with the administration of exogenous IL-2 given in conjunction with T cell infusion. This suggests that it will be safe and perhaps more effective to target these three antigens simultaneously in one T cell product, as proposed with this study. Furthermore, we hypothesize that our HXTCs will be safely tolerated in participants that have been on stable ART with undetectable viral load based on the rationale that these early studies demonstrated the safety of infusing CTLs in higher risk groups including viremic and HIV-infected participants with advanced immunosuppression.

Despite infusing T cells with very limited specificity in order to target a highly mutable virus, only one study showed a single instance of the emergence of escape variants in a severely immunocompromised AIDS patient [79]. Though this demonstrates that escape variants are a low risk, we are further lessening this risk by proposing to infuse broadly-specific T cells. Importantly, not all previous studies excluded the presence of CD4+ T cells in the product and this did not result in increased HIV RNA levels post-infusion. Although CD4+ HIV-specific T cells may be subject to elimination by HIV infection, this risk is lessened by administration only to participants with durable viral suppression on ART, and if functionality and persistence is observed in this phase I study, HIV-specific T cells could be rendered resistant to HIV infection prior to infusion in subsequent trials. The fact that almost all participants who are suppressed on ART have low level (and stable) detectable viremia gives us a quantifiable endpoint following autologous T cell infusion without having to stop therapy in these participants. An impact on low level viremia as measured by a single copy assay (SCA) would be the first signal that these ex vivo enhanced and expanded T cells are having an effect. Taken altogether, the previous human experience with the infusion HIV-specific T cells supports the feasibility and of our novel strategy of polyclonal CD4+ and CD8+ T cells specific for multiple HIV epitopes in multiple antigens in participants with viral suppression on ART.

2.3.2. Safety and Efficacy of antigen specific HIV-specific T cell (HXTC) therapy in humans

Under IND 15984 (HXTC study), we have successfully infused HIV-specific ex-vivo expanded T cells (HXTCs) in four PLWH on suppressive ART to date. The HXTCs were well tolerated with no SAEs reported in any of the participants, with the most common non-serious AE being a transient altered taste during HXTC infusion (expected with DMSO-containing infusions).

Our group has over a decade of experience with safely and effectively treating immunocompromised patients post-transplant with virus-specific T cells and tumor-specific T cells that are manufactured using similar protocols to the HXTC product. Prior work by several groups has demonstrated that CMV, EBV, and adenovirus-specific T cells, including T cells generated using overlapping peptide pools, provide a safe and effective treatment and prophylaxis for viral infections and post-transplant lymphoproliferative disorder (PTLD) in immunocompromised patients post-transplant (**Table 1**).

Table 1: Human Experience–Related INDs, and protocols from co-investigator Catherine Bollard and colleagues.

IND 5049 - Administration of EBV specific cytotoxic T lymphocytes to recipients of mismatched-related or phenotypically similar unrelated donor marrow grafts (ETNA).

IND 6387 – Administration of neomycin resistance gene marked EBV specific cytotoxic T-lymphocytes to patients with relapsed EBV- positive Hodgkin disease (ANGEL).

IND 11186 - Virus specific cytotoxic T-lymphocytes for the prophylaxis of CMV after allogeneic stem cell transplant: a dose-finding trial (VICTA).

IND 12830 – Administration of TGF-β resistant LMP2a-specific cytotoxic T-lymphocytes to patients with relapsed EBV-positive lymphoma (TGFb).

IND 11835 - Administration of virus-specific cytotoxic T-lymphocytes for the prophylaxis and therapy of adenovirus infection post allogeneic stem cell transplant (LYPTAIST).

IND 13958 - Phase I/II study of the administration of multi-virus-specific cytotoxic T lymphocytes (CTLS) expressing CD19 chimeric receptors for prophylaxis of therapy of relapse of acute lymphoblastic leukemia post hemopoietic stem cell transplantation (MULTIPRAT).

IND 14714 - Administration of Tumor-Associated Antigen (TAA)-specific Cytotoxic T-lymphocytes to patients with active or relapsed Hodgkin or non-Hodgkin Lymphoma (TACTAL)

IND 15086 - Administration of rapidly generated LMP, BARF1 and EBNA1 specific Cytotoxic T-lymphocytes to patients with EBV+ Lymphoma (GRALE)

IND 15092 - Administration of Rapidly Generated Multivirus-Specific Cytotoxic T-Lymphocytes for the Prophylaxis and Treatment of EBV, CMV, Adenovirus, HHV6, and BK virus infections post Allogeneic Stem Cell Transplant (ARMS)

IND 15714 - Adoptive Transfer of Cord Blood T cells to Prevent and Treat CMV, EBV, and Adenovirus Infections after Transplantation (ACTCAT2)

IND 15779 - Multivirus-Specific Cytotoxic T-Lymphocytes for the Prophylaxis and Treatment of EBV, CMV, and Adenovirus Infections post Allogeneic Stem Cell Transplant (MUSTAT)

IND 15779 - Administration of Most Closely HLA-matched Multivirus-specific Cytotoxic T-Lymphocytes for the Treatment of EBV, CMV, Adenovirus Infections Post Allogeneic Stem Cell Transplant (CHAPS)

IND 15779 - Treatment of EBV, CMV, and Adenovirus Infections in Primary Immunodeficiency Disorders with Viral-specific Cytotoxic T-Lymphocytes (TREPID)

IND 15772 – Administration of LMP-Specific Cytotoxic T-Lymphocytes to Patients with Relapsed EBV-Positive Lymphoma (ALC12)

2.3.3. Virus specific Cytotoxic T Lymphocytes after allogeneic hematopoietic stem cell transplantation

At St. Jude Children's Research Hospital and Baylor College of Medicine (IND 5049), more than 100 allogeneic HSCT recipients received donor-derived ex vivo expanded EBV-CTLs. The only agent-related adverse events were inflammatory reactions at tumor sites; this was marked in one bone marrow transplant (BMT) recipient with bulky disease at the time of CTL administration and milder in three BMT recipients with subclinical disease (IND 5049).

Subsequently, allogeneic trivirus-(BCM IND 11186), and bivirus-specific (**BCM IND 11835**) CTL derived from HLA-matched related, HLA-mismatched related and HLA-matched unrelated donors (NHLBI-PACT project 00014) were administered to over 40 patients both as prophylaxis and as treatment of viral infections. No adverse events were attributable to the T-cell infusions. None developed more than grade 2 GVHD or other toxicities over the 3 months of safety monitoring after infusion. This study demonstrated that multi-virus-specific T-cells derived from the peripheral blood of seropositive donors were able to expand in vivo and mediate activity against multiple viral reactivations from a single product.

To increase the safety and decrease the manufacturing time of virus-specific T-cells, Bollard and colleagues while at Baylor replaced EBV-transformed B-cell lines and adenoviral vectors as a source of viral antigens with overlapping peptide libraries (pepmixes) spanning the entire protein sequence of protective antigens (those that induce T-cells with protective capacity) from viruses including EBV, CMV, adenoviruses, BK, and HHV6. Large numbers of multi-virus-specific T-cells can be produced after a single stimulation of peripheral blood mononuclear cells (PBMCs) with combined pepmixes. These have been infused in >20 allogeneic HSCT recipients (IND 15092 (Baylor) and IND 15779 (CNMC)). There were no immediate infusion-related toxicities with one incidence of grade 2 GVHD. The polyspecific VSTs expanded in vivo and produced clinical responses in all patients.

2.3.4. Safety and Efficacy of Autologous T-cell therapies for EBV positive Lymphoma

Under **IND 6387**, the Bollard group at the Center for Cell and Gene Therapy (CAGT) at Baylor College of Medicine generated CTL enriched for effector cells specifically targeting LMP antigens (LMP2 +/- LMP1) and administered them to patients with EBV+ lymphoma. No immediate toxicity was observed. After CTL infusion, increased numbers of LMP-specific T-cells were detected in the blood, (range 2 to 70 fold) persisting for up to 3 months. In conclusion, immunotherapy with CTL targeting LMP antigens is well tolerated in patients with EBV+ lymphoma, and can induce complete and sustained clinical responses in 62% of patients. This demonstrated that the anti-

tumor activity of ineffective circulating tumor-specific T cells could be restored by ex vivo activation and expansion.

Bollard and colleagues have also modified T cell manufacturing for EBV-positive lymphoma patients. Dendritic cells loaded with overlapping peptide libraries spanning 4 EBV antigens were used for the first stimulation of T-cells in the presence of cytokines, and pepmix-pulsed, autologous activated T-cells combined with K562 cells expressing co-stimulatory molecules as transgenes were used for a second stimulation. Such T cells have been used safely in >9 individuals with multiple relapsed lymphoma, resulting in increases in the frequency of EBV-specific T-cells, producing tumor responses and no adverse events. This manufacturing protocol is similar to the manufacturing of HXTCs proposed here, suggesting that the adoptive transfer of HXTCs in patients with HIV should also have an excellent safety profile.

2.4. POTENTIAL BENEFITS

The addition of VOR and HIV-specific ex vivo expanded T cells (HXTCs) to a person's ART regimen or the donation of one's blood cells to this research project provide no direct medical benefits to participants. However, participation makes it possible to continue research on HIV, potentially resulting in new treatments for HIV infection. Due to the intensive, demanding nature of study follow-up, administration of experimental product and multiple leukapheresis time points, we will provide an IRB-approved compensation to participants.

3. OBJECTIVES

3.1. Study Objectives

3.1.1. Primary Objectives

3.1.1.1. Evaluate the safety of serial administration of VOR followed by autologous ex vivo expanded HIV-1 specific T-cells (HXTC) therapy in participants maintained on suppressive combination antiretroviral therapy (ART)

3.1.1.2. Evaluate the association of serial VOR dosing and serial HXTC therapy on the frequency of resting CD4 T cell infection (IUPM) via quantitative viral outgrowth (QVOA) in participants who complete the leukapheresis procedure (#2) in Step 6.

3.1.2. Secondary Objectives

3.1.2.1. Explore the ability of combination VOR and HXTC therapy to increase HIV-1 specific immune responses in participants maintained on suppressive ART.

3.1.3. Other Outcome Measures

3.1.3.1. Explore the influence of HXTC therapy combined with serial VOR doses on low-level plasma viremia as measured by single copy assay (SCA) in participants who maintained suppression on ART.

3.1.3.2. Explore the impact of VOR and HXTC therapy on the ability of CD8 T cells to enhance clearance of latently infected cells as they emerge from latency in a latency clearance assay.

3.1.3.3. Explore the impact of VOR and HXTC therapy on integrated proviral DNA quantification.

3.1.3.4. Explore the impact of VOR and HXTC therapy on the presence and persistence of T cell escape variants within the latent reservoir

3.2. **Study Outcome Measures**

3.2.1. **Primary**

The primary outcome will be safety and tolerability of administration of VOR combined with HXTC therapy.

3.2.2. **Secondary**

The secondary outcome will be the impact of VOR and HXTC therapy on the HIV-specific immune response and on the frequency of latent HIV infection, as measured by a QVOA and plasma HIV-1 RNA viremia measured by SCA, an assay with a limit of quantitation of 1 copy/mL.

4. STUDY DESIGN

This is a phase I, single-site, study to evaluate the effects of VOR and HIV-1 Antigen Expanded Specific T Cell Therapy (HXTC) on persistent HIV-1 Infection in HIV-infected individuals suppressed on ART. Overall, twelve participants with durable viral suppression will be enrolled and will complete the study. All participants will be dosed with HXTC and VOR. Participants will continue their baseline ART regimen throughout the study.

4.1. **Step 1 (Visits 1 and 2) – Screening, Enrollment, and Baseline Leukapheresis procedure (Leuk #1)**

During the screening visit, all participants will have the study explained and the informed consent signed. After the informed consent process is completed, participants will be screened for the study and those who meet eligibility requirements will enroll (Visit 2) and have their white blood cells collected via a leukapheresis procedure (Leuk #1). A baseline measurement for the frequency of HIV-1 infection per million resting CD4+ cells (IUPM) of ≥ 0.3 by QVOA allows participants to progress to Step 3, Visit 5.

> *Note: **Participants who exhibited an IUPM ≥ 0.3 in prior UNC IRB-approved studies, will be required to complete the baseline leukapheresis after meeting the eligibility criteria and enrolling.** However, they will not be required to wait for results of the baseline leukapheresis IUPM measurement to move to Step 3 for collection of blood samples for the manufacturing of HXTCs.*

4.2. **Step 2 (Visits 3 and 4) – Omitted from Version 3 of the protocol (V3.0)**

4.3. **Step 3 (Visits 5 and 6) – Production of HXTC Therapy and Pre-Dose Safety Assessment for Initiation of Combination Therapy**

At Step 3, Visit 5, collect up to 245 mL of blood and send ambient temperature overnight to the Program for Cell Enhancement and Technologies for Immunotherapy (CETI) at Children's National Hospital (CNH) in Washington, DC for the manufacturing of HXTCs and HLA testing. This manufacturing process takes approximately 8 weeks.

Participants who participated in studies conducted under IND 15984 (IRB# 17-0468 and IRB# 14-0741) with HXTC cells already produced and stored at CNH, with documentation that adequate cells are available for infusions, can bypass Step 3, Visits 5 and 6 and progress directly to Step 4.

4.4. **Step 4 (Visits 7 – 13) – 1st Series of 10 Doses of VOR with 2 Infusions of HXTCs.**

Successful manufacturing of HXTC cells and acceptable clinical findings during the pre-dose safety assessment at Step 3, Visit 6 determine advancement to Step 4.

Participants receive 10 doses of VOR 400 mg PO every 72 hours. At study Visits 7 and 10, approximately 6 hours after their VOR dose, they will receive an HXTC infusion of up to 1 x 10^8 cells/m^2. Thus, each participant receives ten VOR 400 mg doses and two HXTC infusions (HXTC #1 and #2) in Step 4.

4.5. **Step 5 (Visits 14 – 20) - 2nd Series of 10 Doses of VOR with 3 Infusions of HXTCs**.

Approximately 4 – 5 weeks after the 10th dose of VOR 400 mg (Visit 12), if participants meet the pre-dose safety assessment requirements at Step 4, Visit 13, participants return for their first Step 5 visit (Visit 14).

Participants receive 10 doses of VOR 400 mg PO every 72 hours (total VOR dose #11 – 20). At Visits 14, 16, and 19, participants receive HXTC infusions of up to 1 x 10^8 cells/m^2 each (HXTC #3, #4, and #5). The first 2 HXTC infusions occur approximately 6 hours after their VOR dose; however, the last HXTC infusion (HXTC #5) will occur 1 – 3 days after the last VOR 400 mg dose (Dose #20).

If there are insufficient cells manufactured to allow five HXTC infusions at 1 x 10^8 cell/m^2 each, the study team will review the amount of cells manufactured and change the HXTC dose to be less than 1 x 10^8 cells/m^2 but ≥ 5 x 10^7 cells/m^2 each.

Monitoring for toxicity occurs throughout Steps 4 and 5.

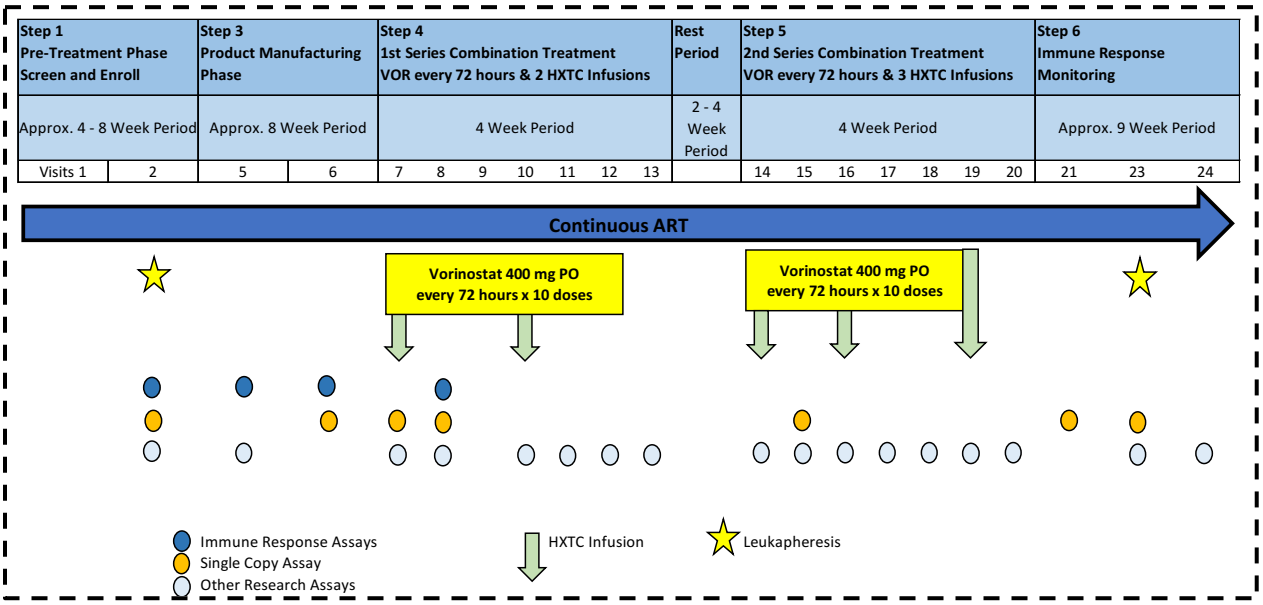
4.6. **Step 6 (Visits 21, 23, 24) – Immune Monitoring and Leuk #2**

Following the final HXTC infusion, participants move into Step 6 for a minimum of three additional visits. The 2nd leukapheresis will occur at Visit 23 (Week 16), approximately 5 weeks after the last HXTC infusion to evaluate the effect of study treatment on the IUPM by QVOA.

