An Exploratory, Open-Label Study of VRC-HIVMAB060-00-AB (VRC01) in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALP	Alkaline Phosphatase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
ATI	Analytical Treatment Interruption
cART	Combination Antiretroviral Therapy
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CHO	Chinese Hamster Ovary
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendment of 1988
COI	Conflict of Interest
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
DCR	Division of Clinical Research
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IV	Intravenous
LIR	Laboratory of Immunoregulation
MAb	Monoclonal Antibody
N	Number (typically refers to number of subjects/sample size)
NCI	National Cancer Institute, NIH
NDA	New Drug Application
NHP	Nonhuman Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OHSRP	Office of Human Subjects Research Protections

PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAR	Suspected Adverse Reaction
SC	Subcutaneous
SMC	Safety Monitoring Committee
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
VRC	Vaccine Research Center/NIAID

PROTOCOL SUMMARY

Full Title:	An Exploratory, Open-Label Study of VRC-HIVMAB060-00-AB (VRC01) in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption
Short Title:	Therapeutic VRC01
Clinical Phase:	1
IND Sponsor:	OCRPRO
Conducted by:	NIAID/LIR
Principal Investigator:	Michael C. Sneller, MD
Sample Size:	N= 30
Accrual Ceiling:	45
Study Population:	HIV-infected adults 18-65 years of age on combination antiretroviral therapy (cART) with suppressed viremia
Accrual Period:	18 months
Study Design:	An exploratory, open-label, single-arm study of VRC-HIVMAB060-00-AB (VRC01) in subjects with chronic HIV infection undergoing analytical treatment interruption
Study Duration:	2 years (June 2015 to June 2017)
Study Agent/ Intervention Description:	HIVMAB060-00-AB (VRC01), 40 mg/kg
Primary Objective:	To evaluate safety and tolerability of multiple doses of VRC01 in study subjects following discontinuation of cART
Secondary Objective:	To evaluate the efficacy of VRC01 as determined by its effect on plasma viral rebound following discontinuation of cART
Exploratory Objectives:	• To examine the capacity of other antibodies (i.e., 3BNC117) that bind to CD4 binding site on gp120 to neutralize VRC01-escape mutants ex vivo; • To investigate whether VRC01-mediated suppression of HIV replication in the absence of cART allows the development of anti-HIV immunity (i.e., cytotoxic T lymphocyte response) in infected individuals who began therapy during the chronic phase of infection; • To evaluate B cell responses to rebounding HIV upon discontinuation of cART; • To examine the relationship between the size of persistent HIV

reservoir and kinetics and timing of plasma viral rebound following analytical treatment interruption (ATI).

Endpoints:

- The rate of occurrence of grade 3 or higher adverse events (AEs), including serious adverse events (SAEs), that, per standard criteria (see safety section), are possibly related to VRC01.
- Number of subjects who experience rebound of plasma viremia and meet criteria to restart cART.

PRÉCIS

Recent advances in antibody cloning technologies have led to the discovery of a number of highly potent, HIV-specific, broadly neutralizing monoclonal antibodies from B cells of HIV-infected individuals. It has been shown that certain broadly neutralizing HIV-specific antibodies can prevent acquisition of the virus, suppress viral replication, delay and/or prevent plasma viral rebound following treatment interruption in Simian Immunodeficiency virus (SIV)-infected animals and block cell-to-cell transmission of laboratory-adapted HIV *in vitro*. However, it is unclear what *in vivo* effects these antibodies might have on plasma viral rebound in HIV-infected individuals following discontinuation of combination antiretroviral therapy (cART).

In this regard, it has been shown that virtually all infected individuals who initiated cART during the chronic phase of infection experience plasma viral rebound upon cessation of therapy. Current research on the treatment of HIV-infected individuals has been heavily focused on developing strategies aimed at achieving sustained virologic remission in the absence of cART. Thus, it is of great interest to investigate whether a potent HIV-specific monoclonal antibody, such as VRC01, can prevent plasma viral rebound in infected individuals upon discontinuation of cART. We propose to examine the effect of VRC01 on plasma viral rebound in HIV-infected individuals following analytical treatment interruption (ATI).

1 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Prolonged suppression of plasma viremia is now achievable in the majority of HIV-infected individuals receiving combination antiretroviral therapy (cART). Consequently, cART has dramatically improved the clinical outcome of infected individuals. However, complete eradication of HIV has not been possible using cART 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 virtually all infected individuals receiving clinically effective doses of cART(2-4). The inability of cART to eradicate HIV is likely due to the persistence of infectious virus in CD4+ T cells and possibly, other cell types(1).

