An Exploratory Study of Combination Therapy with VRC-HIVMAB060-00-AB (VRC01) and 10-1074 in HIV-Infected Individuals Undergoing Sequential Treatment Interruptions

Protocol Short Title: ATIX2

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LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
AR	adverse reaction
ART	combination antiretroviral therapy
AST	aspartate aminotransferase
ATI	analytical treatment interruption
bNAb	broadly neutralizing monoclonal antibody
CC	Clinical Center
CFR	Code of Federal Regulations
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HLA	human leukocyte antigen
hu-mice	humanized mice
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IRB	institutional review board
IV	intravenous
mAb	monoclonal antibody
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cell(s)
PI	principal investigator
RNA	ribonucleic acid
SAE	serious adverse event/serious adverse experience
SAR	suspected adverse reaction
SC	subcutaneous
SHIV	simian human immunodeficiency virus
SRCP	Safety Review and Communications Plan
SUSAR	serious and unexpected suspected adverse reaction
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event

PROTOCOL SUMMARY

Full Title:	**An Exploratory Study of Combination Therapy with VRC-HIVMAB060-00-AB (VRC01) and 10-1074 in HIV-Infected Individuals Undergoing Sequential Treatment Interruptions**
Short Title:	ATIX2
Clinical Phase:	1
IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations
Conducted by:	National Institute of Allergy and Infectious Diseases Laboratory of Immunoregulation
Principal Investigator:	Michael C. Sneller, MD
Sample Size:	N= 50
Accrual Ceiling:	75
Study Population:	HIV-infected adults 18-65 years of age
Accrual Period:	24 months
Study Design:	An exploratory, randomized, double-blinded, placebo-controlled trial of VRC01 plus 10-1074 vs Placebo in subjects with HIV infection
Study Duration:	4 years (March 2019 to March 2023)
Study Agent/ Intervention Description:	10-1074 (30 mg/kg) and VRC01 (40 mg/kg) or Saline Placebo
Primary Objective:	To evaluate the virologic effect of a single administration of VRC01 plus 10-1074 on rebound plasma viremia in subjects undergoing sequential antiretroviral treatment interruptions.
Secondary Objective:	To evaluate the safety of a single dose VRC01 plus 10-1074 in HIV infected individuals
Exploratory Objectives:	To investigate whether a single dose of VRC01 and 10-1074 allows the development of anti-HIV immunity (i.e., cytotoxic T lymphocyte or other immune responses) following the first and second round of analytical treatment interruption (ATI)

To determine changes in markers of immune activation and exhaustion in B and $CD4^+$ and $CD8^+$ T cells

To determine changes in the size of HIV reservoirs following the first and second round of ATI

Endpoints:

Primary: The time to meet criteria for restarting antiretroviral therapy (ART) following the second ATI.

Secondary: The rate of occurrence of grade 3 or higher adverse events (AEs), including serious adverse events (SAEs), that, per standard criteria (see safety Section 12.3.1) are probably or definitely related to the test articles VRC01 and 10-1074.

PRÉCIS

Recent advances in antibody cloning technologies have led to the development of a number of highly potent and human immunodeficiency virus (HIV)-specific broadly neutralizing monoclonal antibodies (bNAbs) from B cells of HIV-infected individuals. It has been shown that certain bNAbs can prevent acquisition of the virus, suppress viral replication, delay and/or prevent plasma viral rebound following treatment interruption in simian/human immunodeficiency virus (SHIV)-infected animals. Preliminary data from clinical trials indicates that bNAbs may delay plasma viral rebound following interruption of antiretroviral therapy (ART) and block cell-to-cell transmission of laboratory-adapted HIV *in vitro*.

In the above studies, suppression of plasma viremia was dependent on maintaining neutralizing serum levels of bNAbs via repeated intravenous (IV) infusions. A recent pre-clinical study in an acute SHIV-macaque model suggests a limited course of passive immunotherapy with two bNAbs (10-1074 and 3BNC117) given shortly after infection, can result in prolonged suppression of plasma viremia that is not dependent on the continuous presence of the bNAbs[18]. Based on $CD8^+$ T cell depletion studies, it appears that the prolonged suppression of plasma viremia observed in these animals resulted from the induction of potent antiviral $CD8^+$ T cell immunity by the short course bNAb treatment. The mechanism by which bNAb therapy could induce such a response is unclear but could involve the early formation of unique bNAb-SHIV immune complexes that subsequently induce an effective and durable T cell response to the virus.

In light of these encouraging preclinical outcomes, it is of considerable interest to investigate whether treatment with a single infusion of two bNAbs (VRC01 and 10-1074) which target different epitopes of HIV gp120 (CD4 binding site and V3 glycan, respectively), during transient plasma viremia can induce long-lasting anti-HIV immunity capable of controlling plasma viremia in the absence of ART.

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Prolonged suppression of plasma viremia is now achievable in the majority of human immunodeficiency (HIV)-infected individuals receiving combination antiretroviral therapy (cART). Consequently, antiretroviral therapy (ART) has dramatically improved the clinical outcome of infected individuals. However, complete eradication of HIV has not been possible using ART alone; and plasma viremia rapidly rebounds in virtually all chronically HIV-infected individuals upon cessation of therapy[1]. Multiple studies have demonstrated that HIV persists in latently infected, resting $CD4^+$ T cells of infected individuals receiving clinically effective doses of ART[2-4]. Persistence of the HIV reservoirs carrying replication-competent virus despite suppression of plasma viremia with ART is considered to be the major obstacle to the eradication of the virus.

Despite the success of ART in suppressing HIV replication and plasma viremia, the burden of taking daily medication for life, long-term toxicity of ART, and the potential for developing resistance to antiretroviral drugs necessitates a continued search for effective alternatives for achieving durable control of HIV replication in infected individuals. Consequently, a major thrust of HIV research over the past decade has been to develop therapeutic strategies that can control HIV replication in the absence of ART. One such strategy is to provide passive immunization via neutralizing monoclonal antibodies (mAbs) against HIV.

Research directed at potential pathways towards the development of an effective HIV vaccine has provided insights into the nature of the immune response to HIV infection[5,6]. Recent advances in antibody cloning technologies and B cell biology have led to the development of several highly potent and broadly neutralizing mAbs (bNAbs) against HIV from B cells of select HIV-infected individuals. These bNAbs effectively neutralize infectivity of the majority of existing HIV-1 isolates *in vitro*[7-9].

Pre-clinical studies in Rhesus macaques have demonstrated that monotherapy with bNAbs can induce transient suppression of plasma viremia with subsequent rebound due to declining serum levels of the administered bNAbs and the emergence of antibody-resistant viral isolates[10]. Administration of combinations of bNAbs targeting non-overlapping epitopes of HIV gp120 can provide prolonged control of active infection in humanized mice (hu-mice) and primate models[10-12] by delaying the development of bNAb resistant virus. Several effector mechanisms are potentially involved in direct suppression of HIV/ simian/human immunodeficiency virus (SHIV) viremia by bNAbs including accelerated clearance of free virons[13] and enhanced clearance of infected cells[14,15].

Phase 1 clinical trials in HIV infection suggest that administration of bNAbs can delay the time to plasma viral rebound following interruption of ART compared to historical controls[16,17].

In the above pre-clinical studies, suppression of plasma viremia was dependent on maintaining neutralizing serum levels of these antibodies via intravenous (IV) infusion of bNAbs. A recent pre-clinical study in an acute SHIV-macaque model suggests a limited course of passive immunotherapy with two bNAbs (10-1074 and 3BNC117) given shortly after infection, can result in prolonged suppression of plasma viremia that is not dependent on the continuous presence of the bNAbs. In this study, animals were infected with $SHIV_{AD8EO}$. Three days after infection (prior to antibody seroconversion), the animals were randomized to receive either a 2-week

course of 10-1074 and 3BNC117 or standard ART[18]. At 15 weeks post-infection, the ART group stopped drugs. Six of the 13 animals treated with 10-1074 and 3BNC117 exhibited prolonged suppression of viremia long after serum levels of infused antibodies became undetectable. In contrast, none of the 3 ART-treated control animals exhibited sustained suppression of plasma viremia following discontinuation of ART. Infusion of a T-cell-depleting anti-CD8β mAb to the 6 controller animals led to depletion of $CD8^+$ T cells and the rapid reappearance of plasma viremia. These findings suggest that the prolonged suppression of viremia observed in these animals resulted from the induction of potent antiviral $CD8^+$ T cell immunity by the short course bNAb treatment. The mechanism by which bNAb therapy could induce such a response is unclear but could involve the early formation of bNAb-SHIV immune complexes. These complexes could subsequently bind to antigen-presenting dendritic cells expressing activating Fc receptors, leading to their activation and antigen presentation to CD4+ and $CD8^+$ T cells that in turn results in generation of effective cell-mediated virologic control[19,20].