All participants who receive greater than 8 doses of VOR (3200 mg) will be required to enter a study cancer registry where they will be contacted once a year for 5 years after completion of their study participation. The registry was created to monitor participants for the development of future malignancies given concern for genotoxic impact with the use of VOR.

NOTE: THE PROTOCOL AMENDMENT FOR VERSION 4.0 DATED 31 JANUARY 2022 ELIMINATED VISITS 22, 25, AND 26 FROM STEP 6 OF THE PROTOCOL.

4.7. **Figure 1: Study Schema**



5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. ***Participant Inclusion Criteria***

5.1.1. ≥ 18 years and < 65 years of age at screening

5.1.2. Ability and willingness of participant to give written informed consent.

NOTE: Due to the lack of foreseeable benefit to study volunteers, the study will not enroll illiterate or mentally incompetent volunteers.

5.1.3. Confirmation of HIV-1 infection

HIV infection is defined as documentation by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

5.1.4. On antiretroviral therapy for at least 24 months and on potent antiretroviral therapy for ≥ 6 months prior to Screening (Visit 1).

Potent ART is defined by current treatment guidelines and consists of at least nucleoside/nucleotide reverse transcriptase inhibitors plus a non-nucleoside reverse transcriptase inhibitor, integrase inhibitor, or a protease inhibitor without interruption (defined as missing more than 9 total days in the 12 weeks prior to Screening).

Other potent fully suppressive antiretroviral combinations will be considered on a case-by-case basis. Prior changes in or elimination of medications for easier dosing schedule, intolerance, toxicity, or other reasons are permitted if an alternative suppressive regimen was maintained.

5.1.5. Ability and willingness of participant to continue ART throughout the study.

5.1.6. Able and willing to adhere to protocol therapy, schedule, and judged adherent to antiretroviral therapy (adherence defined in 5.1.4.)

5.1.7. Plasma HIV-1 RNA < 50 copies/mL at two time points in the previous 12 months prior to study screening (one time point can be at screening) and never ≥ 50 copies/mL on two consecutive time points in the last 24 months.

NOTE: A single unconfirmed plasma HIV RNA ≥ 50 copies/mL but < 1000 c/mL is allowed if a subsequent assay was <50 copies/mL; but none in the 6 months preceding the study screening visit.

5.1.8. Plasma HIV-1 RNA < 50 copies/mL at screening.

5.1.9. CD4+ cell count ≥ 350 cells/mm^3 at screening.

5.1.10. No active HCV infection at or within 90 days of screening.
Note: NO active HCV defined as negative HCVAb or if HCVAb is positive, reflex HCV RNA is negative.

5.1.11. No active HBV infection (measurable HBV DNA or HBsAg+) at or within 90 days of screening.

5.1.12. Women with written documentation of any of the following:
a) prior hysterectomy OR bilateral oophorectomy (removal of both ovaries)
b) bilateral tubal ligation or non-surgical permanent sterilization
c) Women with intact uterus and ovaries who have not had a period for ≥ one year AND have a documented FSH level indicating postmenopausal status.

5.1.13. All male study volunteers must agree not to participate in a conception process (e.g. active attempt to impregnate, sperm donation, in vitro fertilization) and, if participating in sexual activity that could lead to pregnancy, the male study volunteer and his female partner must use two reliable methods of contraception (condoms, with or without a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormonal-based contraception) simultaneously while receiving the protocol-specified study products and for 6 weeks after stopping the study products. Participants must use a reliable barrier method of contraception (condom, cervical cap) along with another form of contraception.

NOTE: For female partners receiving ritonavir, estrogen-based contraceptives are not reliable and an alternative method should be suggested.

5.1.14. Ability and willingness to provide adequate locator information.

5.1.15. Ability and willingness to communicate effectively with study personnel.

5.1.16. Adequate vascular access for HXTC infusion and leukapheresis.

5.1.17. Able to swallow pills without difficulty.

5.1.18. Potential participant must have adequate organ function as indicated by the following laboratory values:

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥125,000 / mcL
Hemoglobin	≥ 12 g/dL (male) and ≥ 11.0 g/dL (females)
System	**Laboratory Value**
Coagulation	
Prothrombin Time (PT) or INR	<1.1 x ULN
Chemistry	

K^+ levels	WNL
Mg^{++} levels[1]	WNL
Glucose	Screening serum glucose ≤ Grade 1 (fasting or non- fasting)
Albumin	≥ 3.5 g/dL or ≥ LLN
Renal	
Creatinine clearance determined by the CKD-Epi equation found at: *https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi*	eGFR > 60mL/min
Hepatic	
Serum total bilirubin	Total bilirubin < 1.1 times the ULN range. If total bilirubin is elevated, direct bilirubin must be < 2 times the ULN range. **NOTE**: If participant is on an atazanavir-containing therapy, then a direct bilirubin should be measured instead of the total bilirubin and must be ≤ 1.0 mg/dL.
AST (SGOT) and ALT (SGPT)	< 1.25 X ULN
Alkaline Phosphatase	< 1.25 X ULN
Lipase	< 1.1 X ULN

[1] LLN for Mg++ per the clinical laboratory's normal range used for this study is a grade 1 event per DAIDS Toxicity Table and is allowed for eligibility

ULN = upper limit of normal LLN = lower limit of normal WNL = within normal limits

5.2. ***Participant Exclusion Criteria***

5.2.1. Known allergy or sensitivity to components of VOR and its analog or to components in the HXTC product.

5.2.2. Women without written documentation of menopause (absence of a period for ≥ one year and FSH level indicating menopause), hysterectomy or bilateral oophorectomy, non-surgical permanent sterilization, or bilateral tubal ligation.

5.2.3. Untreated syphilis infection (defined as a positive rapid plasma reagin (RPR) without clear documentation of treatment).

Note: In cases of untreated syphilis, participant may re-screen following documentation of adequate treatment of syphilis

5.2.4. All male participants expecting to father children within the projected duration of the study.

5.2.5. Receipt of compounds with HDAC inhibitor-like activity, such as valproic acid within 30 days prior to screening.

5.2.6. Use of any investigational antiretroviral agents within 30 days prior to screening.

5.2.7. If the study PI (or designee) is unable to construct a fully active alternative ART regimen based on previous resistance testing and/or treatment history.

5.2.8. Use of the following medications that carry risk of torsade des pointes: amiodarone, arsenic trioxide, astemizole, bepridil, chloroquine, chlorpromazine, cisapride, clarithromycin, diopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, pentamidine, pimozidine, probucol, procanimide, quinidine, sotalol, sparfloxacxin, terfenadine, thioridizine.

5.2.9. Use of any of the following within 90 days prior to screening: immunomodulatory, cytokine, or growth stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, IFN, interleukin-2 (IL-2), coumadin, warfarin, or other Coumadin derivative anticoagulants.

5.2.10. Prior use of any HIV immunotherapy or HIV vaccine within 6 months prior to Screening, except for prior HXTC infusions.

5.2.11. Received any infusion blood product, immune globulin, or hematopoietic growth factors within 90 days prior to study screening.

5.2.12. Pregnancy or breast-feeding.

5.2.13. History or other clinical evidence of severe illness, malignancy, immunodeficiency other than HIV, or any other condition that would make the participant unsuitable for the study in the opinion of the investigator (or designee).

5.2.14. Use of topical steroids over a total area exceeding 15 cm^2 within 30 days prior to Screening.

5.2.15. Treatment for an active AIDS-defining opportunistic infection within 90 days prior to Screening.

5.2.16. Any active malignancy that may require chemotherapy or radiation therapy.

5.2.17. Compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric illness or a physical illness, e.g., infectious disease. Prisoner recruitment and participation is not permitted.

5.2.18. Known psychiatric or substance abuse disorders that would interfere with participant's ability to fully cooperate with the requirements of the trial as assessed by the study investigator (or designee).

5.2.19. History or other clinical evidence, as assessed by the study PI (or designee), of significant or unstable cardiac disease (e.g., angina, congestive heart failure, recent myocardial infarction, significant arrhythmia requiring medical or surgical therapy) or clinically significant electrocardiogram (ECG) abnormalities.

5.2.20. Participation in another investigational clinical research study (with the exception of an antiretroviral treatment trial that uses FDA approved antiretroviral agents) or use of investigational agents within 30 days prior to screening.

NOTE: Co-enrollment in observational only studies is permitted.

NOTE: Co-enrollment in the ACTG 5332 REPRIEVE study (NCT023442900) and using FDA approved pitavastatin is permitted provided participant enrolled on ACTG 5332 and has taken the study provided medication ≥ 4 months.

5.3 Strategies for Recruitment and Retention

There are several venues for recruitment available to the study team:

In the UNC ID clinic and/or other local HIV clinics, there is a large pool of patients with long-term viral suppression on ART interested in participating in research. Many have previously participated in clinical research studies in the past. These individuals will be provided with the opportunity to discuss this study with their provider and the study coordinator.

The UNC acute HIV program actively enrolls persons diagnosed with AHI into treatment protocols and also follows persons off treatment studies in a longitudinal cohort protocol. Currently there are at least 65 active participants who were seen and treated in AHI in the UNC cohort.

Individuals who have signed the UNC CFAR (Center for AIDS Research) database consent as well as those who have signed the consent for the PHI (Primary HIV Infection) studies/database will be identified and approached about the study by either their primary care provider or the study coordinator, after consultation with their primary care provider.

If individuals are interested in participating in the study, they will be provided with appropriate study information and the opportunity to screen. All potential participants will be informed that on rare occasions some of the serious side effects described in this protocol as well as other unpredicted adverse events can occur. They will be told that

their participation in this study will allow researchers the opportunity to collect valuable information about the use of HXTC in individuals with durable viral suppression and its ability to improve immune responses. Potential participants will be informed that there may be no direct and immediate benefits to them as volunteers in this study, but information learned from this study may be of value to the participant and other people with HIV disease.

Participants will be screened and recruited in the Infectious Diseases (ID) Clinic and the Clinical and Translational Research Center (CTRC) of the University of North Carolina (UNC) at Chapel Hill. Study activities can take place in the CTRC unit, the Apheresis Lab, the American Red Cross (ARC) in Durham, NC, and/or the UNC ID Clinic, located in the University of North Carolina Memorial Hospital.

Screening will take place in a step-wise manner. Screening procedures and assessments will include the following: completion of informed consent process, determination of HIV infection status, documentation of stable ART and HIV RNA < 50 copies for ≥ 2 years, locator information, and screening safety laboratory testing and safety procedures.

Screening and enrollment occur in Step 1. After establishment of the baseline safety (Visit 1) parameters and qualifying for the study per the Inclusion and Exclusion Criteria, the participant is enrolled (Visit 2) and completes the baseline leukapheresis. The IUPM measurement of ≥ 0.3 obtained from samples collected during the baseline leukapheresis determine whether the participant moves to Step 3.

5.4. Participant Withdrawal

Handling of Participant Withdrawals or Participant Discontinuation of Study Intervention

Participants failing to meet criteria to advance to Step 4 are not required to complete an end of study visit (Step 6, Visit 23). Reasons for not progressing to Step 4 include:

- Inability to manufacture HXTC product in Step 3
- Failure to meet requirements established for the pre-dose safety assessment for Step 4 at Visit 6.

If the participant withdraws, discontinues, or fails to advance in the study for any reason after initiating VOR dosing and HXTC infusions in Step 4, the participant would be asked to complete an Early Discontinuation Study Visit (Step 6, Visit 23). This visit will occur ≥ 4 weeks but ≤ 8 weeks after the last documented visit or study treatment, whichever occurred last. Participants would then proceed to complete Visit 24.

In scenarios where participants are discontinued or withdrawn after receiving VOR doses in combinations with HXTC infusions, the study PI (or designee) will make every effort to complete the Early Discontinuation Study Visit/End of Study Intervention (Step 6, Visit 23) evaluations.

The Early Discontinuation or End of Study Interventions Visit will include the clinical assessments and required labs per the SOE. The completion of the Leukapheresis procedure at this visit will be determined on a case-by-case basis by the study PI (or designee).

UNC reserves the right to discontinue the study for any reason at any time. The study may also be stopped if, in the opinion of the principal investigator and/or protocol team, the continuation of the study represents an unwarranted medical risk to the participants.

5.5. Premature Termination or Suspension of Study

5.5.1. Study Treatment Stopping Rules or Permanent Treatment Discontinuation

A participant will not receive VOR and/or HXTC infusions if any of the following occurs:

- Pregnancy of study participant
- Treatment related ≥ Grade 3 adverse event
- Requirement for prohibited concomitant medications
- Inability to complete treatments as defined in the protocol
- Request by participant to terminate study treatments
- Clinical reasons believed life-threatening by the PI or designee
- Hematologic dose-limiting toxicity defined as any confirmed toxicity ≥ Grade 2, that cannot clearly be attributed to another reversible cause other than VOR
- Development of a dose-limiting toxicity
- HIV RNA > 150 copies/mL on two consecutive determinations.

Participants who prematurely discontinue study treatment will move to Step 6, Visit 23 and will be followed through Visit 24. See section 5.4, Participant Withdrawal, for details on study procedures to be completed.

5.5.2. Premature Study Discontinuation

A participant may withdraw or be withdrawn from the study if any of the following occurs:

- Pregnancy of study participant
- Failure by the participant to attend multiple clinic visits
- Failure to receive the first HXTC infusion
- Failure to continue to meet pre-dose safety assessment requirements
- Failure to meet baseline IUPM measurement criteria
- Development of an illness that requires treatment with certain medications not allowed in this study
- Inability to manufacture HXTC product for infusion

- Poor adherence to ART as judged by the PI (or designee)
- Request by the participant to withdraw
- Request of the participant's primary care provider if s/he thinks the study is no longer in the best interest of the participant
- Participant judged by the PI (or designee) to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NHLBI, Office for Human Research Protections (OHRP), other government agencies as part of their duties, PI, or industry supporter

6. STUDY INTERVENTION

6.1 HXTC

6.1.1. Collection of 100 mL of Blood

Participants will have 100 mL of blood drawn at Step 3, Visit 5 to make the study product. These whole blood samples are shipped ambient temperature overnight to the CETI Processing Facility at CNH in Washington, DC. This shipment also includes an additional sample for HLA analysis.

If the participant previously participated in another study protocol at UNC and has sufficient product already manufactured under IND 15984, the study will not require an additional blood sample and will use the previously manufactured and stored HXTCs.

6.1.2. Study Product Manufacturing

The study product will be made at an established GMP facility at CNH in Washington, DC. A description of the facilities and their operation can be found in the IND 15984 application under IND Section 7.0 – Product Manufacturing & Characterization Manufacturing Environment.

6.1.2.1. Manufacture of HXTC

Cells.
The cell therapy product for infusion consists of autologous HXTCs targeting the gag, pol, and nef antigens of HIV-1. Blood will be collected by venipuncture and processed according to UNC Clinical and Translational Research Center (CTRC) and shipped ambient to CNH per SOP. Blood will be processed into peripheral blood mononuclear cells (PBMCs) and then used to manufacture three different components: (1) Dendritic cells (DCs) that will be loaded with pepmixes spanning the three target antigens,

irradiated and used as antigen-presenting cells (APCs) for the first stimulation of PBMCs, (2) peptide pulsed autologous T- cell PHA blasts and K562 that will be irradiated and used for the second and subsequent stimulations of HXTCs, and (3) HXTCs generated by stimulation with peptide-pulsed PHA blasts and K562 and which will comprise the final T-cell product.

The flow chart for these procedures is shown in **Figure 2** of the protocol.

Overlapping Peptide Libraries (pepmixes). PepMixes HIV Ultra produced by JPT Peptide Technologies will be used as an antigen source. These pepmixes include a pool of 150 15meric peptides derived from Gag, Pol, and Nef polyprotein designed to cover the high sequence diversity of the HIV-1 virus. The pepmixes were derived from protein sequences of all subtypes of HIV-1/SIVcpz based on the HIV sequence database of the Los Alamos National Lab. The end product pool will be cryopreserved prior to infusion.

Cell Bank System. A formal cell bank system will not be used for the cell therapy product. Back-up cells will be frozen down at various stages during the manufacturing process. Each final product, however, will consist of a single lot of cells designated for a specific participant.