Despite the success of cART in suppressing HIV replication and plasma viremia, the burden of taking daily medication for life, long-term toxicity of cART regimens, and resistance to antiretroviral drugs, necessitates a continued search for effective alternatives for the control of HIV infection. Consequently, a major thrust of HIV research over the past several years has been to develop therapeutic strategies that can control HIV replication in the absence of cART. One such strategy is passive immunization with 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 discovery of several highly potent and broadly neutralizing mAbs against HIV produced by B cells of some HIV-infected individuals(7-9). Several studies have demonstrated that certain broadly neutralizing HIV-specific mAbs can prevent acquisition of the virus, suppress viral replication, prevent plasma viral rebound following treatment interruption in infected animals(10-12), and block cell-to-cell transmission of laboratory-adapted HIV in vitro(13). However, it is unclear what in vivo effects these antibodies might have on HIV-infected humans.

The rebound of HIV plasma viremia observed in infected individuals following withdrawal of suppressive cART occurs as a result of at least two phenomenon: the emergence of virus from the persistent viral reservoir and the spread of virus to neighboring bystander CD4+ T cells. Broadly neutralizing mAbs such as VRC01 can potentially inhibit these events by several mechanisms including: directly binding and neutralizing infectivity of emerging HIV; blocking cell-to-cell spread of HIV; facilitating the clearance of plasma virus via formation of immune complexes; and clearance of HIV-infected cells through initiation of cellular effector responses. Of note, a recent study has demonstrated that several HIV-specific mAbs (including VRC01) inhibited entry into CD4+ T cells of HIV isolated from the latent viral reservoir of infected individuals whose plasma viremia was well controlled by cART(14). Based on these observations, and considering the possibility of biochemical modification to extend serum half-lives of HIV-specific antibodies, it is conceivable that infrequent administration of one or more of such mAbs could result in the maintenance of suppressed plasma viremia in the absence of cART. Thus, it is of interest to investigate whether a potent HIV-specific mAb, such as VRC01, can prevent plasma viral rebound in infected individuals upon discontinuation of cART.

1.1.1 Description of the Study Agent

The study agent, 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). Quality Assurance (QA) lot release testing by the manufacturer and ongoing stability programs verify conformance to product specifications prior to use in clinical trials.

VRC01 is a broadly neutralizing human mAb targeted against the HIV-1 CD4 binding site. It was developed by VRC/NIAID/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 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. Briefly, using polymerase chain reaction (PCR) amplification and cloning of the heavy and light chain variable region genes, a mAb was initially isolated from a single B cell from an HIV-1 infected subject who displayed broadly neutralizing antibodies.

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.

1.1.2 Summary of Previous Pre-Clinical Studies

A repeat dose toxicity study of intravenous (IV) and subcutaneous (SC) administration and 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-GMP pilot lot of VRC01 manufactured at smaller scale using a purification process similar to that of the GMP 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 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.

For the PK analysis, a separate cohort of rats received VRC01 on Day 1 at 4 mg/kg and 40 mg/kg by the IV route of administration and at 40 mg/kg by the SC route of administration. VRC01 levels in serum were determined using an enzyme-linked immunosorbent assay (ELISA). VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life (t1/2) was about 10 days, with clearance of approximately 20 ml/day/kg and volume of distribution that was about 0.28 l/kg.

Nonhuman Primate Studies of VRC01

Several non-GLP studies of VRC01 have been completed in nonhuman primates (NHP) 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

1.1.3 Summary of Relevant Clinical Studies

VRC 601, VRC 602, and HVTN 104 are Phase 1, dose-escalation studies to examine safety, tolerability, dose, and PK of VRC01 when administered to HIV infected (VRC 601) and healthy adults (VRC 602, HVTN 104). Both the IV or SC routes of administration are being evaluated in these studies. The dose groups in these studies are shown in Table 2.

Table 2: Phase 1 dose-escalating studies with IV and SC administration routes

VRC 601	VRC 602	HVTN 104
Group 1: 1 mg/kg IV	Group 1: 5 mg/kg IV	Group 1: 40 mg/kg IV,then 5 infusions 20 mg/kg IV monthly
Group 2: 5 mg/kg IV	Group 2: 20 mg/kg IV	Group 2: 40 mg/kg IV every 2 months, 3 infusions total
Group 3: 5 mg/kg SC	Group 3: 40 mg/kg IV	Group 3: 40 mg/kg IV and then 5 injections of 5 mg/kg SC every 2 weeks, or placebo
Group 4: 20 mg/kg IV	Group 4: 5 mg/kg SC or placebo	
Group 5: 40 mg/kg IV		

All three studies followed their respective dose escalation plans and reached the 40 mg/kg IV administration dose level without the occurrence of any safety pauses or SAEs.

As of January 9, 2015, 87 subjects received one or more study product administrations, including 21 in VRC 601; 28 in VRC 602; and, 38 in HVTN 104. Of the 87 subjects who began study product administration, the schedule completion status is as follows:

- 9 subjects, on a one dose schedule, completed one dose;
- 40 subjects, on a two dose schedule: 37 received two doses, 3 discontinued after one dose; and,
- 38 subjects in HVTN 104, on multi-dose schedules: 36 continuing, 2 discontinued after two doses.