The objective of this study is to investigate whether treatment with a single infusion of two bNAbs that target different epitopes of HIV gp120, during transient viremia can induce long-lasting anti-HIV immunity capable of controlling plasma viremia in the absence of ART.

1.1.1 Description of the Study Agents

VRC-HIVMAB060-00-AB (VRC01), was produced under Current Good Manufacturing Practice (CGMP) by Leidos Biomedical Research, Inc., Frederick, MD, under contract to the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID). Specific manufacturing information is included on the product vial labels and Certificates of Analysis and can be found in the Investigator's Brochure (IB).

VRC01 is a broadly neutralizing human mAb targeted against the HIV-1 CD4 binding site. It was developed by VRC/NIAID/National Institutes of Health (NIH). VRC01 is an IgG1 and is highly somatically mutated from the germ-line precursor. The heavy chain CDR3 region is 14 amino acids long, which is an average length relative to natural antibodies, and the glycosylation pattern is derived from its production in a Chinese hamster ovary (CHO) mammalian cell line.

The study agent was produced using recombinant deoxyribonucleic acid (DNA) technology. The mammalian Glutamine Synthetase Gene Expression System in the Chinese hamster ovary (CHO) cell line developed by Lonza Biologics (Slough, UK) was used to produce the VRC01 drug substance.

The bulk lot of the drug substance was manufactured under CGMP using a stably transfected CHO cell line, purified, and the drug product vials were filled and labeled at the VRC, Vaccine Pilot Plant (Frederick, MD) operated by Leidos Biomedical Research, Inc., Frederick, MD.

Additional details on the VRC-HIVMAB060-00-AB composition and manufacturing can be found in the IB.

10-1074 is a recombinant, fully human mAb of the IgG1λ isotype that specifically binds to the base of the V3 loop within HIV-1 envelope gp120. 10-1074 was isolated from an HIV-infected individual with high titer serum neutralization activity. The mAb was generated by cloning the heavy and light chain variable regions isolated from a single memory B cell. 10-1074 was isolated at the Rockefeller University, cloned and expressed in CHO cells (clone 3G4), and purified using standard methods.

10-1074 Drug Product, manufactured under CGMP by MassBio, is formulated as a sterile solution intended for single-use parenteral administration. Single-use vials contain 10 or 30 mL of 10-1074 at a 20 mg/mL concentration.

Additional details regarding the composition and manufacturing of 10-1074 can be found in the IB.

1.1.2 Summary of Pre-Clinical Studies

VRC01

A single dose pharmacokinetics (PK) study was performed by SRI International (Menlo Park, CA) with VRC01 in male and female Sprague-Dawley rats in accordance with US Food and Drug Administration (FDA) “Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.” This study was conducted with a pre-CGMP pilot lot of VRC01 manufactured at smaller scale using a purification process similar to that of the CGMP clinical-grade drug product.

For the safety assessment, vehicle, 4 mg/kg VRC01, 40 mg/kg VRC01, or 400 mg/kg VRC01 was administered by tail vein injection on Days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via subcutaneous (SC) administration to the dorsal scapular region on Days 1 and 8. Each group contained 10 male and 10 female rats. Five animals per sex were sacrificed on Day 9, one day after the second administration, and the remaining animals were sacrificed on Day 30, 22 days after the second administration.

Results obtained showed that both routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, injection site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate aminotransferase (AST) and alkaline phosphatase (ALP) on Day 9. By Day 30, AST values had returned to normal, and ALP values were returning to normal.

Other than red discoloration of the administration site in one male in the SC group on Day 9, there were no other gross necropsy observations attributable to VRC01 administration. There were no histopathology findings that were considered related to IV administration of VRC01. However, histopathology evaluation revealed subacute inflammation at the SC injection site on Day 9, one day after injection, in all 10 SC administered rats; dermal inflammation was usually minimal or mild while SC inflammation was usually mild, moderate, or marked. By Day 30, this inflammation had completely resolved, and the SC dose site was normal in all rats.

A “no observed effect level” (NOEL) was not determined in this study because transient elevations of AST and ALP were observed on Day 9 after IV administration and transient inflammation at the dose site was observed on Day 9 after SC administration. Because the elevated AST and ALP levels were transient and minor and did not correlate with histopathology findings, the “no observed adverse effect level” (NOAEL) for VRC01 by the IV route of administration in rats was 400 mg/kg, the highest dose used in this study. The systemic NOAEL for the SC route of administration of VRC01 in rats was 40 mg/kg, the only SC dose level examined in this study.

Nonhuman Primate Studies of VRC01

Several non-GLP studies of VRC01 have been completed in non-human primates (NHPs) as pre-clinical proof-of-concept studies for prevention or treatment of HIV infection. Table 1 is a brief summary of the studies performed and supports the plan to evaluate up to 40 mg/kg dose administered IV as a dose range of potential interest. Refer to the IB for additional information about these studies.

Table 1: Pre-clinical proof of concept studies performed with VRC01 in NHP

Study Purpose	Study Outcome
Demonstration of plasma and secretion concentrations of VRC01 given by IV or SC routes in female rhesus macaques	Kinetics of decay of 40 mg/kg of VRC01 given IV or SC in plasma, rectal, vaginal and nasal secretions established
Demonstration of challenge-protection against intrarectal high-dose SHIV SF162P3 in male rhesus macaques	100% protection from challenge demonstrated at 20 mg/kg dose administered IV
Demonstration of challenge-protection against intravaginal high-dose SHIV SF162P3 in female rhesus macaques	100% protection from challenge demonstrated at 20 mg/kg dose administered IV
Demonstration of challenge-protection against intrarectal high-dose SHIV-BaL in male rhesus macaques	100% protection from challenge demonstrated at 20, 5 and 1.25 mg/kg dose administered IV
Demonstration of effect of VRC01 during the acute and chronic phases of SHIV infection in rhesus macaques	VRC01 (40 mg/kg IV) during acute infection led to a reduction in peak viremia and during chronic infection led to control of viremia

10-1074

A GLP-compliant tissue cross-reactivity study, performed on a full panel of tissues from humans and rats, showed concordance of binding, with some exceptions, between the two species. While 10-1074 showed cytoplasmic binding in some tissues (mononuclear leukocytes, liver, pituitary, placenta, and optic nerve), it is generally understood that cytoplasmic binding is considered of little to no toxicologic significance. The antibody 10-1074 was evaluated for safety in a GLP-compliant multidose study in rats. The test article 10-1074 was well tolerated when administered by the intravenous (IV) or subcutaneous (SC) routes, with the majority of findings likely associated with the immune response to the human protein in the rat, or injection site inflammation. It was concluded that the no-observed-adverse-effect-level (NOAEL) was the high dose level (60 mg/kg/injection, twice weekly, for 4 weeks) for all routes of administration (10-1074 IB, v3.0 Aug. 2017).

Summary of antiviral activity of 10-1074 in animal models

Administration of 10-1074 showed *in vivo* antiretroviral activity during chronic HIV-1 or SHIV infection. 10-1074 effectively reduced SHIV plasma viral levels, when administered alone or in combination with 3BNC117, another anti-HIV-1 broadly neutralizing antibody.

When administered alone, 10-1074 transiently reduced HIV-1 plasma viremia in hu-mice, which

was followed by viral rebound and selection of 10-1074-escape mutants. In non-human primates chronically infected with simian/human immunodeficiency virus AD8 (SHIVAD8), two animals administered 10-1074 alone experienced rapid declines of plasma viremia at Day 10 following treatment. Virus rebound became detectable on Day 20 in these two macaques. Sequence analysis revealed that rebounding virus present in both of the 10-1074-treated animals had eliminated the gp120 N332 glycan, rendering the virus resistant to this antibody.