Manufacturing Environment. The cell therapy product described in this section will be manufactured by the Cell Processing Facility (CPF) staff in the Program for CETI at CNH in Washington, DC. These are ISO 7 and ISO 8 manufacturing environments that operate in compliance with current Good Manufacturing Practices as applicable to products intended for Phase I/II clinical trials.

Dendritic Cell Generation. The generation and maturation of DCs is accomplished when peripheral blood mononuclear cells are isolated from whole blood and separated by adherence. Monocytes contained in the adherent fraction are cultured in DC skewing conditions for 4- 5 days. They are then matured with an established cytokine cocktail before use as an antigen presenting cell.

Loading Dendritic Cells With Pepmixes. Mature DCs are pelleted and pulsed with pepmixes using a proprietary algorithm to provide broad coverage of gag, pol, and nef across all clades.

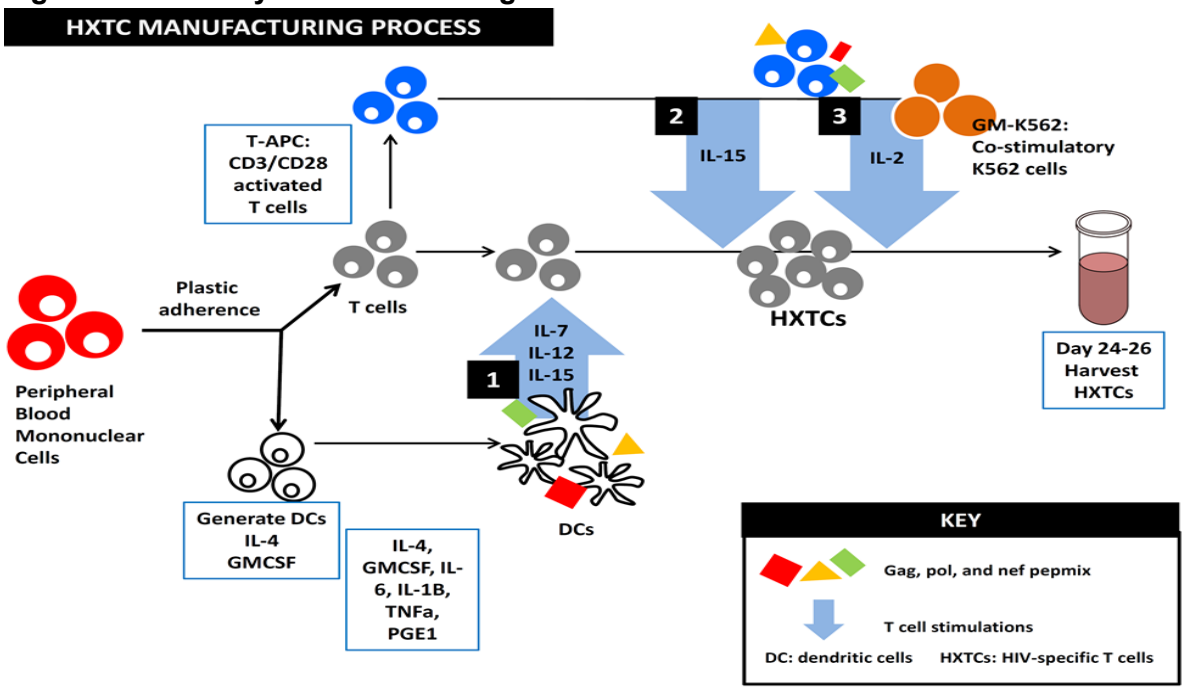
HXTC generation. HXTCs are derived from the non-adherent fraction of PBMCs. T cells are stimulated a minimum of two times using Gag, Pol, and Nef pepmix-pulsed DCs for the first stimulation and pepmix-pulsed,

irradiated PHA blast for the second and any subsequent stimulations, if required for HXTC expansion. Genetically-modified co-stimulatory K562 cells (GM-K562) will be incorporated into the co-culture during the second stimulation, if needed based on insufficient expansion.

Culture of DCs and T cells will be performed in the presence of Atazanavir (AZT) and Enfuvirtide (T20) to inhibit potential HIV replication in cultures. At the end of the culture period, HXTCs will be cryopreserved for infusion and submitted for release testing. For information purposes only, additional assays such as ICS, elispot, and pentamer analysis will be performed based on cell availability and HLA.

Each product will have 4 identifying IDs. All labeling will conform to the labeling procedures required by CETI. All cultureware is labeled with the UNC participant ID (PID) and Study ID (SID) as well as the unique CETI-assigned donor identification number (DIN) and unique product number (P number). Only one participant cell line is ever processed at any one time. Medium prepared and labeled specifically for each participant's cells is always used.

Figure 2: Summary of Manufacturing Process



6.1.3. Cryopreservation of Products

When sufficient cells for participant infusion are obtained, they are characterized and frozen. The number of cells required for five participant doses is based on the participant's body surface area. Sufficient cells to allow for loss during

cryopreservation (+ up to 20%) and for samples required for characterization and safety testing are processed. The product's cells and supernatant will be tested for mycoplasma testing and microbiological testing. Final product will be tested for HLA-typing, and phenotyping, and viability. The final cell suspension will also undergo endotoxin testing. Cryovials or cryocyte bags are labeled with participant's PID, SID, CETI DIN, and P number, type of component, number of cells, and date of freezing. Cryovials or bags are then cryopreserved in a controlled rate freezer and transferred to storage in the Central Processing Facility liquid nitrogen freezer under the auspices of QC (quality control). The storage facility is within clean room space and is fully monitored 24/365.

6.1.4. **Study Product Manufacturing Process**

Reagents. Certificates of analysis for all reagents, materials, and supplies are kept on file indefinitely and the lot numbers, manufacturer, and expiration date of each is captured at each use by means of our inventory control system where only released supplies and reagents are available in the GMP facility, and all supplies and reagents are tracked on the worksheet.

Reagent Qualification. Pepmixes are a mixture of peptides chosen by a proprietary algorithm developed by JPT Peptide Technologies to provide broad coverage of HIV antigens Gag, Pol, and Nef across many clades of HIV. JPT Peptide Technologies will provide these clinical grade pepmixes freeze-dried. One mg of each individual peptide was synthesized and purified by HPLC to a purity of ≥ 90% measured at 220nm using a linear gradient system. The purity and identity of the peptides was confirmed by high-performance liquid chromatography (HPLC) and mass spectroscopy (LC-MS). For pooling, sub-pools of 10-25 peptides were generated. The presence of all peptides within sub-pools was proven by LC-MS analysis of each sub-pool. From each sub-pool at least one peptide was defined as a "marker-peptide" having a unique molecular weight and HPLC retention behavior. Sub-pools were combined and the generated final pool applied to LC-MS. LC-MS data were tracked to show the presence of at least one "marker-peptide" per sub-pool within the final pool confirming that all individual peptides are present in the final pool. The pepmixes are sterile, and endotoxin-free.

Materials and reagents in contact with the product during manufacturing are sterile and pyrogen-free as determined from the manufacturer's certificate of analysis. No antibiotics are used during manufacturing. Records of all testing are kept on file.

Removal of Reagents from Final Product. Cytokines, antiretrovirals, and culture medium are removed by extensive washing of the cells. The final cells are washed four times and re-suspended in balanced salt solution or plasmaLyte containing US Pharmacopeia (USP) human serum albumin and USP dimethyl sulfoxide (DMSO) for cryopreservation.

Antibiotics: Antibiotics are not used during manufacturing.

6.1.5. Product Testing and Release

Test Methods

The following tests are performed by the CETI QC laboratory or a CNH facility per standard operating procedures.

Sterility Testing

The BacT/Alert blood culture system and Fungal Isolator tubes are used to test sterility of the final product, and samples are inoculated into culture medium in anaerobic, aerobic, and fungal culture bottles. Bottles are incubated for 14 days (bacterial) or 21 days (Fungal) with ongoing assessment for contamination.

Mycoplasma

Mycoplasma testing of the final product uses a commercially available MycoAlert (Lonza) by the CETI Quality Control Laboratory. This assay uses the MycoAlert kit, which detects the presence of mycoplasmal enzymes, which catalyze the conversion ADP to ATP and is detectable using luciferase. It is used for in-process testing and to obtain rapid results while results of the culture assays are pending. Data from this test method will be accumulated in preparation for validation against the Points to Consider method.

Endotoxin

Endotoxin levels in the final product will be assayed using the Limulus Amebocyte Lysate assay. For release testing, the Endosafe PTS system will be used. This test is a miniaturized version of the standard LAL assay and the cartridges employed have received FDA approval. The limit of quantitation of the assay is approximately 0.05 EU/mL.

Identity

The identity of the cells will be determined by HLA typing. The final product consists of participant-derived HIV-specific T cells. Therefore, the HLA type of the final product should be identical to that of the participant blood.

Potency

For this phase I study, potency is not a release criterion. However, for safety purposes we will ensure that the immunophenotype excludes the presence of dendritic cells (CD3-CD83+) and GM-K562 cells (CD3-, CD16/56-, CD32+, CD83+) in the product. For informational purposes, the potency of all HXTCs will be evaluated using cytotoxicity and or Elispot assays.

Viability
Viability of the final cell product will be assessed for release using trypan blue exclusion.

Notification of Physician in Case of Positive Sterility Report
The final cell product will be tested for sterility using a BacT/Alert test but will not be available at the time the product is released. Should the BacT/Alert or fungal sterilities be reported as positive after product administration, the UNC Principal Investigator and study team will be immediately notified. CETI will obtain and inform him/her of the identity and antibiotic sensitivity of the organism. CETI will generate a Variance to document and determine corrective actions and their efficacy.

Table 2. Final product testing

Testing	**Test to be used**	**Specificity/ Sensitivity**	**Criteria for Acceptance**	**Results Available Before Administration**
Viability	Trypan Blue	Live cells	>70%	Yes
Sterility	BacT/Alert	Bacteria	Negative at 4 days (cultured for up to 14 days)	Yes
Sterility	Isolator tubes Fungal Culture	Fungus	Negative at 4 days (cultured up to 21 days)	Yes
Mycoplasma	MycoAlert	12 most common species	Negative	Yes
Purity Endotoxin	Endosafe PTS (LAL)	<5.0 EU/kg	<5.0 EU/mL	Yes
Identity	HLA Typing	N/A	Identical to participant	Yes
Phenotype	Flow Cytometry	Cell type	<0.1% CD3-, CD16/56-, CD32+, CD83+ (GM-K562 cells); <2% CD3-/CD83+(DCs)	Yes

6.1.6. **HXTC Storage and Stability**

The samples collected at UNC for product manufacturing are kept in a temperature-controlled storage area of the UNC CFAR HIV and STD Laboratory Core (CHSLC) Lab located in the CTRC Unit in the Burnett-Womack Building next to UNC Hospitals. These samples will be packaged per International Air Transport Association (IATA) regulations, and picked up in the later part of the same day of collection, and sent overnight, delivered at approximately 10 AM the next day at CNH. The shipment of the samples occurs Monday – Thursday to assure that a person is on site at CETI (CNH) to receive the package. The UNC CHSLC Lab communicates with the CETI

site via email, notifying them of shipment, and receipt of package is then verified by CNH. Samples are shipped ambient temperature.

The HXTC final cellular product is cryopreserved and shipped in a liquid nitrogen-charged cryogenic shipper from the manufacturing site in Washington, DC to the Hematopoietic Progenitor Cell (HPC) Lab located in UNC Memorial Hospital in Chapel Hill, NC. The CNH group has extensive experience with the shipping of virus-specific T-cells to distant sites.

6.1.7. **Dosage, Preparation, and Administration of HXTC**

Each dose of HXTC is 1 x 10^8 cells/m^2 and each participant will receive five infusions at this dose, provided there are enough manufactured T-cells. If unable to manufacture enough cells for five infusions at 1 x 10^8 cells/m^2 participants will receive five infusions at a dose ≥ 5 x 10^7 cells/m^2 up to 1 x 10^8 cells/m^2 as determined by the protocol team.

The first HXTC infusion (HXTC #1) will be infused approximately 6 hours after the 1st dose of VOR (Step 4, Visit 7) and the 2nd HXTC infusion (HXTC #2) after the 6th dose of VOR (Visit 10) in Step 4. In Step 5 each participant will receive the next three HXTC infusions. The 3rd HXTC infusion (HXTC #3) will be infused approximately 6 hours after the 11th dose of VOR 400 mg (Step 5, Visit 14) and HXTC infusion #4 will occur approximately 6 hours after the 16th dose (Step 5, Visit 16). The 5th or last HXTC infusion (HXTC #5) occurs 1 to 3 days after the 20th dose of VOR (Visit 19).

In preparation of each HXTC dose of 1 x 10^8 cells/m^2, an extra - volume (1 – 20%) is added to account for cell loss. When possible, CETI will cryopreserved the cells at 1 x 10^8 T cells per mL, allowing the cells to be thawed and injected directly. However, the cell concentrations can vary from time to time; therefore, dosage calculations and body surface area (BSA) are calculated both at CETI (prior to shipment) and then by two independent licensed practitioners at the UNC site prior to administration to confirm accurate dose delivery.

The required amount of HXTCs for the infusions are shipped to the UNC HPC Lab, where they are stored and maintained in in biological safety cabinets (BSC). If extra cells are produced, CETI archives these aliquots at their manufacturing site. These stored aliquots are accessible for additional infusions under IND 15984 or research analysis.

All study HXTC infusion visits occur in the UNC CTRC. After completion of all required clinical assessments prior to the infusion, the HXTC product is thawed, delivered and verified with the study coordinator. Review of the HXTC product occurs prior to administration per the UNC HIV Cure Center SOP entitled Cellular Product Infusion Guidelines and Emergency Management Plan.

Participants are pre-medicated with cetirizine (Zyrtec) and acetaminophen (Tylenol).

- Cetirizine
    - All infusions – administer 10 mg PO
- Acetaminophen
    - All infusions – administer 500 mg PO (weight <65 kg) or 650 mg PO (weight ≥65 kg).

Cell Administration: HXTC will be given by IV infusion at a rate of 4-6 mL/min through a peripheral line.

Post infusion monitoring lasting at least 60 minutes follows each infusion.

Participants will receive supportive care for acute toxicity directly attributable to HXTC, as appropriate.

All treatments will be given at the University of North Carolina at Chapel Hill.

The grading system for drug toxicities is located in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017], which can be found on the DAIDS RSC Web site: *http://rsc.tech-res.com/safetyandpharmacovigilance/*

A period of six weeks following the completion of the last infusion will constitute the time required for clinical safety monitoring and reporting of adverse events related to infusions.

6.2. VORINOSTAT (VOR)

6.2.1. Formulation, Packaging, and Labeling

VOR (N-hydroxy-N'-phenyl-octane-18-diotic acid diamide, N hydroxy-N'-phenyl (9CI) octanediamide, suberoylanilide hydroxamic acid, also known as SAHA, or MK-0683) is an orally available HDAC inhibitor. The physical and chemical properties of VOR are listed in **Table 3**.

Table 3: Properties of VOR

Molecular Formula	$C_{14}H_{20}N_2O_3$
Molecular Weight	264.32
Physical Appearance	White to light orange powder
Solubility	Water (pH = 11.2) ≤5 mg/mL
Moisture (Karl Fischer)	≤1%
Melting Point	159.5 to 160.5ºC
pK_a	8.5 and 11.1
Hygroscopicity	None

Molecular Formula	$C_{14}H_{20}N_2O_3$
Molecular Weight	264.32
Physical Appearance	White to light orange powder
Solubility	Water (pH = 11.2) ≤5 mg/mL
Moisture (Karl Fischer)	≤1%
Hydrates	None
Chirality	None

The oral formulation of VOR is available as a 100-mg capsule. Earlier studies of VOR were performed with formulation strengths of 50 mg and 200 mg. Currently no additional dose images other than the 100 mg strength is manufactured. Each 100 mg ZOLINZA capsule for oral administration contains 100 mg VORINSTAT and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin, and may contain sodium lauryl sulfate.

6.2.2. **VOR Storage and Stability**

VOR will be stored and dispensed by the UNC Hospitals Investigational Drug Services (IDS) Pharmacy. VOR will be dispensed by prescription on a participant specific basis.

Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F) [See USP Controlled Room Temperature.] The IDS staff's responsibilities include maintaining, monitoring and documenting the temperature in the pharmacy supply storage area per institutional guidelines.

Proper Disposal of VOR

The IDS Pharmacy follows the guidance established in their SOP for the disposal of non-hazardous investigational drug.

VOR is an anti-cancer drug. Procedures for proper handling and disposal of anti-cancer drugs are established in the UNC Hospital Policy (Policy Stat ID 4734545) called "Handling and Disposal of Hazardous Drugs (Antineoplastic, Biologic, Cytotoxic, and Immunosuppressant Drugs) dated February 2018.