- Of the 5 subjects discontinued from study product administration, reasons were as follows:
    - 1 lost to follow-up;
    - 1 unable to comply with the study schedule;
    - 1 unrelated adverse event (*Streptococcal* pharyngitis) that precluded timely administration; and,
    - Related adverse events (mild generalized rash; mild chest discomfort).

Cumulatively, across VRC 601 and VRC 602 studies, there were 86 product administrations as follows:

- 6 administrations at 1 mg/kg IV;
- 16 administrations at 5 mg/kg IV;
- 19 administrations at 20 mg/kg IV;
- 21 administrations at 40 mg/kg IV;
- 15 administrations at 5 mg/kg SC; and
- 9 administrations of placebo SC.

Cumulatively, in the HVTN 104 study, there were 138 product administrations as follows:

- 17 administrations at 20 mg/kg IV (Group 1: 10 as 2nd dose; 5 as 3rd dose; 2 as 4th dose);
- 29 administrations at 40 mg/kg IV (Group 1: 12 as 1st dose; Group 2: 11 as 1st dose and 6 as 2nd dose);
- 15 administrations of either VRC01 at 40 mg/kg IV or placebo IV (Group 3 1st dose); and,
- 77 administrations of either VRC01 at 5 mg/kg SC or placebo SC (Group 3: 15 as 2nd dose; 13 as 3rd dose; 13 as 4th dose; 13 as 5th dose; 12 as 6th dose; 7 as 7th dose; 4 as 8th dose).

The PK parameters of passively administered VRC01 to date have been evaluated in a limited number of healthy adults and in HIV-infected adults. The PK results as of May 2014 with these two populations of adults are provided in the IB and are preliminary. The results indicate that PK parameters are comparable in these two adult populations. When administered IV at 20 mg/kg (n=5) or 40 mg/kg (n=4), the mean (+ SD) maximum serum concentration were 870 + 197 and 1611 + 258 mg/L following the first dose, respectively. The elimination half-life was similar in healthy and HIV-infected adults with an overall mean value of 14.6 + 4.8 days following 20 mg/kg or 40 mg/kg doses. In healthy adults at 20 mg/kg IV (n=3) and 40 mg/kg IV (n=4), mean

28 day trough serum concentrations were approximately 32.7 + 9.1 and 60.6 + 20.1 mg/L, respectively, after the first administration. At 28 days after the second IV administration, the mean VRC01 serum levels were 40.6 + 10.7 and 102.6 + 48.8 mg/L. The clearance of VRC01 in healthy adults is estimated to be 466 + 118 mL per day following IV administration of 5-40 mg/kg (n=11) on the basis of these interim data.

An interim analysis of the VRC 601 viral load data obtained from 7 viremic adults through March 18, 2015 shows that VRC01 has a statistically significant *in vivo* virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking cART when enrolled into the study and had not started cART through the time periods used in this viral load analysis. Five of the seven adult subjects had ≥1 $\log_{10}$ copies/mL decrease in viral load, while two subjects had viral load decreases of 0.26 and 0.18 $\log_{10}$ copies/mL, respectively.

These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load post-infusion days 5 through 9 and on day 14;
- The median time to reach ≥0.5 $\log_{10}$ decrease in viral load is 5 days; and,
- The median time to greatest decrease in viral load is 7 days.

A 0.5 $\log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ART. To have clinical benefit, such a change would need to be sustained. In VRC 601, subjects were administered only one dose of VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected. However, the interim data indicate that the established benchmarks can be obtained and support the hypothesis that a schedule with repetitive dosing may have a beneficial clinical effect.

1.2 Rationale

The objectives of this study are to evaluate the safety and tolerability of multiple doses of VRC01 in study subjects following discontinuation of cART, and to evaluate the efficacy of VRC01 as determined by its effect on plasma viral rebound following discontinuation of cART. Up to 30 participants will be enrolled in this open-label, single-arm study. Only study participants on cART with documented suppression of viremia for ≥ 3 years are eligible to participate.

The rationale for using the proposed dose of VRC01 is based on the safety and pharmacokinetic data generated from VRC 601 and 602 as well as pre-clinical NHP studies (Table 1).

Analytical Treatment Interruption (ATI)

Various assays measuring HIV-specific immune responses and the frequency of CD4 cells carrying infectious HIV have been used to assess efficacy of immune-based therapies. To date, none of the assays are clinically validated to predict actual antiviral efficacy. 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 cART. The use of ATI in the design of this study is the only way to determine if administration of VRC01 results in clinically significant antiviral activity, as evidenced by a blunted or absent plasma viral rebound following ATI. We feel that a 24-week ATI, with frequent clinical and laboratory monitoring along with strict criteria for re-initiation of cART, is a safe and acceptable strategy to evaluate the efficacy of VRC01 in this population of HIV-infected adults. This is supported by the results from current and prior therapeutic vaccine studies using ATI (15-18), as well as a recent subgroup analysis of the SMART study (19). Given that essentially all HIV-infected individuals

treated during the chronic phase of HIV infection will experience rebound in plasma viremia following cessation of cART (20, 21), a placebo control group is not necessary to evaluate the potential antiviral efficacy of VRC01 in this early phase study.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate safety and tolerability of multiple doses of VRC01 in study subjects following discontinuation of cART.