In both hu-mice and non-human primates, 10-1074 led to prolonged suppression of plasma viremia when administered in combination with other broadly neutralizing antibodies. Suppression was maintained as long as mAb plasma levels were above a threshold of 1-5 µg/mL[10,21].

For additional details of pre-clinical animal studies, see Section 4.2.7 of the IB.

1.1.3 Summary of Relevant Clinical Studies

1.1.3.1 VRC01 Clinical Studies

Overall, as of January 10, 2017, VRC01 administrations in the dose range from 1 to 40 mg/kg IV and 5 to 40 mg/kg SC have been assessed as well-tolerated in adults and infants and safe for further evaluation. Cumulatively, across all studies, VRC01 has been administered either IV or SC to over 840 HIV-uninfected and HIV-infected adults and 33 HIV-uninfected infants. There has been no serious adverse event (SAE) related to VRC01 that required expedited reporting to the FDA or other regulatory authorities and no study safety pauses for adverse events (AEs). A detailed safety summary can be found in the IB.

In Phase 2 trials, most subjects had no local or systemic reactogenicity symptoms. When present, local and systemic reactogenicity symptoms were of mild or moderate severity. Infusion site pain and/or tenderness developed in 26% of study subjects. Infusion site erythema and/or induration developed in 9% of study subjects. The 3 most common systemic reactogenicity events were malaise (21%), headache (19%), headache followed by nausea (8%) and myalgia (7%).

In Phase 2 trials, there have been 22 related AEs of mild or moderate severity in 15 subjects (2 AEs of change in sleep pattern, 2 AEs of hypogeusia, 5 AEs of urticaria and 1 event each of wheals and erythema-left upper arm/right calf/under right breast, urticaria of upper limbs, urticaria of the face, infusion site pruritus, generalized body itchiness, low neutrophil count, dizziness during infusion, lightheadedness, loose stools, dermatitis, headache, nausea and malaise). There has been one related severe (grade 3) AE of urticaria in 1 subject.
The SC administrations of VRC01 to adults were generally associated with mild local reactions during the infusions that included some pruritus (itchiness), redness and swelling, which resolved within a few minutes to a few hours after the administration was completed. In adults, erythema/induration reactions were reported rarely; the largest diameter for erythema or swelling events that were observed during infusions ranged up to about 9 cm. Grade 1 or 2 erythema and/or induration have been reported frequently following VRC01 SC administration in infants.

1.1.3.2 10-1074 Clinical Studies

10-1074 was evaluated in a Phase 1 study in both HIV-uninfected and HIV-infected individuals (protocol MCA-885). Study subjects were administered one IV infusion of 10-1074 at increasing dose levels (3 mg/kg, 10 mg/kg or 30 mg/kg) and were followed for 24 weeks after infusion.

A total of 33 study subjects enrolled in the study (14 HIV-uninfected and 16 viremic and 3 ART-treated HIV-infected individuals) received 10-1074. Of these, 21 received one infusion of 30 mg/kg. 10-1074 was generally safe and well-tolerated. A total of 57 AEs was reported during a follow-up period of 6 months, 88% of these were of grade 1 severity. The most commonly reported AE deemed possibly related to the study drug was transient, mild headache. There were no SAEs or grade 3 related AEs. A safety data summary is included in the 10-1074 IB.

Thirteen viremic subjects received 10-1074 at 30 mg/kg. Eleven of these subjects had pre-therapy viral isolates sensitive to 10-1074 *in vitro* and showed a rapid decline in viremia by a mean of 1.52 $\log_{10}$ copies/mL. Virologic analysis revealed the emergence of 10-1074-resistant viruses in the first weeks after infusion. Emerging escape variants carried mutations in known contact sites (N332, N334 and D/N425) and were generally resistant to the related V3-specific antibody PGT121, but remained sensitive to antibodies targeting non-overlapping epitopes, such as the anti-CD4-binding-site antibodies, 3BNC117 and VRC01[22].

1.1.3.3 10-1074 used in combination with 3BNC117

Two Phase 1 clinical trials of the combination of 3BNC117 (a bNAb that, like VRC01, recognizes the CD4 binding site on gp120) plus 10-1074 are currently underway. In one study (protocol YCO-0899), HIV-uninfected individuals received 1-3 doses of the antibody combination at 3 or 10 mg/kg versus placebo administered intravenously. Twenty-four subjects are enrolled, and all antibody infusions have been administered. Follow-up is ongoing and study assignment remains blinded.

In the second study (protocol MCA-0906), HIV-infected individuals on or off ART received 1 to 3 doses of 3BNC117 plus 10-1074 at 10 or 30 mg/kg each or placebo. To date, 29 individuals enrolled (25 received the antibody combination and 4 received placebo) in this study; 8 have received 3 infusions of 30 mg/kg, administered 3 weeks apart.

There have been no SAEs, and the safety profile of the combination of 3BNC117 plus 10-1074 is similar to what was observed with either antibody alone. The estimated half-lives of 3BNC117 and 10-1074 in HIV-uninfected individuals, when given in combination, are similar to what was observed when the antibodies were administered individually, i.e. 18 days for 3BNC117 and 24 days for 10-1074.

To date, the combination of 3BNC117 and 10-1074 appears to be well tolerated and able to delay viral rebound in the absence of ART. In MCA-0906, subjects in Group 2 discontinue ART two days after the first infusions of 3BNC117 and 10-1074 (Week 0) and receive two additional combination antibody infusions at Weeks 3 and 6. All 9 subjects enrolled in the treatment interruption group of the study with antibody-sensitive latent viral reservoirs maintained suppression for between 15 and more than 30 weeks (median of 21 weeks), and none developed viruses that were resistant to both antibodies[17].

1.2 Rationale

The rationale for this study is based on a preclinical study demonstrating that a brief course of treatment with two bNAbs that target different epitopes of HIV gp120, during transient viremia can induce long-lasting anti-HIV immunity capable of controlling plasma viremia in the absence of ART[18]. Given the constraints of working in humans with chronic HIV infection, we will attempt to mimic the primate study by first discontinuing ART and monitoring for rebound of plasma viremia. Once plasma viremia is detected at ≥200 copies/mL, subjects will receive a single infusion of VRC01+10-1074 or placebo and restart ART. Twelve weeks after achieving ART-induced viral suppression (plasma viremia <40 copies/mL), subjects will undergo a second analytical treatment interruption (ATI) to determine if transient exposure to bNAb-HIV immune complexes can induce a protective T cell response to HIV that prolongs the time to viral rebound in the absence of VRC01 and 10-1074.

The rationale for using the proposed dose of VRC01 and 10-1074 is based on the safety and pharmacokinetic data generated from Phase 1 human studies.

Analytical Treatment Interruption (ATI)
Various laboratory-based assays measuring the frequency of infected $CD4^+$ T cells carrying HIV proviral DNA and/or replication-competent virus and HIV-specific immune responses have been used to assess efficacy of immune-based therapies. To date, none of the assays are clinically validated to predict actual antiviral efficacy *in vivo*. Thus, ATI has been used to evaluate the antiviral efficacy of immune-based therapies by testing the ability of these interventions to blunt or prevent the viral rebound that occurs following interruption of ART. The use of ATI in the design of this study is the only way to determine if administration of VRC01 and 10-1074 results in clinically relevant antiviral activity in antiretroviral-treated individuals, as evidenced by an delayed or absent plasma viral rebound following interruption of ART. ATI, with frequent clinical and laboratory monitoring along with strict criteria for re-initiation of ART, is a safe and acceptable strategy to evaluate the efficacy of VRC01 and 10-1074 in this population of antiretroviral-treated HIV-infected adults. This is supported by the results from current and prior studies of immune based therapy using ATI to assess virologic efficacy[16,23-28], as well as a subgroup analysis of the SMART study[29]. In addition, a number of recent studies of subjects undergoing similar short-term ATI have not found any persistent changes in the size of the latent reservoir of infected $CD4^+$ T cells following re-suppression by ART[28,30-32].

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the virologic effect of a single administration of VRC01 plus 10-1074 on rebound plasma viremia in subjects undergoing sequential antiretroviral treatment interruptions.

2.2 Secondary Objective

- To evaluate the safety of a single dose VRC01 plus a single dose of 10-1074 in HIV infected individuals.