VOR in capsule form is a low-risk hazardous drug. Gloves must be worn when handling VOR. VOR capsules should not be opened or crushed. Direct contact of the powder in VOR capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly. Your supervisor and employee health should be notified immediately. Personnel should avoid exposure to crushed and/or broken capsules.

Procedures for proper handling and disposal of anti-cancer drugs follow the UNC Hospital Policy Stat ID 4734545. Spills of powder from VOR capsules due to damaged or broken capsules should be cleaned up carefully to minimize inhalation of VOR. The affected area must be washed at least 3 times with ethyl alcohol, followed by water. Direct contact of the powder in VOR capsules with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly.

For the most part, the techniques are merely an extension of good work practices by health-care and similar in principle and practice to Universal Precautions (Centers for Disease Control. 1988. Update: Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and Other Bloodborne Pathogens in Health-Care Settings. Morbidity and Mortality Weekly Report, 37(24):377-382, 387-388.).

The cleanup and disposal of spilled, wasted, or unused medication as well as used syringes must be documented appropriately (i.e., witnessed) in accordance with applicable federal regulations, Good Clinical Practice (GCP) procedures, and the procedures for handling biohazardous substances.

6.2.3. **Dosage, Preparation, and Administration of VOR**

The UNC IDS Pharmacy stores, distributes, and maintains accountability for VOR. The dispensing of each dose will be participant specific and by signed prescription. Upon receipt of the VOR doses from IDS, the study coordinator dispenses VOR to the participant in the research clinic according to the dose, schedule, and supportive care guidelines.

Take each VOR dose with food.

The primary IDS pharmacist will be responsible to the principal investigator for maintaining study drug accountability, reconciliation, and record maintenance during the study, including documentation of the amount of study treatments (VOR) received in IDS and the amount administered to each participant.

Participants will be provided their first dose of VOR 400 mg in Step 3, Visit 6 to take 4 in Step 4, Visit 7. Participants will take this dose at home in the morning prior to coming for Visit 7. The study coordinator will provide participants with individualized dosing instructions, clearly identifying the days they are required to take VOR. The study coordinator will contact participants on each dosing day. Participants will be instructed to contact the study coordinator and be prepared to return to the clinic should any adverse event evolve. Participants will be monitored for the development of toxicities. Participants will take the doses approximately 72 hours apart.

6.3. Concomitant Medications/Treatments

Once a participant enrolls in the study, all medications will be monitored. Participants must report whenever they start a new medication or have changes to their existing medications. This applies to both prescription and over-the-counter medications. Document the initiation and administration of the study agents. The study PI or co-investigators reviews the concomitant medications' and study agents' most recent package inserts and investigator's brochures to obtain the most current information on drug interactions, contraindications, and precautions.

6.3.1. **Required Medications**

All participants must be on ART as specified in the inclusion criteria (Section 5.1). The study does not provide ART medications.

Changes to the participants' ART during the study are permitted for dosing simplification, tolerability issues, or at the investigator's discretion. If the participant develops toxicity related to his/her previously stable ART, then the principal investigator (PI) or protocol team should be consulted and preferably before appropriate therapy modification.

6.3.2. **Permitted Medications**

Regularly prescribed medications such as antipyretics, analgesics, antidepressants, sleep medications, oral contraceptives, megestrol acetate, testosterone, and other medications for chronic conditions that do not interact with VOR or HXTC Therapy;

Antibiotics for bacterial infections;

Maintenance therapy for opportunistic infections that develop while on study according to standards of medical care;

Standard vaccinations (e.g., flu) with the exception of live vaccines are permitted any time;

Intermittent use of inhaled corticosteroids (e.g., for chronic obstructive pulmonary disease [COPD], asthma) is only permitted for participants not receiving ritonavir or cobicistat as part of their current ART regimen and after consultation with the study PI or designee);

Sporadic topical use of corticosteroids (e.g., creams) to small areas of the skin (15 cm^2) after consultation with the PI (or designee) is only permitted for participants who are not receiving ritonavir or cobicistat as part of their current ART regimen; and

For treatment of infusion reactions (Grade 1 and Grade 2) flu-like symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate symptoms under a physician's guidance and for a limited period of time.

6.3.3. **Prohibited Medications**

Prohibited HIV ART: Any investigational ART.

Live vaccines after enrollment and for the duration of the study.

Concomitant immunosuppressive, immunomodulatory, or neoplastic agents;

Use of growth factors, cytokines, or white lineage colony stimulating factors (e.g., granulocyte-colony stimulating factor [G-CSF] and GN-CSF);

Chronic use of topical corticosteroids that are applied to large areas of the skin (exceeding the cumulative area of the palm of the participant's hand) or any corticosteroids or antihistamines used on or near the infusion site;

Note: Refer to exclusion criteria in section 5.2.

7. STUDY SCHEDULE

7.1. Study Procedures

Participant study screening, eligibility, enrollment, baseline leukapheresis, and IUPM measurement are all completed and assessed during Step 1.

Study eligibility is determined at screening. Enrollment (Visit 2) occurs prior to or at the baseline leukapheresis procedure (leuk#1).

Enrolled participants advance to Step 3 if the baseline IUPM measurement is ≥ 0.3.

Study Visit Windows

Study enrollment is within 30 days of screening. The baseline leukapheresis can be performed at enrollment or within 45 days of screening.

While on study, all study windows are in the schedule of events (SOE) and section 7.3.3 (Step 4) and 7.3.4 (Step 5).

7.2. Co-enrollment

Co-enrollment on other studies will be addressed on a case-by-case basis with the study team. Due to the potential interference with the monitoring of the effects of this study's treatments, participants will not be able to be enrolled on other studies of investigational treatment, unless pre-determined by PI (or designee) that investigational treatment on another study is allowed.

7.3. Schedule of Events

A detailed Schedule of Events (SOE) is in Appendix A.

The SOE represents all possible study visits through the last study visit. Exceptions to specific events are noted.

7.3.1. **Step 1 – Screening and Enrollment**

Screening occurs at Visit 1, with potential participants evaluated for eligibility per the inclusion and exclusion criteria. Eligible participants are enrolled at Visit 2.

7.3.1.1. Visit 1 – Screening

Includes informed consent, inclusion/exclusion criteria, demographics, and other procedures per SOE.

Estimated Blood Volume: up to 45 mL

7.3.1.2. Visit 2 – Enrollment and Baseline Leukapheresis

The leukapheresis procedure will follow institutional guidelines for safety and monitoring procedures including CBC with differential prior to the leukapheresis (UNC Apheresis lab) or within 30 days (ARC), and blood pressure and pulse monitoring before, during, and after the procedure.

Estimated Blood Volume: up to 145 mL

Advancement Criteria for Step 3:

1) *Participants with IUPM of ≥ 0.3 as determined by QVOA assay*

NOTE: THE PROTOCOL AMENDMENT FOR VERSION 3.0, DATED 20 DECEMBER 2019 ELIMINATED STEP 2 (VISITS 3 AND 4) OF THE PROTOCOL.

7.3.2. **Step 3 (Visits 5 and 6) – HXTC Manufacturing and Eligibility Visit for Step 4**

Schedule Visit 5 once participant meets advancement criteria for Step 3.

7.3.2.1. Visit 5 – HXTC Manufacturing

The following events occur at this visit:
- Clinical assessments per SOE
- Blood collection for HXTC manufacturing, HLA typing and Donor ID panel

Estimated Blood Volume: up to 245 mL

Ship samples ambient, overnight to CNH. Upon receipt, CNH sends confirmation and assigns the two unique CNH product IDs. (Reference XTRA Lab Manual and XTRA SOP #3.)

7.3.2.2. Visit 6 – Pre-Dose Safety Assessment Visit for Step 4

Schedule Visit 6 after CNH verifies that product manufacturing is complete. The pre-dose visit will be ≤ 21 days prior to Step 4, Visit 7 (Study Week 0).

The pre-dose safety labs must be reviewed and signed off by the study PI or designee prior to Visit 7. If the participant does not meet one or more of the pre-dose safety lab assessments, repeat of the abnormal lab values can occur one time only. If repeat values are within the pre-dose safety lab assessment criteria, participants receive VOR and HXTC infusions at Visit 7.

After repeat testing, participants with any lab values that remain outside the guidelines below but are considered clinically non-significant and documented as such by the study PI (or designee), may proceed to the dosing/infusion visit after review and approval of the case by the protocol and/or safety committee.

Please reference the SOE for clinical and research procedures done at this visit.

Hematology	**Laboratory Value**
ANC	≥1,500 /mcL
Platelets	≥125,000 / mcL
Hemoglobin	≥ 12 g/dL (male) and ≥ 11.0 g/dL (females)
Chemistry	
K^+ levels	WNL
Mg^{++} levels	WNL
Glucose	≤ Grade 1 (fasting or non-fasting)
Renal	
Creatinine	<1.3 X ULN
Hepatic	

Total bilirubin	< 1.1 times the ULN range. If total bilirubin is elevated, direct bilirubin must be < 2 times the ULN range.
AST (SGOT) and ALT (SGPT)	< 1.25 X ULN
Alkaline Phosphatase	<1.25 X ULN
Other Testing	
Serum pregnancy test (all females)	Negative
RPR	No active infection
HIV RNA	<50 copies/ml
CD4	≥350
HBsAg and HCV Ab	Negative or not detectable *Note: positive HCV Ab will reflex to an HCV RNA. In this scenario, a negative HCV RNA will qualify participant.*

Estimated Blood Volume: up to 120 mL

At this visit, participants will be given 1 dose of VOR 400 mg to take home. Upon verification of acceptable labs, participants will be contacted to verify date and time of Visit 7 and also to verify the time participant is to take the first dose of VOR that morning. Plans will be made for participants to return the dose of VOR 400 mg to the study coordinator should the participant fail to have acceptable pre-dose labs for Step 4.

The study coordinator and participant will also discuss the Step 4 visits and VOR dosing schedule. Participants will be given a VOR dosing schedule illustrating the 72-hour dosing schedule (inclusive of date and time) and dates of the HXTC infusions. Participants will be provided with information about VOR as well as information regarding the storage and handling of VOR at home. All of this information will be reviewed prior to sending participants home with the first VOR dose.

Steps 4 and 5
Combined therapy occurs in Steps 4 and 5 – Each participant will receive doses of VOR 400 mg with scheduled HXTC infusions.

In Steps 4 and 5, participants receive a combined total of 20 doses of Vorinostat 400 mg over the course of 3 months with five (5) intermittent scheduled HXTC infusions up to 1 X 10^8 cell/m^2 per dose. Following completion of Step 5, participants will complete 6 additional visits in Step 6 for immune response monitoring**.**

7.3.3. Step 4 (Visits 7 – 13) - First Series of VOR 400 mg x 10 doses and 2 HXTC infusions

Visit Windows for Step 4

Visit #	Visit Evaluations	Visit Window
Visit 7	VOR Dose 1 and HXTC Infusion #1	≤ 21 days after Visit 6
Visit 8	Safety check and Research Labs	1 - 3 days after Visit 7
	VOR Dose #2	3 days after Visit 7 (Dose 1 + 3 days)
Visit 9	VOR Dose #3	6 days after Visit 7 (Dose 1 + 6 days)
	VOR Dose #4	3 days after Visit 9 (Dose 1 + 9 days)
	VOR Dose #5	6 days after Visit 9 (Dose 1 + 12 days)
Visit 10	VOR Dose #6 and HXTC Infusion #2	9 days after Visit 9 (Dose 1 + 15 days)
Visit 11	Safety Check and Research Lab	1 - 3 days after Visit 10
	VOR Dose #7	3 days after Visit 10 (Dose 1 + 18 days)
	VOR Dose #8	6 days after Visit 10 (Dose 1 + 21 days)
	VOR Dose #9	9 days after Visit 10 (Dose 1 + 24 days)
Visit 12	VOR Dose #10	12 days after Visit 10 (Dose 1 + 27 days)
Visit 13	Safety F/U & Step 5 Pre-Dose Clinical Assessment	7-14 days after Visit 12

7.3.3.1. **Visit 7 (Week 0)**

All female participants require a negative POC urine pregnancy test within 48 hours of Visit 7. If, despite the documentation of infertility, a female participant has a positive pregnancy test at this visit, they will be discontinued from the study and not receive the HXTC infusion or additional doses of VOR.

Estimated Blood Volume: up to 60 ml

7.3.3.1.1. **VORINOSTAT 400 mg**

Participants take one dose of VOR 400 mg PO the morning of this visit and document the time of the dose. VOR dosing will be approximately 6 hours (give or take approximately 30 minutes) prior to scheduled HXTC infusion. Participants will contact the study coordinator to inform them of the time that they took the dose of VOR.

If the participant experiences any abnormality, sign, or symptom after taking the dose of VOR, they will contact the study coordinator immediately and, if necessary, come to the clinic for evaluation prior to their infusion time.

7.3.3.1.2. **Pre – HXTC INFUSION**

The participant will come to the CTRC research clinic approximately 3.5 - 4 hours after taking their dose of VOR for pre-infusion evaluations, which includes:

- Review participant allergies

- Establish IV access
- Collect research samples approximately 4 hours after AM VOR dose. Collection can be +/- one hour of the 4-hour time point.
- Clinical assessments per SOE
- Documented PI review of clinical labs from Visit 6 as well as review of clinical assessments done at this visit are required prior to the thawing and infusion of HXTC study product.

Note: Administration of HXTC can be delayed up to 1 week pending resolution of physical findings or lab abnormalities.

7.3.3.1.3. **Administration of HXTCs**

- Verify IV access
- Pre-medicate approximately 30 minutes prior to infusion with:
  - Cetirizine 10 mg PO
  - Acetaminophen 500 mg PO (weight < 65 kg) or 650 mg PO (weight ≥ 65 kg)
- Administer cells per UNC HIV Cure Center SOP for HXTC Infusion and the SOP for Cellular Product Infusion Guidelines and Emergency Management Plan.
  - Administer HXTC dose up to 1 x 10^8 cells/m^2 by IV infusion at a rate of 4-6 mL/min.
- Provide supportive care for acute toxicity as appropriate.
- Assess participant for infusion reaction for 60 minutes post infusion. Monitor the infusion site and vital signs. Document the assessments every 15 minutes for 60 minutes, and then discharge home.

7.3.3.1.4. **Post Infusion**

Provide the participants with the 2nd and 3rd doses of VOR 400 mg to take home.

The study coordinator will contact participants via their preferred way of communication approximately 2 to 3 days after this visit to inquire about any reactions or potential treatment emergent adverse events (TEAE). Instruct the participant to contact the study coordinator or investigator if any adverse events occur not only after the infusions but at any time during the study. Coordinator can combine this assessment with VOR dosing reminder when these events overlap.

7.3.3.2. **Visit 8**

Participants will have a post HXTC infusion follow-up visit per SOE with labs drawn 1 – 3 days post infusion.

Estimated Blood Volume: up to 105 mL

7.3.3.3. Visit 9 - Administration 3rd Dose of VOR 400 mg

- Participants will take VOR 400 mg PO the morning of this visit and document the time taken.
- Participants will contact the study coordinator to inform him/her of the time that they took the dose of VOR.
- Participants will come to study visit after taking their dose.
- Refer to SOE for visit procedures and lab collections.
- Dispense 3 doses of VOR 400 mg for self-administration every 72 hours at home (Doses # 4, 5, and 6).

Estimated Blood Volume: up to 45 mL

7.3.3.4. Visit 10 (VOR Dose #6 and HCTX Infusion #2)

All female participants require a negative POC urine pregnancy test within 48 hours of infusion visit. If, despite the documentation of infertility, a female participant has a positive pregnancy test at this visit, they will be discontinued from the study and not receive the HXTC infusion or additional doses of VOR.

Estimated Total Blood Volume: up to 45 mL

7.3.3.4.1. Administration of the 6th dose of VOR 400 mg

Participants takes VOR 400 mg PO the morning of this visit and document the time. This is the 6th dose in the series of 10 doses.

Reference section 7.3.3.1.1. for dosing time and process prior to infusion.

7.3.3.4.2. Pre – HXTC Infusion

The participant will come to the clinic approximately 3.5 - 4 hours after taking their VOR dose.

Reference section 7.3.3.1.2. and SOE for visit procedures and processes.

Safety evaluations and research lab collection:

- Collect safety labs (STAT) or within 48 hours of the visit.
- Collect research labs on the day of visit only.
    - Collect approximately 4 hours after AM VOR dose. Collection can be +/- one hour of the 4-hour time point.

Documented PI review of clinical labs as well as review of clinical assessments done at this visit are required prior to the thawing and infusion of HXTC study product.

Administration of HXTC can be delayed up to 1 week, pending resolution of physical findings or lab abnormalities.

7.3.3.4.3. **Administration of HXTC Therapy**

Reference section 7.3.3.1.3 for infusion guidelines.

7.3.3.4.4. **Post infusion**

Provide participant with the 7th, 8th, 9th, and 10th doses of VOR 400 mg to take home.