2.2 Secondary Objective

To evaluate the efficacy of VRC01 as determined by its effect on plasma viral rebound following discontinuation of cART.

2.3 Exploratory Objectives

- To investigate whether plasma viral rebound can be prevented or delayed by VRC01 in infected individuals carrying HIV/viral reservoir that does not react to VRC01.
- To examine the capacity of other antibodies (i.e., 3BNC117) that bind to CD4 binding site on gp120 to neutralize VRC01-escape mutants ex vivo.
- To investigate whether VRC01-mediated suppression of HIV replication in the absence of cART allows the development of anti-HIV immunity (i.e., CTL response) in infected individuals who began therapy during the chronic phase of infection.
- To evaluate B cell responses to rebounding HIV upon discontinuation of cART.
- To examine the relationship between the size of persistent HIV reservoir and kinetics and timing of plasma viral rebound following ATI.

3 STUDY DESIGN

3.1 Description of the Study Design

The proposed trial will be a single-arm, open-label study to examine the effect of VRC01 on plasma viral rebound in HIV-infected individuals following an analytical treatment interruption (ATI). Thirty HIV-infected individuals who initiated cART during the chronic phase of infection will be studied. All study participants will receive infusions of VRC01 (40mg/kg) at study days 0, Week 2, Week 4, and every four weeks thereafter for up to 24 weeks (Figure 1).

Analytical treatment interruption

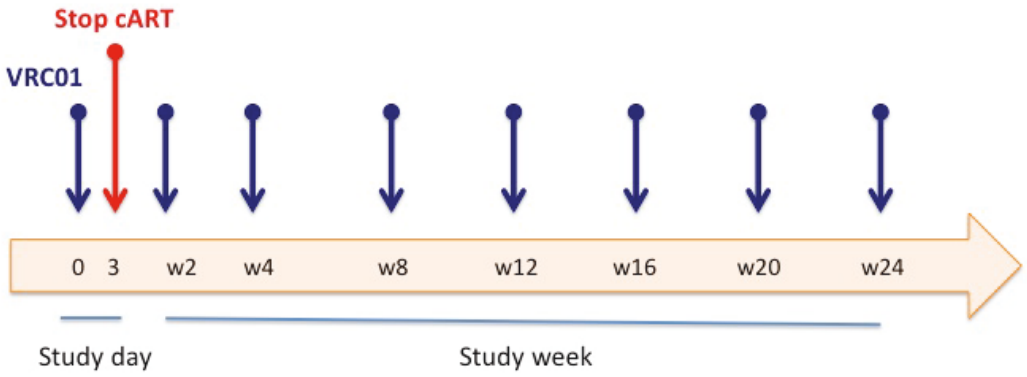
After study day 3, all subjects will undergo an ATI to determine if treatment with VRC01 can prevent rebound of plasma viremia. Individuals taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) will switch to a protease inhibitor or an integrase inhibitor-based regimen 2 weeks prior to enrollment to ensure that the washout period of antiretroviral agents is roughly equal.

All subjects with detectable viremia at Week 28 will be instructed to restart cART. Subjects will also be instructed to restart cART if they meet any of the following criteria during the ATI:

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

- A sustained HIV RNA level of >1,000 copies/mL at two consecutive visits or incremental increases in plasma HIV RNA above 500 copies/ml at three consecutive visits.
- Any HIV-related symptoms
- Pregnancy

Figure 1: Treatment Phase



3.2 Study Endpoints

3.2.1 Primary Endpoint

The rate of occurrence of grade 3 or higher AEs, including SAEs, that, per standard criteria (see safety Section 11.2) are:

- At least possibly related to the test article, and
- Definitely NOT related to a factor other than the test article.

3.2.2 Secondary Endpoints

Number of subjects who experience rebound of plasma viremia and meet criteria to restart cART.

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. Age 18-65 years old.
2. HIV-1 infection and clinically stable.
3. In general good health and with an identified primary health care provider for medical management of HIV infection and willing to maintain a relationship with a primary health care provider for medical management of HIV infection while participating in the study.
4. CD4+ cell count >450 cells/mm^3 at screening.
5. Documentation of continuous cART treatment with suppression of plasma viral level below the limit of detection for ≥3 years. Subjects with "blips" (i.e., detectable viral levels on cART) 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. Willingness to undergo ATI.
7. Laboratory values within pre-defined limits at screening:
    a. Absolute neutrophil count >1,000/mm^3.
    b. Hemoglobin levels >10.0 g/dL for men and >9.0 g/dL for women.
    c. Platelet count >100,000/mm^3.
    d. Prothrombin time (PT) and partial thromboplastin time (PTT) <1.5 upper limit of normal (ULN).
    e. Estimated or a measured creatinine clearance rate of ≥50 mL/min as determined by the NIH Clinical Center laboratory.
    f. AST and ALT levels of <2.5 x ULN.
8. Willingness to have samples stored for future research.