2.3 Exploratory Objectives

- To investigate whether a single dose of VRC01 and 10-1074 allows the development of anti-HIV immunity (i.e., cytotoxic T lymphocyte or other immune responses) following the first and second round of ATI

- To determine changes in markers of immune activation and exhaustion in B and $CD4^+$ and $CD8^+$ T cells

- To determine changes in the size of HIV reservoirs following the first and second round of ATI

3 STUDY DESIGN

3.1 Description of the Study Design (Figure 1)

The trial is a randomized double-blind placebo-controlled study to examine the effect of single infusions of VRC01 and 10-1074 in HIV-infected individuals undergoing sequential antiretroviral treatment interruptions. Participants will be randomized 1:1 to treatment with VRC01 plus 10-1074 or normal saline placebo. Study staff and participants will be blinded to treatment assignments.

First ATI
The day following study enrollment, subjects will stop ART (Day 0). Subjects taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) will switch to a protease or integrase inhibitor-based regimen at least 2 weeks prior to Day 0 to ensure that the washout period of antiretroviral agents is roughly equal. During this first ATI phase of the study, HIV ribonucleic acid (RNA) levels and $CD4^+$ T cell counts will be monitored every 2 weeks until plasma viremia of ≥200 copies/mL is detected.

VRC01 plus 10-1074/ Placebo Treatment Phase
Within 14 days of the first reported plasma viremia value of ≥200 copies/mL, subjects will be randomized 1:1 to receive single sequential infusions of VRC01 and 10-1074 or 2 sequential infusions of saline placebo. All subjects will restart ART the day following their bNAb/placebo infusions.

Second ATI
After re-institution of ART, subjects will have plasma viremia measured every 4 weeks. Twelve weeks after achieving ART-induced viral suppression subjects will undergo a second analytical treatment interruption. Viral suppression is defined as a plasma viremia <40 copies/mL. Transient “blips” in plasma viral levels are allowed as long as blips are <400 copies/mL and succeeding viral levels return to <40 copies/mL on subsequent testing.

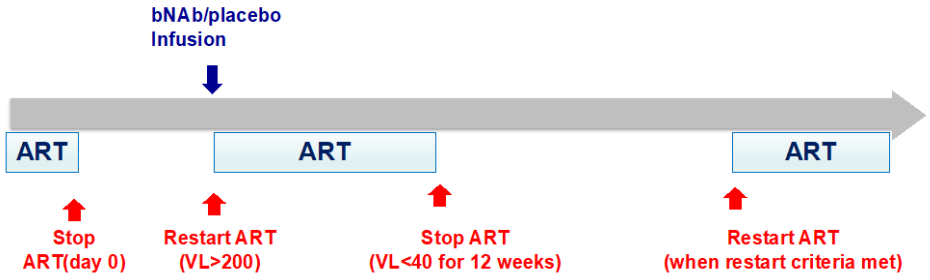
During this second ATI, plasma viremia and $CD4^+$ T cell counts will be monitored every 2 weeks and subjects will restart ART if they meet one or more of the following criteria prior to reaching ATI week 16:

- A confirmed >30% decline in baseline $CD4^+$ T cell count or an absolute $CD4^+$ T cell count <350 cells/mm^3 that is associated with a HIV RNA level >40 copies/mL.

- A sustained (>4 weeks) HIV RNA level of >1,000 copies/mL
- Any HIV-related syndrome (e.g. acute retroviral syndrome, opportunistic infection)
- Pregnancy

Subjects who have not met criteria to restart ART by ATI Week 16 will restart ART if they have measurable viremia (>40 copies/mL). Subjects whose HIV RNA levels are below the limit of detection (<40 copies/mL) at ATI Week 16 may elect to continue on the ATI phase of the study and have their $CD4^+$ T cell counts and HIV RNA levels monitored every 2 weeks until HIV RNA levels become detectable at which time they will restart ART.

Figure 1: Study Outline



3.2 Study Endpoints

3.2.1 Primary Endpoint

The time to meet criteria for restarting antiretroviral therapy (ART) following the second ATI.

3.2.2 Secondary Endpoints

The rate of occurrence of grade 3 or higher AEs, including SAEs, that, per standard criteria (see safety Section 12.3.1) are probably or definitely related to the test articles VRC01 and 10-1074.

4 STUDY POPULATION

4.1 Recruitment Plan

Subjects will be recruited from existing cohorts of individuals participating in NIAID protocols 09-I-0030 and 02-I-0202 who meet the Inclusion/Exclusion Criteria. Additional local and regional recruitment will be done using direct mailing to infectious disease physicians, internet ad campaigns, social media outlets, print ads, and from local clinics via the NIAID patient recruitment contract with Matthews Media Group.

4.2 Subject Inclusion Criteria

1. 18-65 years of age.

2. HIV-1 infection and clinically stable.
3. General good health and has an identified primary health care provider for medical management of HIV infection and is willing to maintain a relationship with a primary health care provider for medical management of HIV infection while participating in the study.
4. $CD4^+$ T cell count >450 cells/mm^3 at screening.
5. Documentation of continuous ART treatment with suppression of plasma viral level below the lower limit of quantification (LLOQ) for the assay used for ≥2 years. Individuals with "blips" (i.e., detectable viral levels on ART) prior to screening may be included provided they satisfy the following criteria:
    a. The blips are <400 copies/mL, and
    b. Succeeding viral levels return to levels below the limit of detection on subsequent testing.
6. Laboratory values within pre-defined limits at screening:
    a. Absolute neutrophil count >1,000/mm3.
    b. Hemoglobin levels >10.0 g/dL for men and >9.0 g/dL for women.
    c. Platelet count >100,000/mm^3.
    d. Estimated or a measured glomerular filtration rate >60 mL/min/1.73 m^2 as determined by the NIH Clinical Center (CC) laboratory.
    e. AST and alanine transaminase (ALT) levels of <2.5 x upper limit of normal (ULN), direct bilirubin within the normal range for the NIH CC laboratory.
7. Willingness to have samples stored for future research.
8. Willingness to undergo ATI
9. Willingness for both male and female subjects to agree to use barrier protection methods or abstinence during the ATI phase of the study to decrease the risk of HIV transmission.

Reproductive Risks

Contraception: The effects of VRC01 and 10-1074 on the developing human fetus are unknown. For this reason, men and women of childbearing potential must agree to use adequate pregnancy prevention. This includes the use an effective method of contraception (i.e. condom with spermicide, diaphragm with spermicide, hormone-eluting IUD, hormone-based contraceptive with condom) for the study duration. Subjects should also agree to use a male or female condom while off ART. Pregnancy prevention must be practiced continuously for the duration of study participation. Females of childbearing-age must have a negative pregnancy test result prior to receiving the infusions of VRC01 and 10-1074/placebo. During the course of the study, if a female subject, or the partner of a male subject suspects or in fact becomes pregnant, the affected subject should inform the study staff immediately, as well as the woman's primary care physician.

4.3 Subject Exclusion Criteria

1. Chronic hepatitis B, as evidenced by a positive test for hepatitis B surface antigen (HBsAg), or chronic hepatitis C virus (HCV) infection, as evidenced by a positive test for HCV RNA. Subjects with a positive test for HCV antibody and a negative test for HCV RNA are eligible.
2. HIV immunotherapy or HIV vaccine(s) received within 1 year prior to screening.
3. Any prior history of receiving 10-1074 or VRC01.
4. Any licensed or experimental non-HIV vaccination (e.g., hepatitis B, influenza, pneumococcal polysaccharide) received within 2 weeks prior to study enrollment.
5. Receipt of other investigational study agent within 28 days of enrollment.
6. Any active malignancy that may require systemic chemotherapy or radiation therapy.
7. Systemic immunosuppressive medications received within 3 months prior to enrollment (Exceptions: [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids administered for non-chronic conditions not expected to recur [length of therapy ≤10 days, with completion in ≥30 days prior to enrollment]).
8. History or other clinical evidence of:
    a. Significant or unstable cardiac or cerebrovascular disease (e.g., angina, congestive heart failure, recent stroke or myocardial infarction).
    b. Severe illness, malignancy, immunodeficiency other than HIV, or any other condition that, in the opinion of the investigator, would make the subject unsuitable for the study.
9. Active drug or alcohol use or any other pattern of behavior that, in the opinion of the investigator, would interfere with adherence to study requirements.
10. Pregnancy or breast-feeding at time of screening.
11. Documented multiclass antiretroviral drug resistance that, in the judgment of the investigator, would pose a risk of virologic failure should additional mutations develop during the study.