The study coordinator will contact participants via their preferred way of communication approximately 2 to 3 days after study product administration to inquire about any reactions or potential TEAEs. Instruct the participant to contact the study coordinator or investigator of any adverse events after this infusion or at any point time during the study. Study coordinator can combine this assessment with VOR dosing reminder when these events overlap.

7.3.3.5. **Visit 11**

The study participant will have a post HXTC infusion follow-up visit per SOE with labs drawn 1 – 3 days post infusion.

Estimated Total Blood Volume: up to 25 mL

7.3.3.6. **Visit 12**

Participants take their last dose in this series (Dose #10) of VOR 400 mg PO in the morning and document the time of the dose. Participants will come to research clinic approximately 4 – 6 hours after this dose.

Participant dose management and coordination with study coordinator will be conducted as described in section 7.3.3.1.1.

Clinical assessments and sample collections will be performed per SOE.

Estimated Blood Volume: up to 60 mL

7.3.3.7. **Visit 13 - Safety Follow-Up and Step 5 Pre-Dose Safety Assessment**

Occurs between 7 and 14 days after Visit 12 and within 21 days of Step 5, Visit 14.

The pre-dose safety labs must be reviewed and signed off by the study PI or designee prior to Visit 14. If the participant does not meet one or more of the requirements of the pre-dose safety lab assessments, repeat of the abnormal lab/s can occur one time only.

After repeat testing, any lab values that remain outside the guidelines listed below but are considered clinically non-significant and documented as such by the study PI (or designee), may proceed to the dosing/infusion visit after review and approval of the case by the protocol and/or safety committee.

Please reference the SOE for clinical and research procedures done at this visit.

Hematology	**Laboratory Value**
ANC	≥1,500 /mcL
Platelets	≥125,000 /mcL
Hemoglobin	≥ 12 g/dL (male) and ≥ 11.0 g/dL (females)
Chemistry	
K^+ levels	WNL
Mg^{++} levels	WNL
Glucose	≤ Grade 1 (fasting or non- fasting)
Renal	
Creatinine	<1.3 X ULN
Hepatic	
Total bilirubin	< 1.6 times the ULN range. If total bilirubin is elevated, direct bilirubin must be < 2 times the ULN range.
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Alkaline Phosphatase	≤ 2.5 X ULN
Other Testing	
Serum pregnancy test (all females)	Negative
RPR	No active infection
HIV RNA	< 50 copies

CD4	≥350

Estimated Blood Volume: up to 60 mL

Participants will be given 1 dose of VOR 400 mg to take home. Upon verification of acceptable labs, participants will be contacted to verify date and time of Visit 14 and also to verify the time participant is to take the 11th dose of VOR that morning. Plans will be made for participants to return the dose of VOR 400 mg to the study coordinator should the participant fail to have acceptable pre-dose labs for Step 5.

The study coordinator and the participant will discuss Step 5 visit schedule and VOR dosing schedule. Participant will be given a VOR dosing schedule/calendar illustrating the 72-hour dosing schedule (inclusive of date and time) and the dates of the HXTC infusions. Participants will be provided with information about VOR as well as information regarding the storage and handling of VOR at home. All of this information will be reviewed prior to sending participant home with the 11th VOR dose.

7.3.4. Step 5 (Visits 14 – 20) Second Series of VOR 400 mg x 10 doses and three HXTC Infusions

Participants with acceptable pre-dose safety labs as determined in Visit 13 are eligible to start dosing with VOR and receive their 3rd HXTC infusion in Step 5, Visit 14.

Visit Windows for Step 5

Visit #	Visit Evaluations	Visit Window
Visit 14	VOR Dose #11 and HXTC Infusion #3	≤ 21 days after Visit 13
Visit 15	Safety check and Research Labs	1 - 3 days after Visit 14
	VOR Dose #12	3 days after Visit 14 (Dose 11 + 3 days)
	VOR Dose #13	6 days after Visit 14 (Dose 11 + 6 days)
	VOR Dose #14	9 days after Visit 14 (Dose 11 + 9 days)
	VOR Dose #15	12 days after Visit 14 (Dose 11 + 12 days)
Visit 16	VOR Dose #16 and HXTC Infusion #4	15 days after Visit 14 (Dose 11 + 15 days)
Visit 17	Safety Check and Research Lab	1 - 3 days after Visit 16
	VOR Dose #17	3 days after Visit 16 (Dose 11 + 18 days)
	VOR Dose #18	6 days after Visit 16 (Dose 11 + 21 days)
	VOR Dose #19	9 days after Visit 16 (Dose 11 + 24 days)
Visit 18	VOR Dose #20	12 days after Visit 16 (Dose 11 + 27 days)
Visit 19	HXTC Infusion #5	1-3 days after Visit 18
Visit 20	Safety Check and Research Lab	1-3 days after Visit 19

7.3.4.1. **Visit 14 – 1st Visit of 2nd series**

All female participants will be required to have a negative POC urine pregnancy test within 48 hours of Visit 14. If, despite the documentation of infertility, a female participant has a positive pregnancy test at this visit, she will be discontinued from the study and not receive any additional VOR doses or HXTC infusions.

Estimated Blood Volume: up to 25 mL

7.3.4.1.1. **VORINOSTAT 400 mg**

Participants take one dose of VOR 400 mg PO the morning of this visit and document the time of the dose. This is the first dose (Dose #11) in the 2nd series of 10 doses.

Reference section 7.3.3.1.1 for dosing time and process prior to infusion.

7.3.4.1.2. **Pre - 3rd HXTC Infusion**

The participant will come to the clinic approximately 3.5 - 4 hours after taking their VOR dose for pre-infusion evaluations.

Reference section 7.3.3.1.2. and SOE for visit procedures and processes.

Documented PI review of clinical labs from Visit 13 as well as review of clinical assessments done at this visit are required prior to the thawing and infusion of HXTC study product.

Note: Administration of HXTC can be delayed up to 1 week pending resolution of physical findings or lab abnormalities.

7.3.4.1.3. **Administration of HXTC**

Reference section 7.3.3.1.3 for infusion guidelines.

7.3.4.1.4. **Post Infusion**

Provide participant with doses #12 – #16 of VOR 400 mg to take home.

The study coordinator will contact participants via their preferred way of communication approximately 2 to 3 days after study product administration to inquire about any reactions or potential TEAEs. Instruct the participant to contact the study coordinator or investigator if such any adverse events occur after this infusion or at any point during the study. The study coordinator can combine this assessment with VOR dosing reminder when these events overlap.

7.3.4.2. **Visit 15 – Safety Follow-Up Visit**

The study participant will have a post HXTC infusion follow-up visit per SOE with labs drawn 1 – 3 days post infusion.

Estimated Blood Volume: up to 55 mL

7.3.4.3. **Visit 16 - Dose #6 of VOR and 4th HXTC Infusion**

All female participants require a negative POC urine pregnancy test within 48 hours of infusion visit. If, despite the documentation of infertility, a female participant has a positive pregnancy test at this visit, they will be discontinued from the study and not receive the HXTC infusion or additional doses of VOR.

Estimated Total Blood Volume: up to 45 mL

7.3.4.3.1. **VORINOSTAT 400 mg**

Participants take VOR 400 mg PO the morning of this visit and document the time. This is the 6th dose in the series of 10 doses.

Reference section 7.3.3.1.1. for dosing time and process prior to infusion.

7.3.4.3.2. **Pre – HXTC Infusion**

Safety evaluations and research lab collection:

- Collect safety labs (STAT) or within 48 hours of the visit.
- Collect research labs on the day of visit only.
    - Collect approximately 4 hours after AM VOR dose. Collection can be +/- one hour of the 4-hour time point.

Documented PI review of clinical labs as well as review of clinical assessments done at this visit are required prior to the thawing and infusion of HXTC study product.

Administration of HXTC can be delayed up to 1 week, pending resolution of physical findings or lab abnormalities.

7.3.4.3.3. **Administration of HXTC Therapy**

Reference section 7.3.3.1.3 for infusion guidelines.

7.3.4.3.4. **Post Infusion**

Provide participant with the last four (4) doses of VOR 400 mg to take home.

The study coordinator will contact participants via their preferred way of communication approximately 2 to 3 days after study product administration to inquire about any reactions or potential TEAEs. Instruct the participant to contact the study coordinator or investigator if any adverse events occur after this infusion or at any point during the study. Study coordinator can combine this assessment with VOR dosing reminder when these events overlap.

7.3.4.4. **Visit 17 – Safety follow-up**

The study participant will have a post HXTC infusion follow-up visit per SOE with labs drawn 1 – 3 days post infusion.

Estimated Total Blood Volume: up to 25 mL

7.3.4.5. **Visit 18 – Last dose of VOR 400mg - Dose #20)**

Participants take their last dose (Dose #20) of VOR 400 mg PO in the morning and document the time of the dose. Participants will come to research clinic approximately 4 – 6 hours after this dose.

Clinical assessments and sample collections will be performed per SOE.

Estimated Blood Volume: up to 35 mL

7.3.4.6. **Visit 19 – 5th and final HXTC Infusion**

All female participants require a negative POC urine pregnancy test within 48 hours of infusion visit. If, despite the documentation of infertility, a female participant has a positive pregnancy test at this visit, they will be

discontinued from the study and not receive the HXTC infusion or additional doses of VOR.

Estimated Blood Volume: up to 25 mL

7.3.4.6.1. **Pre – HXTC Infusion**

Reference section 7.3.3.1.2. and SOE for visit procedures and processes.

Safety evaluations and research lab collection:

- Collect safety labs (STAT) or within 48 hours of the visit.
- Collect research labs on the day of visit only.

Documented PI review of clinical labs as well as review of clinical assessments done at Visit 18 as well clinical assessments from this visit are required prior to the thawing and infusion of HXTC study product.

Administration of HXTC can be delayed up to 1 week, pending resolution of physical findings or lab abnormalities.

7.3.4.6.2. **Administration of HXTC Infusion**

Please reference section 7.3.3.1.3. for infusion guidelines.

7.3.4.6.3. **Post Infusion**

The study coordinator will contact participants via their preferred way of communication approximately 2 to 3 days after this visit to inquire about any reactions or potential TEAEs. Instruct the participant to contact the study coordinator or investigator if any such adverse events occur after this infusion or at any point during the study.

7.3.4.7. **Visit 20 - Safety Follow-up**

The study participant will have a follow-up visit per SOE with labs drawn 1 – 3 days post infusion.

Estimated Total Blood Volume: up to 25 mL

7.3.5. **Step 6 (Visits 21, 23 and 24) Immune Monitoring Follow-up**

These last three visits (Visits 21, 23 and 24) are longitudinal follow-up to evaluate for a sustained immune response. There is a leukapheresis at Visit 23 to measure the effect on the frequency of resting cell infection by QVOA.

NOTE: THE PROTOCOL AMENDMENT FOR VERSION 4.0 DATED 31 JANUARY 2022 ELIMINATED STEP 6 VISITS 22, 25, AND 26 OF THE PROTOCOL.

7.3.5.1. **Visit 21**

The clinical and research assessments and procedures occur per SOE at Visit 21.

Estimated Blood Volume: up to 50 mL

7.3.5.2. **Visit 23 and End of Study Intervention Visit**

The clinical and research assessments and procedures occur per SOE at Visit 23.

A leukapheresis is performed at this visit.

Estimated Total Blood Volume: up to 70 mL

7.3.5.3. **Visit 24**

In addition to the participants completing all study visits, participants terminated, at any time point after initiating Step 4, will complete this visit after completing Visit 23.

The clinical and research assessments and procedures occur per SOE at Visits 24.

Estimated Blood Volume: up to 55mL

Visit 24 will be the last study visit and the end of study.

7.4. Screening Failure and Re-screening Procedures

Participants unable to meet laboratory values as defined in the protocol and defined inclusion/exclusion criteria may repeat the disqualifying lab/s once to meet eligibility prior to enrolling at Visit 2.

Participants unable to meet protocol defined eligibility criteria at the Screening Visit after repeating disqualifying labs per protocol, can re-screen again at the Principal

Investigator's (or designee) discretion. In such cases, the participant keeps the same PID.

7.4.1. Failure of the frequency of resting CD4+ T cell infection to be ≥ 0.3 infected cells per million as determined by QVOA assay at baseline evaluation.

If a participant fails to have a frequency of resting CD4+ T cell infection to be ≥ 0.3 infected cells per million as determined by QVOA assay at the baseline leukapheresis in Step 1, study participation is terminated. The SID for this participant will be retired and will not be used again. These participants will be replaced in the study.

7.4.2. Inability to manufacture HXTC therapy or failure to meet release criteria

In the unlikely event that product or sufficient product is not successfully manufactured for participants, these participants would not proceed to Step 4 and would not undergo any further study procedures.

These participants may undergo a single repeat blood draw of 100mL to allow a second attempt at manufacturing product.

If the participant refuses to repeat the blood draw or the product cannot be manufactured after receipt of the 2nd 100 mL sample, the participant will be terminated from the study. The SID for this participant will be retired and will not be used again. These participants will be replaced in the study.

7.4.3. Inability to meet the pre-dose lab guidelines for study progression based on clinical evaluations at Step 3, Visit 7 and at Step 4, Visit 13.

If a participant's failure to move to Step 4 or Step 5 is due to an inability to meet one of the pre-dose safety laboratory assessments parameters, repeat the failed criteria one time only.

Participants failing to advance to Step 4, without receiving any combination treatment of VOR and HXTC, will terminate from the study. The SID for this participant will be retired and will not be used again. These participants will be replaced in the study.

Participants completing combination dosing in Step 4 and/or Step 5 who then fail to meet safety assessment requirements, will not receive further doses of VOR or HXTC. Participants will proceed to complete the early discontinuation visit per Step 6, Visit 23 (when clinically acceptable, per PI assessment) and continue to complete the longitudinal assessment at Visit 24.

7.5. Early Discontinuation Visit (Step 6, Visit 23)

Complete this visit any time a participant discontinues early from the study. This is the End of Study Intervention Visit and completed when participants complete study interventions, whether pre-maturely (as with an early discontinuation or upon successful completion of the study.

Perform the Early Discontinuation or End of Study Intervention Visit assessments and procedures per the SOE.

The Leukapheresis is completed on all participants who have completed all dosing visits. If a participant terminates early, completion of the leukapheresis at Visit 23 will be determined by study PI or the study team.

Estimated Blood Volume: up to 65 mL

8. STUDY PROCEDURES/EVALUATIONS

8.1. Description of Evaluations

Evaluation of participants occur by physical examinations, medical history, clinical laboratory tests, research lab assay results, vital sign measurements, and adverse event evaluations. Safety assessments will include grading of the frequency and severity of adverse events associated with study treatment including, but not limited to, clinical laboratory values, physical examination and evaluations of infusion site reactions.

8.1.1. **Clinical Evaluations and Procedures**

8.1.1.1. Informed Consent

Prior to performing any study-related procedure or assessments, the study coordinator discusses the study with the potential participant and obtains signed informed consent. This communication will be documented. Labs/procedures completed during a routine clinical care appointment that are the same as the study screening labs and/or procedures and completed within the 14 days preceding the screening visit can be used to qualify the participant upon approval by the study PI or designee.

8.1.1.2. Study Eligibility

Determination of study eligibility by the Inclusion and Exclusion criteria occurs at Screening and prior to enrollment at Step 1, Visit 2. Potential participants failing eligibility will be considered a screen failure. (Please reference section 7.4.),

8.1.1.3. Advancement Criteria

There is one time point when participants are required to meet Advancement Criteria to continue on study:

Step 1 to Step 3

The leukapheresis procedure performed at or after enrollment in Step 1, Visit 2 determines the criteria required to advance to Step 3. Failure to meet the criteria results in participant's termination from the study.

Advancement Criteria for Step 3

- Participants with frequency of resting CD4+ T cell infection of < 0.3 IUPM by QVOA will not progress to Step 3, as a further decrease from this low frequency of infection cannot be definitively measured given the QVOA assay threshold.

8.1.1.4. Pre-Dose Lab Assessments

There are two time points in the study when the participant completes Pre-Dose Safety Lab Assessments. The lab results obtained in these assessments must be within the study established parameters for the administration of VOR to occur. Labs that fall outside the parameters can be repeated one time only to qualify participants to proceed.

After repeat testing, any lab values that remain outside the guidelines but considered clinically non-significant and documented as such by the study PI (or designee), must be reviewed and approved by the protocol and/or safety committee prior to dosing/infusion visit.

The time points of Pre-Dose Lab Assessments are:

1. Step 3, Visit 6 (1st Series of VOR doses (10) and two HXTC infusions)
2. Step 4, Visit 13 (2nd Series of VOR doses (10) and three HXTC infusions)

8.1.1.5. Complete Medical Histories

Significant medical history should be obtained during the Screening visit. All concurrent medical conditions in the last 30 days and any significant medical conditions (e.g., hospitalizations, surgeries, prior medical history) should be collected. Medical history obtained at Screening will include demographic information (e.g., date of birth, gender, race, and ethnicity, etc.), participant's medical history, and HIV history.