Reproductive Risks

Contraception: The effects of VRC01 on the developing human fetus are unknown. For this reason, men and women of childbearing potential must agree to use adequate pregnancy prevention per the investigator. This includes highly reliable established lifestyle of complete abstinence of potentially reproductive sexual activity, or use of BOTH a long term hormonal or barrier (e.g. implant, depot injection, IUD in female participant or female partner of participant) method of contraception that is fully effective prior to dosing, COMBINED WITH a barrier method (male or female condom) for all potentially reproductive sexual activity. Pregnancy prevention must be maintained as effective and practiced continuously for the duration of study participation. Females of childbearing-age must have a negative pregnancy test result prior to receiving VRC01. During the course of the study, if a female participant, or the partner of a male participant suspects or in fact becomes pregnant, the effected participant should inform the study staff immediately, as well as the woman's primary care physician.

Subjects must use safe sex practices during the trial, and particularly during the ATI phase, when risk of transmission of HIV may be increased.

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. Documented virologic failure to >1 cART regimen.
3. HIV immunotherapy or vaccine(s) received within 1 year prior to screening.
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 (Not excluded: [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 disease (e.g., angina, congestive heart failure, recent 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. Breast-feeding.

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.

4.4 Justification for Exclusion of Children (Special Populations)

Exclusion of Children:
Because there are insufficient data regarding dosing or adverse events available in adults to judge the potential risk in children, children are excluded from this study.

5 STUDY AGENT/INTERVENTIONS

5.1 Disposition and Dispensation

Study agent will be distributed via the NIH Central Pharmacy according to standard pharmacy procedures.

5.1.1 Formulation, Packaging and Labeling

VRC01 vials are filled at 2.25± 0.1 mL/vial in 3 mL glass vials at a concentration of 100 (±10) mg/mL. Vials contain a clear, colorless to yellow liquid with no visible particles, which is an isotonic, sterile solution. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and thus do not contain a preservative.

In calculating the dose to administer and number of vials to thaw, it should be assumed that the concentration is 100 mg/mL and that a volume of about 2 mL can be withdrawn from a vial. Preparation of VRC01 for IV administration will require a 100 mL bag of 0.9% sodium chloride for injection, USP (normal saline). Note that the normal saline bags referred to as "100 mL bags" in the IV administration instructions will typically have 103 mL volume before any VRC01 is added and this is acceptable in the context of the instructions below.

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.

5.2 Study Agent Storage and Stability

The 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 at -45°C to -10°C is acceptable.

The site pharmacist must promptly report any storage temperature deviations outside of the normal allowance for the storage device to the PI and the 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.

5.3 Preparation, Administration, and Dosage of Study Agent

Results from a stability study conducted with VRC01 show that the product is stable in the vial for 8 hours at refrigerated and room temperature. The following instructions apply to preparing the product for infusion:

- Thaw the vial(s) containing VRC01 at ambient temperature (15°C to 25°C).
- Keep the material at refrigerated or room temperature during the entire preparation period until use.

Preparation is to be done in a clean preparation unit with limited access. Assure that only the required vials are present in the preparation unit during dilution, and medication labels are strictly segregated to avoid mix-ups.

It is expected that each vial will be used for about 2 mL withdrawal volume (200 mg VRC01); however, more may be withdrawn if it is possible to do so. For each IV infusion order, the subject's weight and dose level will be included in the pharmacy order. The IV bag prepared by the pharmacy will include information regarding the total amount (mg) of VRC01 added to the 103 mL normal saline bag and the final volume of the bag. The nurse responsible for administration and another clinician will each check the bag label and confirm that the identifier is correct and that the correct total milligrams to be administered is shown based on subject weight and dosage level before beginning the IV administration.

The dose of VRC01 for this study is 40 mg/kg with 100 mL normal saline. To prepare an IV infusion, the pharmacist will calculate the total milligrams needed, thaw the minimum number of vials needed to obtain the full dose and add the calculated total milligrams needed to a 103 mL bag of normal saline using good pharmacy practices to maintain sterility. After thawing, the vials should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL. The bag of normal saline has the capacity to accept up to 100 mL of added product and this will be sufficient to accommodate all the planned dose levels for the eligible subjects in this study. Any unused portion of a VRC01 vial will not be used for another subject.

The investigational study product solution will typically be administered by IV infusion over at least 60 minutes using a volumetric pump. The mL/hr infusion rate may vary based on the total volume needed to administer the full dose. 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. Prior to each administration, temperature, blood pressure, heart rate (pulse) and weight will be recorded and a targeted physical examination (based on signs, reported symptoms or interim medical history) may be conducted. Vital signs (temperature, blood pressure, heart rate) will be measured 30 minutes into the infusion and at the end of the infusion. Following each administration, the subject will be observed for 30 minutes and vital signs will be taken before the subject leaves the clinic.