Co-enrollment Guidelines: Co-enrollment in other trials is restricted to observational studies or those evaluating the use of a licensed medication and is subject to approval of the principal investigator (PI).

4.4 Justification for Exclusion of Children (Special Populations)

Exclusion of Children:
Children are excluded from this study because there are insufficient data for adults regarding dosing of VRC01 and 10-1074 and AEs to judge the potential risk(s) in children.

4.5 Enrollment of NIH Employees

NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the “NIH information sheet on Employee Research Participation.”

For NIH employees:

- NIH staff may be a vulnerable class of subjects.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees.
- The employee subject's privacy and confidentiality will be preserved in accordance with NIH CC and NIAID policies, which define the scope and limitations of the protections.
- For NIH employee subjects, consent will be obtained by an individual independent of the employee's team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.
- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

5 STUDY AGENT/INTERVENTIONS

5.1 Regimen

10-1074 (30 mg/kg) and VRC01 (40 mg/kg) or matching placebos will be administered intravenously as single sequential infusions given at the end of the first ATI period (see Figure 1).

5.1.1 Formulation, Packaging and Labeling

10-1074 is provided by MassBio in single-use vials containing 30 mL of 10-1074 at a 20 mg/mL concentration.

VRC01 is provided by the VRC Pilot Plant operated by Leidos Biomedical Research, Inc., Frederick, MD, and is supplied at a concentration of 100 mg/mL. Two fill volumes are available, 2.25 ± 0.1 mL in a 3 mL glass vial and 6.25 ± 0.1 mL in a 10 mL glass vial.

Study agent vials will be individually labeled with the name of the material, volume, lot number, concentration, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

10-1074 should be stored at 2 - 8°C. Each vial is single use only. Partially used vials or solutions must not be used to prepare another dose and instead should be handled for destruction according to CC Pharmacy regulations for the disposal of biological agents.

The VRC01 product label designates the long-term storage temperature as -35°C to -15°C. Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions between -45°C and -10°C is acceptable. Following thaw, vials of VRC01 may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

The site pharmacist must promptly report any storage temperature deviations outside of the normal allowance for the storage device to the PI and the investigational new drug (IND) Sponsor. The product must be quarantined in a separate area. The IND Sponsor's authorized representative will notify the site pharmacist if continued clinical use of the product is acceptable.

5.2 Preparation, Administration, and Dosage of Study Agent

The dose of 10-1074 for this study is 30 mg/kg in 250 mL normal saline with overfill (20 mL). The dose of VRC01 is 40 mg/kg in 100 mL of normal saline. The placebo will be matching volumes of normal saline alone. The two antibodies will be mixed in separate bags of saline for sequential administration.

To prepare an IV infusion of 10-1074, the pharmacist will calculate the total milligrams of each antibody needed and add the calculated total milligrams needed to a 250 mL of normal saline with 20 mL overfill using good pharmacy practices to maintain sterility. The infusion solution must be used within 3 hours. Any unused portion of an antibody vial will not be used for another subject.

To prepare an IV infusion of VRC01, the pharmacist will calculate the total milligrams needed, retrieve the minimum number of thawed, particle free vials needed to prepare the full dose and add the calculated total milligrams needed to a 100 mL bag of normal saline using good pharmacy practices to maintain sterility (details for thawing vials are provided in the IB, Section 6.1.1). Prior to preparation for administration, vials should be gently swirled for 30 seconds, avoiding foaming. DO NOT SHAKE THE VIALS. Typically, 50 to 100 mL of additional volume may be added to a 100 mL bag of normal saline. The pharmacist should test the capacity of the brand of saline bags that will be used at the site to confirm the capacity to add this additional volume. After product preparation in IV bags, the prepared VRC01 may be stored at 2°C to 8°C up to 24 hours or at room temperature (maximum 30°C) for a maximum of 8 hours total including the infusion time.

The antibodies (or normal saline placebo) will be administered sequentially by IV infusion (10-1074/placebo first, followed by VRC01/placebo). Each infusion will be given over 60 minutes using a volumetric pump and then the line will be flushed with 20 mL normal saline. The total time needed to administer the dose may be longer than 60 minutes based on factors such as subject tolerance.

For women of childbearing potential, study agent administration may not proceed unless a negative pregnancy test has been obtained within the previous 24 hours. Vital signs (temperature, blood pressure, heart rate) will be measured 30 minutes into the infusion and at the end of the infusion. Following the completion of the VRC01/placebo infusion, the subject will be observed for 30 minutes and vital signs will be taken before the subject leaves the clinic.

5.2.1 Dose Adjustments and Modifications

Mild-moderate infusion related symptoms (Grade I-II), should they develop, will be managed by temporarily stopping the infusion until symptoms have resolved. For symptoms such as fever, myalgia, or urticaria, symptomatic treatment with standard doses of acetaminophen, ibuprofen, or antihistamines may be given. Once symptoms have resolved, the infusion will be restarted at a reduced rate. If symptoms recur following a reduced infusion rate and symptomatic treatment, the infusion will again be stopped until symptoms resolved and restarted at a lower rate. If the infusion cannot be completed within a 3-hour (10-1074) or 8-hour (VRC01) time frame because of recurrent symptoms, the infusion(s) will be discontinued and the subject will be monitored/treated as may be clinically indicated until deemed to have reached a stable and appropriate condition for discharge/departure.

5.3 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be recorded in Clinical Research Information Management System of the NIAID (CRIMSON). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in CRIMSON are concomitant prescription medications, over-the-counter medications, and non-prescription medications taken at the time of AEs (all grades).

5.4 Prohibited Medications and Procedures

Treatment with immunosuppressive medications during the study is prohibited. Prohibited immunosuppressive medications do not include [1] corticosteroid nasal spray or inhaler; [2] topical corticosteroids for mild, uncomplicated dermatitis; or [3] oral/parenteral corticosteroids given for non-chronic conditions not expected to recur with a length of therapy ≤10 days.

6 STUDY SCHEDULE

For all the study visits, unless otherwise specified, subjects will come to the NIH CC to undergo the procedures. Unless otherwise specified, the visit window for the post-entry study visits is ± 5 days.

6.1 Screening

Screening may occur over the course of several contacts/visits. All inclusion and exclusion criteria must be assessed within 8 weeks before enrollment, unless otherwise specified in the eligibility criteria.

After signing informed consent, subjects will undergo the following procedures:

- Medical history and physical examination, including weight and vital signs.
- Assessment of concomitant medications
- Blood collection for:
    - HBsAg and Hepatitis C antibody serology
    - Complete blood count (CBC) with differential, prothrombin time (PT), activated partial thromboplastin time (aPTT)
    - Chemistry panel to include: alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, total and direct bilirubin, and serum albumin levels
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV and HCV viral RNA levels
- Storage of serum and plasma (if needed for repeat HIV antibody testing or viral RNA levels)
- Urinalysis
- Serum or urine pregnancy test for women of child-bearing potential

Subjects taking NNRTI-based regimens will be asked to switch to a Protease of Integrase-based regimens at least 2 weeks before returning for Enrollment/Baseline visit.

6.2 Enrollment/Baseline

Participants will undergo the following procedures:

- Medical history and physical examination, including weight and vital signs
- Assessment of concomitant medications
- HIV transmission risk behavior assessment and counseling
- Blood collection for:
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV viral RNA levels
    - Human leukocyte antigen (HLA) typing (if not already on file)
    - Storage of plasma, serum and peripheral blood mononuclear cells (PBMCs)
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
    - Serum or urine pregnancy test (women of child-bearing potential)

6.3 First ATI Phase

The day following the enrollment visit, the participants will be instructed to stop their ART.

Storage of plasma, serum, and cells may be done at ATI Week 2, 4 and every 2 weeks thereafter for the duration of the first ATI phase. Flow cytometry (including CD4 count) and plasma HIV viral RNA levels will be done every 2 weeks for the duration of the ATI Phase. HIV genotype will be obtained on all samples with HIV viral levels >1,000 copies/mL. For select participants residing outside the local (Bethesda, MD) area, blood samples for blood draw only visits, may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for

testing. Samples collected at clinics or at Quest may be labeled with a coded identifier, gender, and date of birth, as required by the local facility.