8.1.1.6. Update Medical History at all clinical visits

Any reported signs and symptoms or new diagnoses occurring after the participant signs the study consent but prior to the administration of the first

study dose will be recorded in the medical history (pre-existing condition) unless reported event is related to a protocol-related procedure.

8.1.1.7. Complete Physical Exams

A complete physical examination (PE) is done at the following visits:

- Step 1, Visit 1 - Screening
- Step 3, Visit 6
- Step 4, Visit 13 (Study Week 6)
- Step 6, Visit 23 (Study Week 16)
- Early Discontinuation Visit (same as End of Study Intervention Visit in SOE - Step 6, Visit 23 (Study Week 16)

The PE will include a complete review of systems, vital signs, and weight. Measure Height at the Screening Visit only. The complete physical examination will include examination of skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, psychological and neurologic systems.

8.1.1.8. Directed or Targeted Physical Exams

A targeted PE is done at all other visits where a complete PE is not performed, per the SOE. A directed physical examination includes vital signs and addresses any previously identified or new event that the participant experiences since the last study visit or any unresolved signs or symptoms previously experienced. This assessment includes updates to signs and symptoms, and clinical assessment of HIV disease.

8.1.1.9. Vital Signs

Temperature, respiration, pulse, blood pressure, and weight (without shoes) at each study visit. Complete vital sign measurements after 5 minutes in the sitting position. Repeat vital signs may also be captured as necessary to elucidate the course of any untoward event or AE.

8.1.1.10. Height – required at study screening visit only without shoes.

8.1.1.11. ART History

May consist of a combination of participant report and clinical records where available. During the study, all modifications to the participant's ART regimen, including any ARV interruptions, dose modifications, formulations modifications, starts, and permanent discontinuations since the last study visit or at the study visit must be recorded.

8.1.1.12. ART Adherence

ART adherence will be reviewed at every visit. Any missed doses while on study should be discussed with Study PI (or designee). Continuance on study will be contingent on adherence.

8.1.1.13. Concomitant Medication History

Include all current medications and any PRN medications used within the past 30 days.

- All medication taken within 30 days of study screening.
- After study entry, record only new and discontinued over-the-counter, herbal, dietary and vitamin supplements, and prescription medications.
- Document all doses of VOR and HXTC therapy and permanent discontinuation.

8.1.1.14. Signs, Symptoms, and Diagnosis of Illnesses and Diseases

At screening, all signs and symptoms, regardless of grade, that occurred within the 30 days before entry must be recorded. After study entry, record any new diagnosis or illnesses that develop.

After study entry, grade ≥3 signs and symptoms must be recorded. Record only signs and symptoms that are related to VOR or HXTC therapy and all signs and symptoms that lead to a change in treatment, regardless of grade.

8.1.1.15. Blood collection

Please reference SOE in Appendix A

8.1.1.16. Urine Collection

Please reference SOE in Appendix A

8.1.1.17. Assessment of adverse events

Please reference protocol section 9.1

8.1.1.18. Leukapheresis

Participants will undergo two Leukapheresis procedures. The baseline leukapheresis will be completed at or after Visit 2. Participants will advance to Step 3 based on an IUPM measurement ≥ 0.3. The 2nd leukapheresis will take place at the End of Study Intervention visit in Step 6, Visit 23.

All protocol required leukapheresis products will be transported on the day of collection to the Margolis Laboratory on the UNC campus.

All leukapheresis procedures will occur at the UNC Apheresis Lab located in the UNC Blood Bank or at a local contracted blood collection center.

Note: Refer to the UNC Apheresis SOP and Study Specific Lab Manual for procedures specific to this study.

If participants experience a Grade 3 or higher toxicity in the screening leukapheresis, they will be discontinued from study, as completing the leukapheresis procedures is a requirement of the study screening process. Participants who experience a Grade 3 or higher toxicity related to any additional leukapheresis will be evaluated on a case by case basis to understand the cause of the Grade 3 event. If the clinical situations (i.e., vasovagal response) that lead to the discontinuation of the leukapheresis procedure is determined by the study PI in collaboration with the Apheresis Medical Director to be situational and poses no apparent harm to the participant, the leukapheresis procedure may be repeated. However, if determined by the study PI, Apheresis Medical Director, and/or the Medical Monitor that repeated leukapheresis would be harmful to the participant, then he/she will be terminated from the study.

The only exception to this discontinuation policy includes elevations in blood pressure (BP). Transiently elevated BPs to Grades 2 and 3 are frequently observed during this procedure, secondary to the BP cuff placement and nervousness of the participant. Elevated BP observed during the leukapheresis procedure will be monitored via Apheresis Lab policies. These will be noted and documented but will not be used to discontinue study participation.

8.1.1.19. Pre-HXTC Infusion Medications (cetirizine and acetaminophen) and other Medications for Administration in the Advent of a Hypersensitivity or Anaphylactic Reaction

- Licensed study staff will administer cetirizine (PO) and the acetaminophen (PO).
- Administration of medications for treatment of adverse reactions to the HXTC will follow hospital policy and the UNC HIV Cure Center SOP entitled Cellular Product Infusion Guidelines and Emergency Management Plan.

8.1.1.20. HXTC Infusion

The HXTC will be administered by staff competent in cellular product infusion; the study PI (or designee) or a licensed physician assistant (PA)/nurse practitioner (NP) or RN. A research assistant (RA) may obtain and record vital signs and provide other participant care necessary during the HXTC infusion.

8.1.1.21. Product Infusion Reaction Evaluations

Participants will be monitored for up to 1 hour following treatment while the participant remains in the clinic. Participants will be instructed to contact study staff about any reactions that occur after receipt of the HXTC therapy. The study staff will contact the participants via telephone or their preferred way of communication approximately 2 to 3 days after the study product administration to inquire about reactions or any potential TEAEs. Infusion reactions will be graded according to the DAIDS toxicity grading table.

8.1.2. **Clinical Laboratory Procedures**

These laboratory evaluations will be conducted primarily at one of the clinical site laboratories available to the research team. Details of specimen collection are found in the Lab Procedures Manual for this study.

At designated visits, the study PI (or designee) assesses the clinical events and the laboratory test results and determines whether the participant can receive VOR doses or HXTC infusions. If values are outside the study reference range, the PI (or designee) determines if the abnormal value is clinically significant and if study treatments can continue. Report all abnormal laboratory values that the investigator deems clinically significant as AEs.

All participants will have safety labs (CBC with differential and chemistries) done throughout the study to monitor for any adverse events due to the administration of VOR and HXTC therapy. Labs that are abnormal and meet grading standards per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017], will be re-assessed based on these initial parameters.

Blood specimens will be collected and evaluated at either UNC McLendon Hospital Lab or LabCorp.

8.1.2.1. **HIV -1 Infection Documentation**

8.1.2.2. **Donor ID Panel Testing**

The following tests will be performed on samples collected at Step 3, Visit 4. These samples will either be sent to HPC Lab or LabCorp for testing. Test kits, tubes, and sample processing is done in the HPC lab.

- AbO/Rh
- HBsAg
- HB Core antibody
- HIV1/2 plus O
- Syphilis (T. Pallidum IgG)
- HTLV I/II
- CMV total
- HIV-1/HBV/HCV Ulrio NAT
- West Nile Virus NAT
- T. Cruz (Chagas) antibody

8.1.2.3. **Clinical Chemistry**

Assessments include Sodium (Na), potassium (K), chloride (Cl), bicarbonate (CO2), glucose, blood urea nitrogen (BUN), creatinine, calcium (Ca), magnesium (Mg), ALT, AST, alkaline phosphatase, total bilirubin.

In addition to the labs listed above, the following labs will be done at screening and Visit 23 only:

- Direct bilirubin will be obtained if participant is on atazanavir.
- Lipase, albumin, total protein, cholesterol, and triglycerides

8.1.2.4. **Hematology** – All assessments include CBC with WBC differential

8.1.2.5. **Safety Labs**

All participants will have safety labs (CBC with differential and chemistries) done at protocol required visits. Labs from the screening visit will be considered baseline. All lab values obtained pre- and post-dosing that are abnormal and meet grading standards per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017 will be re-assessed based on these initial parameters.

Creatinine clearance calculations will use the CKD-EPI equation. This calculation can be found at
https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi

The creatinine clearance will be required for study enrollment eligibility. The study assesses serum creatinine level at all the safety lab checks and uses the serum creatinine value for toxicity grading and as confirmation to progress to each dosing Step. Grade the serum creatinine per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017.

8.1.2.6. **Prothrombin time (PT), INR, and APTT** - at Screening Visit only.

8.1.2.7. **Follicle Stimulating Hormone (FSH) Test**

This test is done at screening to document menopause in women who have been without a period for > 12 months.

8.1.2.8. **HBsAg and Hep C Antibody** Both hepatitis tests must be negative or non-detected to be included on the study. A positive HCV AB test reflexed to Hepatitis C RNA revealing a negative result is acceptable.

8.1.2.9. **RPR**

If positive and participant has documentation of recent appropriate treatment, they may continue in study. Completion of RPR testing occurs again at Step 3, Visit 6 and Step 4, Visit 13.

8.1.2.10. **HIV-1 RNA**

The definition for the HIV-1 RNA quantitative PCR “less than (<) level/limit of detection” or “undetectable per institutional standard” for the purpose of this study will be <50 copies/mL.

8.1.2.11. **CD4+ T cell differential panel**

8.1.2.12. **Serum and Point of Care (POCT) Urine Pregnancy test**

A negative serum pregnancy test (to rule out pregnancy) is required on all women at screening and VOR pre-dose assessment visits, regardless of documented procedures that prohibit pregnancy. The use of the POCT urine pregnancy test as confirmation of negative pregnancy status is acceptable at all visits except screening.

All women regardless of child bearing potential will have a pregnancy test prior to the first VOR dose, prior to the first dose in subsequent series of dosing, as well as at each HXTC infusion. The test must be negative within 48 hours of the dose. Because the study has no direct clinical benefit, this added protection is warranted.

8.1.2.13. **Urinalysis**

Perform this test at Screening and the End of Study Intervention (Visit 23) to establish baseline and evaluate if any changes occurred post therapeutic interventions. Dipstick testing (including protein, glucose, hemoglobin, pH, and ketone) will be done. Microscopic analysis will only be done in the event of abnormal results from dipstick testing.

8.1.3. **Research Laboratory Procedures**

8.1.3.1. **Research analysis to be performed per the SOE**

8.1.3.2. **Immune Response Assay**

Immune responses are assessed using IFNγ ELispot response to individual epitopes. Changes in the magnitude of response to any single epitope reflects immune responses induced as a consequence of dosing with VOR-HXTC. T cell phenotype and markers of exhaustion pre and post VOR-HXTC administration will also be evaluated. Tetramer staining and Vβ usage analysis will also be performed in order to track the fate of the infused HXTCs.

8.1.3.3. **Stored Plasma for Single Copy Assay**

Plasma for HIV-1 RNA SCA will be obtained as required per the SOE and stored for batched analyses**.** PBMCs will be processed off these samples and stored for future study analysis.

8.1.3.4. **PBMCs for HDAC Responsive Gene Measurement**

PBMCs will be used to confirm pharmacologic effect of VOR on cellular targets *in vivo*. We will isolate total RNA from PBMCs and evaluate the expression of several genes with predictable behavior in response to HDAC inhibition *in vitro* and *in vivo*.

8.1.3.5. **Limiting Dilution Cultures of Resting CD4+ T Cells to Quantify Resting Cell Infection**

Lymphocytes are obtained by continuous-flow leukapheresis and resting CD4 positive T-cells are isolated as previously described [51]. A maximum likelihood method will be used to calculate the infectious units per million of resting CD4+ T-cells. Exploratory assays for quantitation of resting cell infection may include digital droplet PCR of resting cell associated RNA.

8.1.3.6. **Clinical Pharmacokinetics**

We will collect a PK sample at designated time points throughout the study. Please reference SOE for exact time points.

8.1.3.7. **Ex-vivo Latent Clearance Assay**

Resting CD4 cells are isolated via negative selection from a leukapheresis product and then activated. After 15 days of culture, each well is assessed for the presence of residual HIV infection with an HIV-1 gag p24 ELISA performed on supernatant.

8.1.3.8. **Epitope Mapping**

If sufficient cells are available we will perform Epitope mapping of the HXTC product and compare circulating HIV-1 reactive T cell frequencies pre- and post- VOR administration and HXTC infusions. We will also conduct mapping of individual HIV-1 reactivated T cell epitopes targeted by T cell populations and their dominance hierarchies pre- and post-administration of VOR doses and HXTC infusions in Steps 4 and 5.

8.1.3.9. **HLA Typing**

HLA typing is performed on participant peripheral blood at the time of blood collection for HXTC manufacture. For product release, HLA typing will also be performed on the final product to confirm identity. In addition, HLA typing results will be used to inform epitope specific responses as part of the HXTC product characterization.

8.1.3.10. **Specimen Preparation, Handling, and Shipping**
Specimen processing and shipment will follow the Study SOPs and Lab Procedures Manual.

8.1.4. **Sample Storage**
Participants sign a separate consent for the use and storage of these blood samples for research analysis associated with this study. The research analysis includes genetic testing, and this information will be included in the blood storage consent reviewed with the participants. Participants can opt out of genetic testing.

Any remaining specimens that will be stored for future research will be stored safely and securely in a research specimen storage laboratory at the University of North Carolina at Chapel Hill (UNC-CH). No protected health information (PHI) is included with the samples. All samples are identified by coded number only.

The link between Participant Identifier Code on the samples and PHI is maintained in a secured file on a secured server in the control of the principal investigator at UNC-CH. Future researchers would not have access to this link. Only study personnel, people who work at the research specimen storage laboratory at UNC-CH and IRB approved researchers will have access to the participants' samples. Since all the stored specimens are de-identified, the people who work at the research specimen storage laboratory will not have any personally identifying information that would link to a participant. The IRB approved researchers who receive the specimens may receive information pertaining to lab assay values, age, and sex of the specimen donor, but will not be given the name or any other information that identifies the donor/participant. These samples will be stored indefinitely.

9. CLINICAL MANAGEMENT ISSUES

Criteria for participant management, treatment interruption, and study discontinuation will be mandated only for toxicities possibly, probably, or definitely related to HXTC and/or VOR.

NOTE: In the event that a participant develops toxicity related to his/her previously-stable ART, consultation with the protocol team will be required (preferably before appropriate therapy modification). Toxicities due to drugs in the antiretroviral regimen should be managed according to standard clinical practice, with the goal of maintaining continuous therapy, if possible.

AEs assessed as related to non-study drugs (concomitant medications) should be handled according to the relevant package inserts and the best medical judgment of the site investigator or designee.

Infusion site reactions will be graded according to the DAIDS toxicity grading table.

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017], which is available on the DAIDS RSC website.

9.1. Toxicity

Only toxicities considered related to HXTC and/or VOR will be managed directly by this protocol.

Participants will be monitored closely for adverse effects. Toxicities will be characterized in terms including duration, intensity, and time to onset. Safety endpoints will include all adverse experiences, in addition to laboratory safety assessments and vital signs.

For this study, the hemoglobin will be graded using version 2.1 [July 2017] of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events where a hemoglobin <11 mg/dl for men and <10.5 for women will be considered a Grade 1 toxicity.

9.1.1. **Grade 1 or 2 Toxicity**

Participants who develop a Grade 1 or 2 AE or toxicity that occurs following an HXTC infusion or VOR dosing that is thought to be possibly, probably, or definitely related to HXTC and/or VOR should be discussed with the study team.

In the event of a grade 1 toxicity related to hemoglobin or anemia the study team should be contacted to guide the elimination of research labs as needed to avoid a grade 2 toxicity related to hemoglobin.

9.1.2. **Grade 3 Toxicity**

For participants who develop a Grade 3 AE that occurs following an HXTC infusion or VOR dosing not specifically discussed below that is judged by a site investigator to be at least possibly study treatment-related, the protocol team must be notified within 24 hours. Participants with a study treatment-related Grade 3 AE will not receive any additional doses of study treatment/product. Participants experiencing Grade 3 AEs should be followed closely and if the AE does not return to Grade ≤ 2 within 2 weeks, the protocol team should again be notified within 24 hours.

For participants who experience a Grade 3 AE that is judged not related to the study drug by the investigator or designee, continued study participation is at the discretion of the principal investigator in consultation with the protocol team.

9.1.3. **Grade 4 Toxicity**

For participants who develop a Grade 4 AE that occurs following an HXTC infusion or VOR dosing not specifically discussed below that is judged by a site investigator or designee to be at least possibly study treatment-related, the protocol team must be notified within 24 hours. Participants with a study treatment-related Grade 4 AE will not receive any additional doses of study treatment/product. Participants experiencing Grade 4 AEs should be followed closely with additional clinical assessments and laboratory testing as clinically indicated. If the AE does not return to Grade ≤ 2 within 2 weeks, the protocol team should again be notified within 24 hours.