5.3.1 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 and myalgia, a dose of acetaminophen (650 mg) may be given. Once symptoms have resolved, the infusion will be restarted at half the initial rate. If symptoms recur with 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 4-hour time frame because of recurrent symptoms, the infusion will be discontinued for that visit.

5.3.2 Duration of Therapy

The total duration of therapy is 24 weeks.

5.4 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be recorded in 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).

5.5 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-length of therapy ≤10 days.

6 STUDY SCHEDULE

For all the study visits, unless otherwise specified, subjects will come to the NIH Clinical Center 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 a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- Assessment of concomitant medications
- Blood collection for:
    - HBsAg and Hepatitis C antibody serology
    - Anti-HIV antibody test. Subjects with previous confirmed Anti-HIV serology from the NIH will not have this repeated.
    - Complete blood count (CBC) with differential, PT, activated PTT
    - Chemistry panel to include: ALT, AST, alkaline phosphatase, 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
- Electrocardiogram (ECG)

6.2 Enrollment/Baseline

The enrollment visit may take place over 2 visits to accommodate the baseline pre-treatment apheresis procedure. The first dose of VRC01 will be administered at this visit, and enrollment is defined as the day of receipt of the first dose of VRC01.

Subjects will undergo the following procedures (prior to the first dose of study drug):

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- Assessment of concomitant medications
- HIV transmission risk behavior assessment and counseling

- Leukapheresis for research studies
- Blood collection for:
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV viral RNA levels
    - HLA typing (if not already on file)
    - Storage of plasma, serum and PBMCs
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels
- Serum or urine pregnancy test (for women of child-bearing potential-obtained within 24 hours prior to infusion)

6.3 Study Phase

Treatment Phase

Subjects will be administered VRC01 on study day 0. All subjects will discontinue their cART regimen after study day 3. Subsequent infusions of VRC01 will occur at study Week 2, 4, and every four weeks thereafter until study Week 24 for a total of 8 doses (see Figure 1).

Storage of plasma, cells, and plasma HIV viremia will be done at study day 3, Week 1, 2, 3, and 4 and every 2 weeks thereafter for the duration of the ATI. Flow cytometry with CD4 count will be done every 2 weeks for the duration of the ATI.

At infusion visits (study Week 2, 4, 8, 12, 16, 20 and 24), the following will be done in addition to the plasma HIV viral load:

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- Assessment of concomitant medications
- Assessment of any new or unresolved AEs/intercurrent illnesses
- Blood collection (Week 4, 8, 12, 16, 20, and 24):
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, CPK, total and direct bilirubin, and serum albumin levels
- Serum or urine pregnancy test for women of child-bearing potential (results must be reviewed prior to infusion)
- Serum for storage (except for Week 2)
- Optional leukapheresis for research studies will be done within 14 days after the week 24 infusion
- HIV transmission risk behavior assessment and counseling

If a subject develops one or more criteria for ending ATI prior to Week 24, he/she will be asked to return for assessment and confirmation of the laboratory/clinical abnormality. If the criteria for ending ATI are met, no further VRC01 infusions will be given; the subject will be instructed to restart cART and continue to be followed for 24 weeks after the last VRC01 infusion. He/she will undergo the schedule of procedures described in Section 6.4.

6.4 Follow-up Period

At the Week 28 visit, all subjects with detectable viremia will be instructed to restart cART. After restarting cART, subjects will be seen every 4 weeks for 20 weeks. At these visits, subjects will undergo the following procedures:

- Medical history and a targeted physical examination, including weight, vital signs, and a symptom-directed evaluation based on symptoms or complaints reported by each participant
- Assessment of any new or unresolved AEs/intercurrent illnesses
- Blood collection for:
    - CBC with differential
    - Chemistry panels, to include: ALT, AST, alkaline phosphatase, creatinine, total and direct bilirubin, and serum albumin levels
    - Flow cytometry panel (includes CD4+ cell count)
    - Plasma HIV viral load
    - HIV genotype (Week 28/prior to restarting cART only)
    - Storage of plasma and PBMCs

If a subject does not have detectable viremia at Week 28, they may elect to remain off cART until viremia becomes detectable. For such subjects, laboratory studies will be continued per the schedule outlined in Section 6.3 (except for the collection of serum for storage) until viremia is detected; at which time they will be instructed to restart cART and be followed every four weeks for 20 weeks as described in this section. Management of cART during the follow-up period will be according to standard guidelines (http://aidsinfo.nih.gov/guidelines).

7 STUDY EVALUATIONS

7.1 Clinical Evaluations

- Subjects will undergo a medical history and physical examination.
- Phlebotomy: Blood will be collected for routine serologic, hematologic, and clinical chemistry evaluations as described in Section 6.