During the first ATI Phase, participants will be evaluated at the CC outpatient clinic every 4 weeks. At these clinic visits, the following will be done in addition to the flow cytometry panel and plasma HIV viral level:

- Interval medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each subject
- Assessment of concomitant medications
- Assessment of any new or unresolved AEs/intercurrent illnesses
- Blood collection:
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
    - HIV transmission risk behavior assessment and counseling

For participants who are unable to return to the NIH CC during the COVID-19 pandemic/epidemic due to travel restrictions, blood samples may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for testing which will include; CBC with differential, plasma HIV viral level, and flow cytometry. Chemistry panels may be collected and run at Quest Diagnostics laboratories with results sent to the NIH. A study provider (Nurse Practitioner, Physician's Assistant, or Physician) will contact participants by phone and obtain an interval medical history.

6.4 Treatment Phase

When a single plasma viral level that is ≥200 copies/mL is detected, the participant will return within 14 days for randomization and entry into the Treatment Phase of the study. Following randomization, participants will receive single infusions of 10-1074/placebo and VRC01/ placebo given sequentially at the same visit. All participants will be instructed to restart ART the day following study infusions. Participants will be contacted by phone 72 hours after the study infusions to verbally asses for any reactogenicity symptoms (e.g. rash, arthalgias, fever).

During the Treatment Phase of the study, participants will be seen on the day of bNAb/placebo infusion and every 4 weeks thereafter and undergo the following study procedures.

- Interval medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each subject
- Assessment of any new or unresolved AEs or intercurrent illnesses
- Blood collection for:
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
    - Plasma HIV viral level
    - Flow cytometry panel
    - Storage of serum, plasma and PBMCs

- Serum or urine pregnancy test for women of child-bearing potential (at infusion visit only)

For participants who are unable to return to the NIH CC during the COVID-19 pandemic/epidemic due to travel restrictions, blood samples may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for testing which will include; CBC with differential, plasma HIV viral level, and flow cytometry. Chemistry panels may be collected and run at Quest Diagnostics Laboratories with results sent to the NIH. A study provider (Nurse Practitioner, Physician's Assistant, or Physician) will contact participants by phone and obtain an interval medical history.

6.5 Second ATI Phase

The second ATI Phase will begin after the participant's plasma viral level reaches <40 copies/mL and is sustained at this level for 12 weeks. Blips of low-level viremia during this period will be allowed provided these "blips" are <400 copies/mL and succeeding viral levels return to <40 copies/mL on subsequent testing. After 12 weeks of sustained suppression of plasma viremia, the participant will stop ART and be monitored as described in Section 6.3. Participants will remain off ART until they meet one or more of the ART restart criteria described in Section 3.1.

6.6 Follow-up Phase

When participants meet criteria to restart ART, they will restart treatment and enter the Follow-up Phase. Participants will be seen 4, 12, and 24 weeks after restarting ART to ensure re-suppression of viremia. At each visit participants will undergo the following study procedures.

- Interval medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each subject
- Assessment of any new or unresolved AEs or intercurrent illnesses
- Blood collection for:
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, ALP, creatinine, total and direct bilirubin, and serum albumin levels
    - Plasma HIV viral level
    - Flow cytometry panel to include CD4 count
    - Storage of serum, plasma and PBMCs

For participants who are unable to return to the NIH CC during the COVID-19 pandemic due to travel restrictions, blood samples may be collected at their local clinics or Quest Diagnostics and sent to the NIH CC for testing which will include; CBC with differential, plasma HIV viral level, and flow cytometry. A study provider (Nurse Practitioner, Physician's Assistant, or Physician) will contact participants by phone and obtain an interval medical history.

7 STUDY EVALUATIONS

7.1 Clinical Evaluations

- Participants will undergo a medical history and physical examination.

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

- HIV viral RNA levels
- HIV genotype (if viral level is >1,000 copies/mL)
- Flow cytometry with $CD4^+$ T cell count
- Routine serologic, hematologic, and clinical chemistry evaluations as described in Section 6

Other research evaluations measuring the effect of VRC01 and 10-1074 on the HIV pathogenesis may include:

- Frequency of $CD4^+$ T cells carrying HIV proviral DNA and cell-associated HIV RNA
- Levels of cell-associated infectious virus
- Sequencing of viral DNA and RNA
- Neutralization assays using replication-competent HIV against bNAbs
- Frequency of HIV-specific $CD4^+$ and $CD8^+$ T cells
- Markers of T-cell activation, immune exhaustion, and inflammation

8 POTENTIAL RISKS AND BENEFITS

8.1 Potential Risks

General Risks of MAb Treatment

Administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies; however, these reactions are rare and more often associated with mAb targeted to human proteins or with the use of chimeric human-murine mAbs, which would have a risk of human anti-mouse antibodies. Both VRC01 and 10-1074 are targeted to a viral antigen (HIV gp120) and are human mAbs; thus, it is expected these mAbs will have a low risk of such side effects. VRC01 and 10-1074 when given individually have both been well tolerated in Phase 1/2 studies with no safety concerns identified.

Typically, the side effects of mAbs are mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Most infusion-related events occur within the first 24 hours after beginning administration. Severe reactions, such as anaphylaxis, angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins or when a nonhuman mAb, such as a chimeric murine mAb, is used.

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms

may not appear until several days after the exposure to the mAb and is noted to be more common with chimeric types of mAbs.

Analytical treatment interruption (ATI)

The risks from an ATI, performed under close virologic and immunological monitoring are minimal in this subject population. There is a theoretical risk that ATI could lead to the development of HIV drug resistance. This may be a particular concern for individuals taking NNRTIs. However, this potential risk with NNRTIs is essentially eliminated by undertaking the procedures described in Section 3.1. Given the study population, the frequency of immunological and virologic monitoring, and strict criteria for restarting ART, it is extremely unlikely that the ATI will lead to the development of any opportunistic infections or acquired immune deficiency syndrome (AIDS)-defining conditions.

During the ATI phase, participants may transmit HIV infection if they do not adhere to safe sex practices.

Phlebotomy/Insertion of IV Catheter
This may be associated with discomfort, bruising, local hematoma formation and, on rare occasions, infections, lightheadedness, and fainting.

The amount of blood drawn for research purposes will be within the limits allowed for adult participants by the NIH CC (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

HLA typing
Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic disorders, or a faster progression to AIDS. HLA typing will be performed on samples collected from all the enrolled participants. Results from the HLA typing will become part of each participant's medical record at NIH. Medical records containing this information are maintained in a secure place.

8.2 Potential Benefits

Study participants may not receive direct health benefit from study participation or study infusions. Others may benefit from knowledge gained in this study that may aid in the development better HIV treatments.

9 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

- **Intended Use:** Stored blood samples and data collected under this protocol may be used to study the effect of bNAb treatment and ATI on the virologic and immunologic parameters listed in Section 7.2.1. Samples may also be used to study other aspects of the immunopathogenesis of HIV infection or measure serum levels of antiretroviral agents during ATI.
- **Storage:** Access to stored samples will be limited using a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators.

Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

- **Tracking:** Samples will be tracked utilizing the repository operated by Leidos Biomedical, Inc. Data will be stored and maintained in the NIAID CRIMSON database.
- **Disposition at the Completion of the Protocol:** At the completion of the protocol (termination), samples and data will either be destroyed, or after Institutional Review Board (IRB) approval, transferred to another existing protocol.
- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
    - Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIH IRB.
    - Additionally, participants may decide at any point not to have their samples stored. In this case, the PI will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH.

10 DATA SHARING PLAN

What data will be shared?

We will share human data generated in this study for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- Identified data in the Biomedical Translational Research Information System (BTRIS).
- De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- At the time of publication or shortly thereafter.

11 REMUNERATION PLAN FOR PARTICIPANTS

Eligible participants will be compensated for travel according to the NIAID/NIH travel policy. Participants will receive financial compensation for time and inconvenience according to the NIH CC volunteer guidelines: screening ($50), clinic visits ($30), research blood draw ($70), study infusion ($80). For participants who complete all the follow up phase visits, there is a $200 completion bonus.