9.1.4. **HXTC Infusion-related Toxicities**

Infusion reactions should be graded according to the criteria for acute systemic allergic reaction located in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017], which can be found on the DAIDS RSC Web site: *http://rsc.tech-res.com/safetyandpharmacovigilance/*.

These reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

9.1.4.1. Grade 1 or 2 Local or Systemic Reactions

Local reactions of mild (Grade 1) or moderate (Grade 2) severity will usually resolve spontaneously. If needed, they may be managed with local application of cold packs, oral acetaminophen, oral non-steroidal anti-inflammatory agents, or a combination of these measures as appropriate.

9.1.4.2. Grade 3 or 4 Local or Systemic Reactions

For severe (Grade 3) or potentially life-threatening (Grade 4) local reactions, the protocol team must be notified within 24 hours. For Grade 4 local reactions, definitive medical and/or surgical intervention should be undertaken as appropriate. Further infusions should not be administered prior to consultation with the core protocol team.

9.1.5. **Systemic Reactions**

The protocol team should be contacted within 24 hours for any non-local Grade 3 or 4 AE thought definitely, possibly, or probably related to study treatment. Additional study product should not be administered prior to consultation with the

protocol team. For severe infusion (Grade 3 or 4) reactions, appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, and oxygen should be available for use in the treatment of such reactions. Participants should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the site investigator should institute treatment measures according to the best available medical practice.

9.1.5.1. Grade 1 or 2 Local or Systemic Reactions

Local reactions of mild (Grade 1) or moderate (Grade 2) severity will usually resolve spontaneously. If needed, they may be managed with a combination of medical treatment measures as appropriate.

9.2. Toxicity Management

9.2.1. Adverse Events

Reports of AEs will be elicited by verbally questioning the participant at all visits. The study coordinator will also telephone the participant approximately 2 to 3 days after the HXTC study product administration to inquire about any potential treatment emergent adverse events (TEAE). The participant will be instructed to contact the study coordinator or investigator if such events occur at any point during the study.

Any events spontaneously reported by the participant or observed by the study team will be recorded.

If an AE occurs, the study coordinator, in collaboration with the PI or designee, will evaluate the severity and seriousness of the AE and the relationship to the study product, and will document the findings. Appropriate countermeasures, including medical intervention or procedures, must be instituted if indicated clinically.

AEs occurring at the HXTC administration site should be reported and analyzed in accordance with standard practices for clinical testing of novel therapeutic candidates.

All reactions will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 [July 2017], which is available on the DAIDS RSC website: *http://rsc.techres.com/safetyandpharmacovigilance/*.

9.2.2. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable or unintended sign (including an abnormal lab finding, for example), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE does include a/an:

- Exacerbation of a pre-existing illness
- Increase in frequency or intensity of a pre-existing episodic event or condition
- Condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study
- Continuous persistent diseases or symptoms present at Baseline that worsen following the start of the study

An AE does not include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition that led to the procedure is an AE
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social, or convenience admissions)
- The disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition
- Overdose of either the study medication or concurrent medications without any signs or symptoms

In general, abnormal laboratory findings (e.g., clinical chemistries, hematology, urinalysis) or abnormal assessments (e.g., vital signs) are not recorded as AEs unless they are considered clinically significant by the investigator. If an abnormal lab finding is considered clinically significant, it must be recorded in the AE log as follows:

- If it contributes to a clinical diagnosis, the diagnosis must be recorded as the AE (e.g., a clinically significant elevation in blood glucose must be recorded as "diabetes" if a clinical diagnosis is made)
- Or if an abnormal finding does not indicate a clinical diagnosis, the abnormality itself must be recorded

9.2.3. **Adverse Event Reporting Period**

The AE reporting period for each participant begins when the participant signs the consent and lasts through the 30 days following the EOS visit in Step 6, Visit 24. During Step 1 and Step 3 (prior to study product administration), any AE that occurs will be collected as concurrent medical history (pre-existing condition) and not as an AE, unless it is due to a protocol–related procedure (e.g., leukapheresis or large blood collection for HXTC manufacturing).

AEs leading to discontinuation, AEs of ≥ Grade 3 severity, related adverse events, and lab abnormalities as well as safety concerns will be recorded in the database as well as communicated in a timely manner to the UNC IRB, Children's National Health System IRB, NHLBI, FDA, and Merck per the reporting requirements of each regulatory entity.

The Sponsor of this study is UNC-CH. The principal investigator (Dr. David Margolis) at UNC-CH will be responsible for reporting to all the regulatory bodies and funding sources listed above.

9.2.4. **Documentation of Adverse Events**

Throughout the trial, the study coordinator will monitor closely for the development of AEs and the investigator or designee will determine clinical significance of AEs, and initiation of medical interventions if required.

Record the following in the participants' study chart:

- Concise diagnosis
- Onset date
- Criteria for regarding as an AE
- Setting
- Resolution date
- Severity (per DAIDS toxicity grading table)
- Relation to the study product (unrelated, unlikely, possibly, probably, definitely); an AE may be considered related if it follows a reasonable temporal sequence from administration of the study product, confirmed by improvement when the product is stopped and re-appears on repeated exposure
- Study product change (interrupted or discontinued)
- Seriousness (not serious, fatal, life-threatening, leads to or prolongs hospitalization, results in persistent or significant disability or incapacity, congenital anomaly or birth defect, important medical event)

9.2.5. **Definition of a Serious Adverse Event**

As provided in Title 21 CFR part 312, an SAE is an 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 or incapacity
- A congenital anomaly or birth defect
- Important medical event that may not result in death, be life-threating, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical and surgical intervention to prevent one of the outcomes

Any death (regardless of cause) that occurs from the time of the study product administration until 32 weeks after the final study product administration, and any death occurring after this time that is judged at least possibly related to prior treatment with the study product, will be promptly reported.

9.2.6. Definition of a Serious Unexpected Adverse Event

A serious adverse drug reaction is defined as an SAE that is not identified in the IB(s).

9.2.7. Reporting of Serious Adverse Events

All SAEs occurring during the study will be reported to the UNC IRB per the UNC IRB reporting requirements, NHLBI, the FDA, CNH IRB, and Merck, if required within 24 hours of knowledge of the occurrence. A written report (UNC IRB Unanticipated Problem Report Form and, if required Med Watch Form FDA 3500) will be faxed or sent within 24 hours of knowledge of the occurrence. Additional information will be supplied as requested. The funding source of this study is the NHLBI. The principal investigator (David Margolis, MD) at UNC-CH will be responsible for reporting to all of the regulatory and funding agencies.

9.2.8. Follow-Up of AEs and SAEs

All AEs and SAEs must be followed until resolution, become chronic, or stable. The resolution status of such an event must be documented. In addition, the principal investigator should report all follow-up for reportable SAEs to the UNC and CNH IRBs, NHLBI, FDA, and Merck.

9.2.9. Post-Study AEs and SAEs

Investigators are not obligated to actively seek AEs and SAEs in former study participants. However, if the PI learns of an SAE during the 30 days following the final study visit, the PI must promptly notify the NHLBI.

9.3. Discontinuation of HXTC and/or VOR

Participants who prematurely discontinue the HXTC infusions or VOR should continue to undergo the protocol evaluations as per the Schedule of Events.

The End of Study Intervention visit (Study Visit 23) will be also conducted any time a participant discontinues early from the study after receiving combination therapy with VOR and HXTCs in Steps 4 and 5 or upon the successful completion of the study interventions. If HXTC or VOR has been administered, the investigator must make every effort to perform the evaluations four weeks after the participant's last dose but not more than 8 weeks in cases where the participant does not agree to conduct the remaining scheduled visits. Participants terminating early from the study after receiving combination therapy will be asked to complete the follow-up visit (Study Visit 24) after Visit 23 in Step 6.

9.4. Pregnancy

If the pregnancy test is positive at screening, the potential participant will not be allowed to enroll on the study. No further evaluations are necessary.

If the participant becomes pregnant during the study, then study treatment must be discontinued immediately. The participant may continue in the study in an off treatment/on study status for safety labs only. The participant will be followed until the pregnancy outcome and up to 8 weeks after the delivery.

All participants who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the UNC and CNH IRBs if required per their reporting requirements, the NHLBI, the FDA (US Food and Drug Administration), and Merck Research Laboratories.

If a partner to a male study participant becomes pregnant, while male participant is actively on study, the pregnancy must be reported. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the UNC and CNH IRBs if required per their reporting requirements, NHLBI, FDA, and Merck without delay and within 24 hours if the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a participant or participant's partner (spontaneously reported to them) that occurs during the study or within 12 weeks of completing the study.

We will obtain a medical release or separate consent granting permission to follow the health of both the pregnant participant and her unborn child. We will conduct a post-delivery interview and complete a case report form (CRF) to collect the data related to the pregnancy outcome.

The Sponsor of this study is the University of North Carolina at Chapel Hill. The principal investigator (Dr. David Margolis) at UNC-CH will be responsible for reporting to all regulatory agencies and funding sources listed above.

10. STATISTICAL CONSIDERATIONS

10.1. General Design

This is a phase I, single-site study to evaluate the effects of VOR and HXTC therapy on persistent HIV-1 Infection in HIV-infected individuals suppressed on ART. Twelve participants with durable viral suppression will be enrolled and will complete the study. All participants will receive the same treatment and if eligible, will be dosed with VOR and receive HXTC infusions. Participants will continue their baseline ART regimen throughout the study.

If the baseline IUPM ≥ 0.3, participants will have a blood sample sent to CNH for production of HXTCs. Upon release of HXTC, participants will be clinically assessed to complete the two treatment series with oral VOR 400 mg doses combined with HXTC infusions over a 3 month period. VOR will be administered every 72 hours and each treatment series will consist of 10 doses of VOR 400 mg.

In Step 4 (Series 1), participants will receive two HXTC infusions along with 10 doses of VOR 400 mg. The HXTC infusions will be administered 6 hours after the 1st and 6th VOR doses.

In Step 5 (Series 2), participants will receive three infusions along with 10 doses of VOR 400 mg. The first two infusions will be administered 6 hours after the 11th and 16th doses of VOR. The 5th and final HXTC infusion will occur 1 – 3 days after the 20th VOR dose.

The 2nd and final leukapheresis will occur at least 4 weeks after the last HXTC infusion.

Resting cell infection frequency will be determined pre VOR-HXTC dosing with the baseline leukapheresis and post VOR-HXTC dosing with 2nd leukapheresis.

Longitudinal follow-up to measure the effectiveness of the intervention will continue for 9 weeks after the last HXTC infusion. Serial blood draws will be obtained pre and post-VOR-HXTC dosing throughout the study to monitor immune response.

10.1.1. **Study Hypothesis**

We hypothesize that HXTCs can be safely combined with VOR, and allow depletion of persistent HIV infection.

10.2. Outcome Measures

10.2.1. **Primary Endpoints**

10.2.1.1. Safety

Occurrence of at least one ≥ Grade 3 adverse event including signs/symptoms, lab toxicities, and/or clinical events that is possibly or definitely related to VOR or HXTC any time from the first day of study treatment through Step 6, Visit 23.

Safety data will include local and systemic signs and symptoms, laboratory measures of safety/toxicity, and all adverse and serious adverse events. Safety data will be routinely collected throughout the duration of the study.

NOTE: The occurrence of a Grade 3 infusion reaction that is sustained for less than 48 hours will not be included as a primary safety endpoint.

10.2.1.2. Change in the frequency of HIV infection per million resting CD4+T cells (RCI) from baseline to post-VOR/HXTC

10.2.2. **Secondary Endpoints**

10.2.2.1. The ability of combination VOR and HXTC therapy to increase HIV-1 specific immune responses in participants maintained on suppressive ART

10.3. Sample Size Considerations

For n=12 participants, if there are no primary adverse events (AEs), then the exact 95% confidence interval (CI) for the true AE rate will be [0.00, 0.26]. Thus, if no AEs are observed, one can confidently rule out event rates greater than 26%. If there is one AE among the 12 participants, then the exact 95% CI will be [0.00, 0.38].

10.4. Safety

Since the trial will be stopped if two participants experience a study treatment-related toxicity of Grade 3 or higher, the criterion for safety of this study is grade 3 or 4 toxicity in no more than 1 of 12 participants. If 0 of 12 participants experience toxicity, we will have 95% confidence that the true toxicity rate is 22% or less and 80% confidence that it is 13% or less, based on 1-sided exact binomial confidence limits. If 1 participant has toxicity, the corresponding 95% and 80% 1-sided upper confidence limits are 34% and 23%, respectively.

Any participant who is not administered the full study treatment through Step 6 will be replaced until the target enrollment of participants is met.

Because a focus of the study is on safety and potential adverse events, accrual will be staggered such that enrollment and treatment administration will include a maximum of 2 participants per week, and never more than 1 on any day.

10.5. Monitoring

Formal review will be performed at yearly intervals during the conduct of this study, and will be reviewed by an independent Safety Monitoring Committee (SMC). This review will be based on assessment of participant safety, and will serve as a basis for allowing enrollment to continue.

Observed proportion with >6 fold change from baseline	Exact 95% confidence interval
6/12=0.50	[0.21, 0.79]
7/12=0.58	[0.28, 0.85]
8/12=0.67	[0.35, 0.90]
9/12=0.75	[0.43, 0.95]
10/12=0.83	[0.52, 0.98]
11/12=0.92	[0.62, 1.00]
12/12=1.00	[0.74, 1.00]

Table 5: Confidence Intervals for Depletion of the Latent Reservoir

The SMC will receive monthly study progress and safety monitoring reports. Study feasibility and the achievement of study milestones will be assessed in these reports. Additionally, accrual, baseline characteristics, conduct of the study (including premature study discontinuations), any interruptions of ART, virologic failures, and all reported toxicities and events will be monitored during the study and sent to and discussed with the protocol team on a regular monthly basis. The study protocol team will review the individual safety data monthly to assess relation of all reported toxicities and AEs to the study treatment. The monthly data will be shared with the SMC for review.

It will be the responsibility of the study protocol team to interpret the toxicity data, make decisions needed to protect participants from undue risk, and determine whether or not participant replacements are needed.

If at any time during the study, two or more participants experience a toxicity that is Grade 3 or higher and definitely, probably, or possibly related to study treatment (as judged by the protocol team), then enrollment into the study will be temporarily suspended and the independent SMC will be asked to review all safety data; review the relation to study treatment of the event(s); and recommend how the study should proceed with respect to resuming enrollment and continuing study treatment.

Site monitors, independently contracted by the UNC HIV Cure Center, per contract with NIH/NHLBI will visit the clinical research site to review participants' records, including consent forms, CRFs, medical records (e.g., physicians' progress notes, nurses' notes, individuals' hospital charts), and laboratory records to ensure protection of study participants, compliance with the EC/IRB approved protocol/amendments, and accuracy and completeness of records. The monitors will inspect sites' regulatory files to ensure that local regulatory requirements, in addition to U.S. Federal regulations, are being followed. They will also inspect sites' pharmacies to review product storage and management.

10.6. Efficacy

Due to the small size of this pilot, proof-of-concept trial, interim analyses for efficacy would not be appropriate.

We will recruit and screen up to 48 participants to obtain 12 participants with evaluable data to study and compare pre-VOR/HXTC and post-VOR/HXTC frequency of HIV infection per million resting $CD4^+$T cells, and will analyze using a non-parametric 2-sided sign test to determine whether or not a significant decrease of IUPM is observed, as below in section 10.7.

10.7. Analysis

10.7.1. Primary Analysis

For the safety endpoint, we will record and describe all study treatment-related adverse events through the end of study.

Ultimately, we aim to detect a significant depletion of the latent reservoir, by measuring the frequency of resting cell infection using the QVOA. We will analyze pre-VOR/HXTC and post-VOR/HXTC frequency of HIV infection per million resting CD4+T cells using a non-parametric 2-sided sign test (and the Wilcoxon signed rank test if no assay censoring) to determine whether or not a significant decrease of IUPM is observed. With 12 participants there is 80% power to reject H0 (change expected with ART alone) in favor of HA (greater change than expected with ART) if

the true probability of observing a decrease in IUPM in a participant after VOR/HXTC is 0.93.

In addition to summarizing the number and proportion of participants who show decrease in IUPM after VOR/HXTC, we will describe the magnitude of the changes in decrease in IUPM after VOR/HXTC via the median fold-change and corresponding 95% confidence interval. We will also summarize the proportion of participants with >6-fold decreases; this magnitude change is rarely seen in participants on stable ART [64]. We will therefore consider a >6 fold change from baseline to post VOR-HXTC treatment as significant on an individual participant basis. For n=12 participants, precision calculations are analogous to those for safety endpoints. In particular, if all 12 participants have a >6 fold change from baseline, then the exact 95% confidence interval (CI) for the probability of significant depletion of the latent reservoir would be [0.74, 1.00], i.e., one could confidently rule out depletion probabilities less than 74%. If 11 of 12 participants achieve significant depletion, the 95% CI would be [0.62, 1.00]. Other possible observed proportions and 95% CIs are given in Table 5.