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

- HIV viral RNA levels
- Flow cytometry with CD4+ cell count
- Serum for levels of VRC01 and antibody to VRC01

Leukapheresis: Will be performed for research studies including, but not limited to, measurements of the frequency of CD4+ T cells carrying replication-competent HIV by quantitative coculture assays. These studies will address the exploratory endpoints. If leukapheresis cannot be performed for technical reasons (e.g., poor venous access), 80 ml of blood will be drawn instead.

Other research evaluations measuring the effect of VRC01 on the HIV pathogenesis may include:

- Frequency of $CD4^+$ T cells carrying HIV proviral DNA and cell-associated HIV RNA
- Frequency of HIV-specific $CD4^+$ and $CD8^+$ T cells
- T-cell activation and soluble markers of inflammation
- Residual (1-40 copies/mL) plasma viremia

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 murine monoclonal antibodies, which would have a risk of human anti-mouse antibodies. In this regard, as VRC01 is targeted to a viral antigen and is a human monoclonal antibody, it is expected to have a low risk of such side effects.

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.

As indicated in Section 1.1.3, no signficant (>Grade 1) adverse events related to VRCO1 have been seen to date in the two ongoing human trials.

Analytical treatment interruption

The risks from a 24-week 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(22). Given the study population, the short duration of the ATI, the frequency of immunological and virologic monitoring, and strict criteria for restarting cART, it is extremely unlikely that the ATI will lead to the development of any opportunistic infections or AIDS-defining conditions.

During the ATI phase, subjects 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 subjects by the NIH Clinical Center (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 subjects. Results from the HLA typing will become part of each subject's medical record at NIH. Medical records containing this information are maintained in a secure place.

8.2 Potential Benefits

Study subjects will 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 VRC01 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 NIAID IRB.
    - Additionally, subjects may decide at any point not to have their samples stored. In this case, the principal investigator 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 REMUNERATION PLAN FOR SUBJECTS

Eligible subjects will be compensated for travel according to the NIAID/NIH travel policy. Subjects will receive financial compensation for time and inconvenience according to the NIH Clinical Center volunteer guidelines: screening ($50), leukapheresis ($200 for a 2-pass leukapheresis procedure), research blood draw ($40), clinic visits ($30), VRC01 infusion ($80). If subject does not qualify or declines leukapheresis, an additional 80 mL research blood will be drawn and subject may be compensated an additional $25 for inconvenience.

11 ASSESSMENT OF SAFETY

11.1 Definitions

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

Suspected adverse reaction (SAR)
An adverse event for which there is a reasonable possibility that the investigational agent caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction which implies a high degree of certainty

Serious adverse event (SAE)
A Serious Adverse Event 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 Investigator's Brochure 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 SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated problem (UP)
An unanticipated problem 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; Investigator's Brochure, or other study documents; and
   b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. 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 unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

11.2 Documenting, Recording, and Reporting Adverse Events

All AEs occurring from the time of first dose of VRC01 through the specified study follow-up period (24 weeks after final VRC01 dose) will be documented, recorded, and reported.

At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the subject's medical record/source document,
- recorded in Crimson, and
- reported as outlined below (e.g., IND Sponsor, Institutional Review Board [IRB], and Food and Drug Administration [FDA]).

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

11.3 Investigator Assessment of Adverse Events

The Investigator will assess 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.

11.3.1 Severity

The principal investigator 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 2.0, November, 2014, which can be found at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.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.

11.4 Investigator Reporting Responsibilities to the Sponsor

11.4.1 Adverse Events

AE data will be submitted to the IND Sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

11.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO 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.

CSO CONTACT INFORMATION:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

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

SAEs that have not resolved by the end of the follow-up period are followed until 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 CRF and the SERF.

SAEs that occur after the study follow-up period (24 weeks after final VRC01 dose) that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

11.4.3 Unanticipated Problems

Unanticipated Problems that are also AEs must be reported to the CSO and sent 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 CSO.

11.4.4 Protocol Specified Events

Autoimmune disorders are AEs of special interest. These protocol specified events must be reported to the CSO on a SERF within 3 business days of site the awareness.

11.4.5 Pregnancy

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

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's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (e.g., congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy, the following steps will be taken:

- Discontinuation of the study agents.
- 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.

11.5 Investigator Reporting Responsibilities to the NIAID IRB

11.5.1 Definitions

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

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

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH Human Research Protection 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 participants
    b. Decreases potential benefits to participants
    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

11.5.2 Expedited Reporting to the NIAID IRB

Serious and non-serious UPs, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. SAEs that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator awareness, regardless of expectedness.

11.5.3 Waiver of Reporting Anticipated Protocol Deviations, Expected UP nonAEs and Deaths to the NIAID IRB

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in HIV(+) population. If the rate of these events exceeds the rate expected by the study team, the events

will be classified and reported as though they are unanticipated problems. Deaths related to the natural history of HIV (+) population will be reported at the time of continuing review.