12 ASSESSMENT OF SAFETY

12.1 Documenting, Recording, and Reporting Adverse Events

At designated visits with the subject, information regarding AEs will be elicited by appropriate questioning and examinations, and it will be:

- Immediately documented in the electronic database and medical record.
- Reported as outlined below (e.g., IND sponsor, IRB, FDA).
- A laboratory abnormality will not be reported as an adverse event if ALL of the following criteria are met:
    - It is no more than “Grade 1” or “Mild” per the protocol specified toxicity table (or investigator assessment if not listed on the table); AND
    - It does NOT require an intervention (e.g., discontinuation of treatment, dose reduction/delay, additional assessments, or treatment); AND
    - It is assessed by the PI as NOT related to the study agent(s); AND
    - It is assessed by the PI as NOT clinically significant (e.g., the abnormal value does NOT suggest a disease or organ toxicity)

All abnormal laboratory findings will be reviewed on a routine bases by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above.

12.2 Definitions for Sponsor Reporting

Adverse event (AE)
An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject’s participation in the research, whether or not considered related to the research.

Adverse reaction (AR)
An adverse reaction (AR) is an AE that is caused by an investigational agent (drug or biologic).

Suspected adverse reaction (SAR)
A SAR is an AE for which there is a reasonable possibility that the investigational agent caused the AE. ‘Reasonable possibility’ means that there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about the causality than an AR, which implies a high degree of certainty.

Serious adverse event (SAE)
An SAE is an AE that results in one or more of the following outcomes:

- Death
- A life-threatening (i.e., an immediate threat to life) event
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect
- A medically important event*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected adverse event
An AE is unexpected if it is not listed in the IB or package insert (for marketed products), or it is not listed at the specificity or severity that has been observed. It is the responsibility of the IND sponsor to make this determination.

Serious and unexpected suspected adverse reaction (SUSAR)
A serious and unexpected suspected AR (SUSAR) is a SAR that is both serious and unexpected.

Unanticipated problem (UP)
An unanticipated problem (UP) is an event, incident, experience, or outcome that is—

1. Unexpected in terms of nature, severity, or frequency in relation to—
    a. The research risks that are described in the IRB-approved research protocol and informed consent document; IB, or other study documents; and
    b. The characteristics of the subject population being studied; and
2. Related or possibly to participation in the research; and
3. Suggests the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (per the IND sponsor, an AE with a serious outcome will be considered increased risk).

Unanticipated problem that is not an adverse event (UPnonAE)
An UP that is not an AE (UPnonAE) is an incident, experience, or outcome that is not associated with an AE, which meets the 3 criteria of a UP. Examples include breaches of confidentiality, accidental destruction of study records, and unaccounted-for study drug.

Protocol Deviation
Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations (PD) are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol
- Those that are identified before they occur, but cannot be prevented
- Those that are discovered after they occur

Serious: A UP or PD is serious if it meets the definition of a Serious Adverse Event (see above) or if it compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as:

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to subjects
    b. Decreases potential benefits to subjects
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

12.3 Investigator Assessment of Adverse Events

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

All AEs occurring from the time when the first infusion is administered through the specified study follow-up period will be documented, recorded, and reported. The PI will evaluate all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

12.3.1 Severity and Causality

The PI will grade the severity of each AE according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July, 2017, which can be found at
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Causality (likelihood that the event is related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely related

- Reasonable temporal relationship
- Follows a known response pattern
- Clear evidence to suggest a causal relationship
- There is no alternative etiology

Probably related

- Reasonable temporal relationship
- Follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology

Possibly related

- Reasonable temporal relationship
- Little evidence for a more likely alternative etiology

Unlikely related

- Does not have a reasonable temporal relationship
  OR
- Good evidence for a more likely alternative etiology

Not related

- Does not have a temporal relationship
  OR
- Definitely due to an alternative etiology

Note:
Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

12.4 Investigator Reporting Responsibilities to the Sponsor

12.4.1 Adverse Events

Line listings, frequency tables, and other summary AE data will be submitted to the IND sponsor per the Safety Review and Communications Plan (SRCP – see below), or as needed for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

12.4.2 Serious Adverse Events (SAEs)

SAEs (whether or not they are also UPs) must be reported on the appropriate SAE/UP report form and sent to the sponsor Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life-threatening SAEs must be reported within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

Sponsor clinical safety office contact information:
OCRPRO Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

12.4.3 Unanticipated Problems (UPs)

Non-serious AEs that are UPs must also be reported on the NIH Reportable Events Form and sent to the CSO by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs are not reported to the sponsor CSO.

12.4.4 Pregnancy

All pregnancies will be reported on the Pregnancy Notification/Outcome Form to the CSO within 1 business day from site awareness.

Pregnancy itself is not an AE. However, complications of pregnancies are AEs and may be SAEs and events that meet SAE criteria during pregnancy, delivery, or in the neonate (e.g., congenital anomaly/birth defect) are reportable on the SERF.

Pertinent obstetrical information for all pregnancies, including pregnancies disclosed by the subject as occurring in a partner of a male subject, will be reported to the CSO via fax or e-mail within 3 business days from the site awareness of the pregnancy.

Pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site awareness on a protocol-specified form. In the event of pregnancy, the following steps will be taken:

- Discontinuation of the study agents
- Unblind subject (Group 1 only)
- Withdraw from the study but continue following for safety
- Report to Medical Monitor and the IRB
- Advise research subject to notify the obstetrician of study agent exposure

12.5 Investigator Reporting Responsibilities to the NIH IRB

- Assessment of Safety: AEs and other reportable events are defined in Policy 801: Reporting Research Events
- Reporting to the NIAID Clinical Director: The principal investigator will report UPs, major protocol deviations, and deaths to the NIAID Clinical Director according to institutional timelines.
- Unanticipated problems, non-compliance, and other reportable events will be reported to the NIH IRB according to Policy 801.

12.6 Follow-up of Adverse Events and Serious Adverse Events

AEs that occur following the first dose of bNAb or placebo are followed until the final outcome is known or until the end of the study follow-up period.

SAEs that that are assessed by the investigator to be possibly, probably, or definitely related to study agent/placebo and that have not resolved by the end of the follow-up period will be followed until the final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g. the subject is lost to follow up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE Case Report form.

SAEs that occur after study completion that are reported to and are assessed by the investigator to be possibly, probably, or definitely related must be reported to the CSO, as described above.

12.7 Sponsor's Reporting Responsibilities

SUSARs as defined in 21 Code of Federal Regulations (CFR) 312.32 and determined by the IND sponsor will be reported to the FDA and all participating investigators as IND safety reports.

The IND sponsor will also submit an IND annual report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

12.8 Halting Criteria for the Protocol

Halting the study requires immediate discontinuation of the study agents administered for all subjects and suspension of enrollment until a decision is made about whether or not to continue study agent administration.

The halting criteria (as determined by the study PI and IND sponsor secondary to aggregate data review) for this study include:

- Any SAE or grade 4 AE that is possibly, probably, definitely related to the study agent; OR
- Any safety issue that the study PI or IND sponsor determines should halt the study.

Any related AE that is ≥ grade 3 (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills) will be reviewed within 48 hours of site awareness, by the PI and IND sponsor medical monitor, to consider the need for halting the protocol.

The PI and/or CSO will determine if the study should be halted. In addition, the FDA or Data and Safety Monitoring Board (DSMB) may halt the study at any time following review of any safety concerns.

12.8.1 Reporting of Study Halting

If a halting rule is met, a description of the AE(s) or safety issue must be reported by the PI, within one business day, to the CSO and to the IRB *and DSMB* by fax or email. The sponsor will notify the FDA as soon as possible that the study has been halted.

12.8.2 Resumption of a Halted Study

The IND Sponsor, in collaboration with the DSMB and PI will determine if it is safe to resume the study. The PI will notify the IRB and DSMB of the decision on resumption of the study. The sponsor will notify the FDA as soon as possible that the study has been resumed after a halt.

12.9 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn for any of the following:

- An individual subject's decision. (The PI will attempt to determine the reason for the subject's decision and will strongly suggest a follow-up plan to help ensure the subject safely returns to baseline or better, if possible).
- Inability to receive both study infusions due to infusion-related AE.
- Co-enrollment in a study with an investigational research agent (rare exception granted by the PI).
- Any clinical AE, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Subjects will be followed for the duration of the study for indicated safety assessments.
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- Pregnancy.