For the first 6 participants who had HIV RNA expression per million resting CD4+T cells measured after VOR exposure (ex vivo exposure to VOR in the screening step; in vivo exposure to first VOR dose), as a gateway to advance through the study protocol, we will assess within-participant RNA changes. We will analyze using the non-parametric 2-sided Wilcoxon rank sum test to determine whether or not a significant increase of RNA expression is observed in these participants comparing RNA levels measured in each of 24-36 replicate pools of 1 million resting CD4+ cells. Pools with undetectable RNA will be considered as 0 copies and analyzed as the lowest rank in this rank-based statistical test.

For the first 6 participants, the pre-VOR RNA expression will be determined as the median RNA copies over the individual pools of one million participant cells tested prior to VOR (setting undetectable RNA pools as 0 copies), and the post-VOR RNA expression level will be similarly determined. Changes in RNA expression will be evaluated by the sign test and the proportion of participants with increases versus decreases. Summaries of the magnitude of changes will be examined in terms of median fold-changes.

10.7.2. **Secondary Analysis**

The virologic analysis will include comparison of the SCA levels pre-treatment (screening and entry) compared to post-treatment in Steps 5 and 6. We assume that the probability would be 0.10 (10%) for a baseline (pre-entry, entry) detectable SCA ≥ 1 copy and the probability would be at least 0.29 (29%) for a post-treatment measure for analyses. The assumption that 10% of participants with a quantifiable SCA at screening will have SCA below the limit of detection at a pre-treatment

measure is an estimate based on data from A5244 in which 6 of 50 (12%) enrolled participants had undetectable SCA at pre-entry and 5 of 51 (10%) at entry after having a screening SCA ≥ 1 copy [65].

For additional secondary endpoints, most endpoints are defined as change in a quantitative measure from baseline to post-infusion (e.g., change from baseline to week 13 in HIV-1 RNA by SCA). Assuming two-sided 0.05 significance, 5000 empirical simulations from a normal distribution with mean change equal to 1 standard deviation with n=12 evaluable participants achieved 85% power to detect a statistically significant change from baseline to post-infusion using an exact Wilcoxon signed-rank test (paired data). Thus, with n=12 there is reasonable power to detect a mean change of 1 standard deviation (SD) or larger. Observed virologic measurements may not be normally distributed or may be partially censored due to assay limits of quantification, and thus, an exact Wilcoxon signed-rank test will be used. Potential immune correlates of antiviral impact will be assessed via exact, non-parametric Spearman rank correlation based methods.

Descriptive statistics and graphical data displays will be used to summarize in vivo measurements of HIV-specific T-cells over the pre- to post-infusion period to assess the pattern and magnitudes of T-cell expansion and persistence for each virus. Measurements of immunity will be evaluated by descriptive statistics at each time point and analyzed by exact, nonparametric methods for paired data to compare changes from pre- to post-infusion. HIV-1 specific immune responses using standard immunoassays and measures of HIV-1 persistence will be analyzed similarly.

11. ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1. Ethical Standard

The principal investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

11.2. Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

11.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The principal investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates and/or family/friends and think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical and research record.

11.4. Amendments

Upon receiving final IRB/EC and any other applicable regulatory approval(s) for any amendment after Version 1.0, UNC should implement the amendment immediately. UNC is required to submit amendments to NHLBI. A copy of the final amendment approvals and documents issued by the NHLBI should be retained in the site's regulatory files.

11.5. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB(s), the FDA, the NHLBI, or the industry supporters or designee.

11.6. Study Discontinuation

The study may be discontinued at any time by the UNC-CH IRB, the NHLBI, the industry supporters, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. DATA COLLECTION, MONITORING, AND ADVERSE EVENT REPORTING

12.1. Records to be kept

Source documents will be provided for each participant. Participants will be identified by name in the source documents but will not be identified by name in the database or on any report associated with the study. Participants will be identified by the participant identification number (PID) and study identification number (SID) provided by the study database upon screening.

12.2. Role of the Data Manager

It is the responsibility of the study site to assure the quality of data for this study. This role extends from protocol development to generation of the final study databases.

12.3. Clinical Site Monitoring and Record Availability

12.3.1. **Clinical Site Monitors**

Site monitors will visit the site to review the individual participant records, including consent forms, source documents, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

12.3.2. **Site Investigators**

The site principal investigator will make study documents (e.g., consent forms, drug distribution forms, and source documents) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NHLBI, and the industry supporters or designee for confirmation of the study data.

12.3.3. **Adverse Events Reporting to NHLBI**

All human participant research supported by NHLBI must include procedures for identifying, monitoring, and reporting all AEs, including both serious (SAE) and non-serious events, and UPs. All NHLBI human participant research will follow a uniform policy, which is based on the FDA/Office for Human Research Protections (OHRP) regulations and guidance including definitions and timelines.

The study site will reference the IRB-approved Study Progress and Safety Monitoring Plan (SPSMP) and report all SAE, AE, and UP Events per reporting timelines outlined in this document.

12.4. Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used in this study. This SAE Reporting Category is redefined in the DSMP.

The study products, for which expedited reporting is required, are: HIV Expanded T-Cells (HXTC) and VOR.

12.5. Expedited AE Reporting Period

The expedited AE reporting period for this protocol is the entire study duration for an individual participant, once treatment is initiated (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to NHLBI, FDA, or UNC IRB per their reporting requirements if the study staff become aware of the events on a passive basis (from publicly available information).

13. PUBLICATION/DATA SHARING POLICY

Publication of the results of this trial will be governed by NHLBI (NIH) policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporters prior to submission.

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Appendix A: Schedule of Events (SOE)

	Step 1 Pre-Treatment			**~~Step 2~~**	**Step 3 HXTC Production**	
Evaluations	**Screen**	**Enrollment**	**Leukapheresis (#1)**	**Step 2 Eliminated**	**Cell Collection for HXTC**	**Pre-Treatment Screen**
Visit Window		**≤30 days**	**≤45 days**		**4-6 weeks after leukapheresis**	**4- 10 weeks after Visit 5**
			at or after enrollment			≤21 days before visit 6
Study Week						
Study Visit	**1**	**2**	**2.1**	**~~3~~ 4**	**5**	**6**
Clinical Procedures						
Consent, Eligibility, Demographics & Medical History	X			Step 2 Eliminated		
Assignment of PID	X					
Assignment of SID		X			X[1]	
Complete Physical Examination (vital signs & weight)	X					
Height^	X					
Assess venous access	X					
Advancement Criteria			X			
Pre-Dose Clinical Assessment						X
Targeted Clinical Assessment[2]					X	X
Review medical history (including new medical conditions)		X			X	X
Assess Adverse Event	X		X		X	X
Review ART & ART Adherence	X	X	X		X	X
Review Concomitant Medication	X	X	X		X	X
Phone Assessment						
Vorinostat Administration (400 mg) (home)						
CTL Infusion						
CTL Pre-medication						
Post infusion assessment						
Leukapheresis (& meal)			X			
Clinical Laboratory Procedures						
Chemistries	X◊			Step 2 Eliminated		X[3]
Coagulations (PT/INR/PTT)	X					
CBC with differential	X		X∞			X
Pregnancy Test or FSH Test	X					X
CD4+ T Cell Differential Panel	X					X
HIV-1 RNA PCR	X					X
HBsAg & HCV Ab	X					X
Donor ID Panel [4]					X	
RPR	X					X
Urine Pregnancy – POCT[5]						
Urinalysis	X					
Research Laboratory Procedures [4]						
Single Copy Assay			X	Step 2 Eliminated		X
PBMC for HDAC Responsive Gene Measurement		X[6]			X	
Single PK sample (VOR)						
Cells for CTL production					X	
HLA typing					X	
Immune Response, Viral Inhibition & Epitope Mapping		X[10]	X[L]		X	X[10]
Resting Cell Assay and CTL Latency						

	Step 4: Second Series of VOR 400 mg x 10 doses at 72 hours and 2 HXTC infusions												
Evaluations	**VOR Dose #1 and HXTC infusion #1**	**Safety check and research labs**	**VOR Dose #2**	**VOR Dose #3**	**VOR Dose #4**	**VOR Dose #5**	**VOR Dose #6 and HXTC Infusion #2**	**Safety check and research labs**	**VOR Dose #7**	**VOR Dose #8**	**VOR Dose #9**	**VOR Dose #10**	**Clinical Assessment – Pre-Step 5**
Visit Windows - reference table in section 7.3.3													
Study Week	**0**			**1**		**2**			**3**		**4**		**6**
Study Visit	**7**	**8**		**9**			**10**	**11**				**12**	**13**
Clinical Procedures													
Consent, Eligibility, Demographics & Medical History													
Assignment of PID													
Assignment of SID													
Complete Physical Examination (vital signs & weight)													X
Height													
Assess venous access													
Advancement Criteria													
Pre-Dose Clinical Assessment													X
Targeted Clinical Assessment[2]	X	X		X			X	X				X	
Review medical history (including new medical conditions)	X	X		X			X	X				X	X
Assess Adverse Event	X	X		X			X	X				X	X
Review ART & ART Adherence	X	X		X			X	X				X	X
Review Concomitant Medication	X	X		X			X	X				X	X
Phone Assessment	(T)		(T)	(T)	(T)	(T)	(T)		(T)	(T)	(T)	(T)	
Vorinostat Administration (400 mg) (home)	X		X	X	X	X	X		X	X	X	X	
CTL Infusion	X						X						
CTL Pre-medication	X						X						
Post infusion assessment	X	X					X	X					
Leukapheresis (& meal)													
Clinical Laboratory Procedures													
Chemistries		X[3]		X[3]			X[3,7 8]					X[3]	X[3]
Coagulations (PT/INR/PTT)													
CBC with differential		X		X			X[7,8]					X	X
Pregnancy Test or FSH Test													X
CD4+ T Cell Differential Panel													X
HIV-1 RNA PCR													X
HBsAg & HCV Ab													
Donor ID Panel [4]													
RPR													X
Urine Pregnancy – POCT[5]	X[7,8]						X[7,8]						
Urinalysis													
Research Laboratory Procedures [4]													
Single Copy Assay	X	X											
PBMC for HDAC Responsive Gene Measurement	X[6]	X					X[6]	X				X	X
Single PK sample (VOR)	X												
Cells for CTL production													
HLA typing													
Immune Response & Epitope Mapping		X											
Resting Cell Assay and CTL latency													

	Step 5: Second Series of VOR 400 mg x 10 doses at 72 hours and 3 HXTC infusions													
Evaluations	**VOR Dose #11 and HXTC infusion #1**	**Safety check research labs**	**VOR Dose #12**	**VOR Dose #13**	**VOR Dose #14**	**VOR Dose #15**	**VOR Dose #16 and HXTC Infusion #2**	**Safety check and research labs**	**VOR Dose #17**	**VOR Dose #18**	**VOR Dose #19**	**VOR Dose #20**	**HXTC Infusion #5**	**Safety check and research labs**
Visit Window - reference table in section 7.3.4.														
Study Week	**8**			**9**			**10**			**11**			**12**	
Study Visit	**14**	**15**					**16**	**17**				**18**	**19**	**20**
Clinical Procedures														
Consent, Eligibility, Demographics & Medical History														
Assignment of PID														
Assignment of SID														
Complete Physical Examination (vital signs & weight)														
Height														
Assess venous access														
Advancement Criteria														
Pre-Dose Clinical Assessment														
Targeted Clinical Assessment[2]	X	X					X	X				X	X	X
Review medical history (including new medical conditions)	X	X					X	X				X	X	X
Assess Adverse Event	X	X					X	X				X	X	X
Review ART & ART Adherence	X	X					X	X				X	X	X
Review Concomitant Medication	X	X					X	X				X	X	X
Phone Assessment	(T)		(T)	(T)	(T)	(T)	(T)		(T)	(T)	(T)	(T)	(T)	
Vorinostat Administration (400 mg) (home)	X		X	X	X	X	X		X	X	X	X		
CTL Infusion	X						X						X	
CTL Pre-medication	X						X						X	
Post infusion assessment	X	X					X						X	
Leukapheresis (& meal)														
Clinical Laboratory Procedures														
Chemistries		X[3]					X[3,7,8]					X[3]		
Coagulations (PT/INR/PTT)														
CBC with differential		X					X[7,8]					X		
Pregnancy Test or FSH Test														
CD4+ T Cell Differential Panel														
HIV-1 RNA PCR														
HBsAg & HCV Ab														
Donor ID Panel [4]														
RPR														
Urine Pregnancy – POCT[5]	X[7,8]						X[7,8]						X[7,8]	
Urinalysis														
Research Laboratory Procedures [4]														
Single Copy Assay		X												
PBMC - HDAC Responsive Gene Measurement	X	X					X[6]	X				X	X	X
Single PK sample (VOR)							X							
Cells for CTL production														
HLA typing														
Immune Response, Viral Inhibition & Epitope Mapping														
Resting Cell Assay and CTL latency														

	Step 6; Immune Monitoring					
Evaluations	**IM Visit #1**	**IM Visit #2 Eliminated**	**IM Visit #3 & Leukapheresis #2**	**IM Visit #4**	**IM Visit #5 Eliminated**	**IM Visit #6 Eliminated**
Time to Visit	**~ 7 days after Visit 19**		**~ 4 weeks after Visit 19**	**~ 9 weeks after Visit 19**		
Visit Windows	**3 days (+/-)**		**1 week (+/-)**	**1 weeks (+/-)**		
Study Week	**13**		**16**	**21**		
Study Visit	**21**	**22**	**23**	**24**	**25**	**26**
Clinical Procedures						
Consent, Eligibility, Demographics & Medical History		**Visit Eliminated**			**Visit Eliminated**	**Visit Eliminated**
Assignment of PID						
Assignment of SID						
Complete Physical Examination (vital signs & weight)			X			
Height						
Assess venous access						
Advancement Criteria						
Pre-Dose Clinical Assessment						
Targeted Clinical Assessment[2]	X			X		
Review medical history (including new medical conditions)	X		X	X		
Assess Adverse Event	X		X	X		
Review ART & ART Adherence	X		X	X		
Review Concomitant Medication	X		X	X		
Phone Assessment						
Vorinostat Administration (400 mg) (clinic)						
CTL Infusion						
CTL Pre-medication						
Post infusion assessment						
Leukapheresis (& meal)			X			
Clinical Laboratory Procedures						
Chemistries	X[3]	**Visit Eliminated**	X[◊]		**Visit Eliminated**	**Visit Eliminated**
Coagulations (PT/INR/PTT)						
CBC with differential	X		X∞	X		
Pregnancy Test or FSH Test						
CD4+ T Cell Differential Panel	X		X	X		
HIV-1 RNA PCR	X		X	X		
HBsAg & HCV Ab						
Donor ID Panel [4]						
RPR						
Urine Pregnancy – POCT[5]						
Urinalysis			X			
Research Laboratory Procedures [4]						
Single Copy Assay	X	**Visit Eliminated**	X		**Visit Eliminated**	**Visit Eliminated**
PBMC for HDAC Responsive Gene Measurement						
Single PK sample (VOR)						
Cells for CTL production						
HLA typing						
Immune Response, Viral Inhibition & Epitope Mapping						
Resting Cell Assay and CTL Latency			X[L]	X		

Legend

[1] CNH product ID will be assigned at this time.

^ Height will be obtained at screening in the CTRC – without shoes.

[2] Targeted clinical assessments are driven by signs and/or symptoms experienced since the last visit or unresolved signs or symptoms experienced previously and included weight and vital signs (temperature, blood pressure, pulse and respirations).

◊ Clinical labs for screening only include sodium (Na), potassium (K), chloride (Cl), bicarbonate (CO_2), glucose, blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk Phos), total bilirubin (total bili). A direct bilirubin will be obtained if participant is on atazanavir. Lipase, albumin, total protein, triglyceride and cholesterol are obtained at screening and Visit 23 only.

[3] Clinical safety laboratory tests: Na, K, Cl, CO_2, Cr, glucose, LT, AST, alk phos, total bili, Ca and Mg.

[4] Reference Study Specific Lab Manual for collection and processing requirements for research samples.

∞ CBC is required for Apheresis procedures. Labs for UNC can be obtained up to 24 hours prior to visit or STAT on the day of the procedure. The CBC for the American Red Cross or other local blood collection agency will be drawn per facility requirement up to 30 days prior to the collection.

[5] POCT pregnancy testing will be done on all women prior to initiation of VOR and at all HXTC infusions.

[6] Draw 25.5 mL (3 – 8.5 mL ACD tubes) at these selected time points.

[L] Samples come from the leukapheresis product and are sent to Margolis Lab at UNC ambient for processing.

(T) Participants will be contacted via agreed upon communication mechanism to assess for adverse events.

[7] Labs may be obtained up to 48 hours prior to visit.

[8] Draw labs STAT, if done on day of visit. Results must be obtained and reviewed prior to procedure or infusion.

[10] If enrollment occurs on the day of the baseline leukapheresis, draw these samples on Visits 5 and 6, as indicated on the SOE.