If possible, all subjects who withdraw prematurely will be followed for 24 weeks for all the study evaluations.

12.10 Replacement for Withdrawn Subjects

Any subject who withdraws from the study, or who discontinues the study agent, prematurely, and whose reasons for withdrawing from the study or discontinuing study agent administration are unrelated to any real or perceived effect of the study agent or their administration, may be replaced at the discretion of the PI.

12.11 Safety Oversight

12.11.1 Safety Review and Communications Plan (SRCP)

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the IND sponsor CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

12.11.2 Sponsor Medical Monitor

A medical monitor, representing the IND sponsor (Office of Clinical Research Policy and Regulatory Operations [OCRPRO]), has been appointed for the safety oversight in this clinical study. The sponsor medical monitor will be responsible for performing safety assessments as outlined in the SRCP.

12.12 Data Safety Monitoring Board (DSMB)

The NIAID Intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The Board will review the study prior to initiation and twice a year thereafter. An alternative schedule may be indicated (i.e., interim analysis). The Board may convene additional reviews as necessary. The Board will

review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs, all UPs, and all IND Safety Reports will be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the Board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB(s).

13 CLINICAL MONITORING STRUCTURE

Site Monitoring Plan

As per International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP) 5.18 and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the *"NIAID Intramural Clinical Monitoring Guidelines."* Monitors under contract to the NIAID/ OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the informed consent form (ICF) process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare CRIMSON data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP], FDA), and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, CRIMSON data abstracts, and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the PI and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

13.1 Study Blinding and Unblinding

Study subjects and site staff (except for the NIH pharmacists) will be blinded to the subject treatment arm assignments (e.g., active treatment or control). Any discussion about the study product assignment between the pharmacy staff and any other protocol staff is prohibited. The DSMB members also are unblinded to the treatment assignment for the review of trial safety.

When a subject leaves the trial prior to study completion, the subject will be told he or she must wait until the all the subjects are unblinded to learn about his or her treatment assignment.

Emergency unblinding decisions will be made by the PI and the PI may request unblinding before halting or pausing the study if a subject meets criteria outlined in Section 12.8 and 12.9. If time permits, the sponsor medical monitor will be consulted before emergency unblinding occurs.

14 STATISTICAL CONSIDERATIONS

Efficacy Analysis

The primary outcome is the time from the start of the second treatment interruption until the subject meets criteria to restart ART. The probabilities of remaining below restart criteria for different amounts of time will be displayed using Kaplan-Meier plots and compared using the log-rank test. Secondary analyses will compare time to other milestones such as VL>400 and VL>1,000.

Safety Analysis

The proportion of subjects with grade 3 or higher AEs will be computed in each arm, along with 95% exact confidence intervals using the Clopper/Pearson method. The between-arm difference in the proportion of subjects with an AE of grade 3 or higher will be compared using Fisher's exact test and its associated confidence interval obtained by inverting two 1-sided tests at alpha=0.025.

Sample Size

Using control data from another similar trial, we modeled the time T (in days) to meet restart criteria as a Weibull distribution with survival function $P(T>t)=\exp[-(\lambda t)^p]$, where $\lambda=\exp(-3.861)=0.021$ and $p=1.957$. From these parameters, we estimated the median time to meet restart criteria as 39.486 days in the control arm. We can express the treatment effect in terms of either the hazard ratio θ or the factor β by which treatment increases the median time to meet restart criteria; β and θ are related by $\beta= \theta^{-1/p}$.

Assuming 25 subjects per arm are followed for 180 days, nearly everyone in both arms would be expected to meet restart criteria by 180 days. Power for a 40%, 50%, and 60% reduction in hazard is approximately 44%, 69%, and 90%, respectively (Table 2). These hazard reductions correspond to 30%, 42.5%, and 60% increases in the median time to meet restart criteria. Therefore, power is approximately 90% if the bNAb increases the median time to meet restart criteria by 60% relative to the placebo arm.

Table 2. Power under different treatment effects, expressed as either reduction in hazard or percent increase in median time to meet restart criteria.

Reduction in hazard	% Increase in median time to meet restart criteria	Power
40%	30%	44%
50%	42.5%	69%
60%	60%	90%

In terms of safety, a sample size of 25 subjects in the bNAb arm provides approximately 93% probability of detecting at least one AE that occurs in 10% or more of the population.

Table 3. Probability that at least 1 of 25 people in the bNAb arm will experience an AE that occurs in at least 10% of the population.

	AE frequency 1%	AE frequency 5%	AE frequency 10%
Probability of at least 1	22%	72%	93%

Futility

If results are sufficiently unpromising at the approximate halfway point (after 13 per arm have been evaluated for the primary outcome), the trial will be stopped for futility. Specifically, we will compute the conditional probability of a statistically significant result at the end of the trial, given the current data in each arm. This will be computed assuming a true treatment effect of a 60% increase in the median time to meet restart criteria. A recommendation for stopping for futility will be made If conditional power under this large assumed effect drops below 30%. This corresponds to seeing either no between-arm difference or a worse outcome in the bNAb arm at the approximate halfway point. A copy of the futility analysis will be made available to the DSMB.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject’s medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.1.1 Non-English–Speaking Subjects

If a non-English-speaking subject is eligible for enrollment, the subject will be consented using the process outlined in the HRPP Standard Operating Procedure Number 12: Requirements for Informed Consent. All instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

Illiterate English-Speaking Subjects

As the majority of the subject populations from which the study subjects are drawn are literate, written consent will typically be provided. However, this population does have a small rate of illiteracy, and oral consent will be obtained for illiterate subjects as consistent with HRPP Standard Operating Procedure Number 12: Requirements for Informed Consent without separate IRB approval for each specific use. At Continuing Reviews, the NIH IRB will be informed of the number of illiterate subjects who provided consent verbally.

15.2 Participant Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, NIAID, OHRP, or the sponsor's designee.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from subjects during study visits and telephone calls or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. Corrections to CRIMSON shall be tracked electronically with time, date, individual making the correction, and what was changed.

The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

16.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the International Conference for Harmonization Good Clinical Practice Guidelines. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to NIAID/OCRPRO with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from NIAID/OCRPRO.

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Appendix A: Schedule of Events

	Screening and Baseline		First ATI Phase			Treatment Phase						Second ATI Phase				Follow-up Phase		
Study Time Point	Screen	Base line	Week 2	Week 4	Weeks 6-End ATI	Infusion Visit	ART Start	Week 4	Week 8	Week 12-End Tx Phase	Last Dose of ART	Week 2	Week 4	Week 6-Week 16	Repeat-End ATI	Week 4	Week 12	Week 24
ASSESSMENTS																		
Consent	X				Continue Schedule of Procedures					Continue Schedule of Procedures until Subject's VL is < 40 copies for 12 Weeks				Continue Schedule of Procedures				
Vital Signs	X	X		X		X		X	X				X			X	X	X
H & P	X	X		X				X	X				X		PRN	X	X	X
HIV Counseling		X		X									X					
MEDICATIONS																		
Last Dose of cART		X									X							
VRC01 & 10-1074 Infusion						X												
Restart cART							X								X			
CLINICAL LABS																		
CBC/Diff	X	X		X				X	X				X			X	X	X
aPTT/PT	X																	
Acute/Hepatic /Mineral	X	X		X				X	X				X			X	X	X
Urinalysis	X																	
Pregnancy*	X	X				X												
HBsAg, Anti-HCV, HCV RNA,	X																	
HLA Typing**		X																
RESEARCH LABS																		
HIV-1 RNA	X	X	X	X		X		X	X			X	X		PRN	X	X	X
Flow Cytometry***	X	X	X	X		X		X	X			X	X		PRN	X	X	X
Serum storage		X						X	X							X	X	
Plasma storage	X	X	X	X		X		X	X			X	X		PRN	X	X	X
PBMCs storage		X		X				X	X				X			X	X	X
Estimated Volume per Visit	**30**	106	33	88		10		96	96			33	105		10	96	96	

* for women of childbearing potential

** if not already on file

***includes $CD4^+$ T cell count

PRN: as needed depending on when subject meets criteria to restart cART