11.5.4 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of continuing review:

- Serious and non-serious unanticipated problems.
- Expected serious adverse events that are possibly, probably, or definitely related to the research.
- Serious adverse events that are not related to the research.
- All adverse events, except expected AEs granted a waiver of reporting.
- Serious and Non-Serious Protocol deviations.
- Serious, continuing, and minor non-compliance.
- Any trends or events which in the opinion of the investigator should be reported.

11.6 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (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.

11.7 Pausing Rules for an Individual Subject

Pausing is the suspension of administration of study agent to a single subject until a decision is made whether or not to resume administration of the study agent.

The pausing criteria for a single subject in this study include any of the following:

- A subject experiences an SAE or grade 3 or greater AE (not including transient, subjective infusion-related symptoms such as malaise, fatigue, headache, chills, or total bilirubin in subjects taking atazanavir) that is unexpected (as determined by the IND sponsor) and is possibly, probably, or definitely related to the study agent;

- Any safety issue that the Site Investigator determines should pause administration of a study agent to a single subject.

The CSO, in collaboration with the PI, may also pause for an entire group if a safety concern is identified.

11.7.1 Reporting a Pause

If a pausing criteria is met, a description of the AE(s) or safety issue must be reported by the PI, within 1 business day, to the CSO, the IRB by fax or email.

11.7.2 Resumption of a Paused Study

The CSO in collaboration with the PI will determine whether or not it is safe to resume administration of the study agent to the subject.

The PI will notify the IRB of the decision on resumption of the study agent.

11.7.3 Discontinuation of Study Agent

A subject who does not resume study agent will continue to be followed for safety.

11.8 Halting Rules for the Protocol

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

The halting rules are:

- Any SAE or grade 4 AE that is possibly, probably, or definitely related to the study agent; OR
- Any death regardless of relation to study agent; OR
- Any safety issue that the study principal investigator or IND sponsor determines should halt the study.
- Pre-defined futility criteria for virologic failure are met (see Section 13).

  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 may halt the study at any time following review of any safety concerns.

11.8.1 Reporting a Study Halt

If a halting rule is met, a description of the adverse event(s) or safety issue must be reported by the PI, within one business day, to the CSO, the IRB by fax or email.

11.8.2 Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI will determine if it is safe to resume the study.

The PI will notify the IRB of the decision on resumption of the study.

11.8.3 Discontinuation of Study Agent

Subjects who do not resume study agent will continue to be followed for safety.

11.9 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).
- Co-enrollment in a study with an investigational research agent (rare exception granted by the PI).
- Any SAE or grade 4 systemic infusion related symptom(s) or AE that is considered to be related to the study agent.
- Clinically significant type 1 hypersensitivity reaction associated with the study agent. In the event of a type 1 hypersensitivity reaction that is NOT considered to be clinically significant, (e.g., brief, mild, and self-limited skin reaction without other symptoms), the PI, in consultation with the sponsor medical monitor, may consider possible additional infusions of the study agent with appropriate precautions.
- 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
- Participant misses more than 1 study infusion
- The investigator determines that continued participation in the study would not be in the best interest of the subject.

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

11.9.1 Replacement of Withdrawn Subjects or Subjects who Discontinued Study Agent

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 its administration will be replaced up to the screening limit for the study.

11.10 Safety Oversight

11.10.1 Safety Review and Communications Plan (SRCP)

An SRCP has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the principal investigator, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

11.10.2 Sponsor Medical Monitor (SMM)

A medical monitor, representing the IND sponsor (OCRPRO), has been appointed for the safety oversight in this clinical study. The SMM will be responsible for performing safety assessments as outlined in the SRCP.

12 CLINICAL MONITORING STRUCTURE

12.1 Site Monitoring Plan

As per 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 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 principal investigator 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 STATISTICAL CONSIDERATIONS

The primary safety outcome is the occurrence of grade 3 or higher adverse events. An exact 95% confidence interval for the probability of adverse events will be computed using the Clopper-Pearson method. The primary efficacy outcome is rebound of plasma viremia requiring a restart of cART. An exact 95% confidence interval will be computed for the rebound probability using the Clopper-Pearson method. Changes from baseline in continuous measurements will be analyzed using paired t-tests or, if data are skewed, the Wilcoxon signed rank statistic.

In terms of safety, a sample size of 30 patients provides a 95.8% chance of observing an adverse event of probability 10% or greater. Table 3 shows the chance of observing at least one adverse event of given probability.

Table 3: Chance of AE of Given Probability

0.025	0.050	0.075	0.100	0.125	0.150
0.532	0.785	0.904	0.958	0.982	0.992

The second row is the probability of observing at least one adverse event of probability given in the first row.

With 30 patients, the approximate width of a 95% confidence interval for the probability of rebound is ±0.18. For example, if half of the 30 patients rebound, the approximate confidence interval will be 0.50±0.18=(0.32,0.68). Exact 95% confidence intervals for different observed numbers of rebounders among 30 patients are shown in Table 4. For example, if 10 out of 30 patients rebound, the exact 95% confidence interval for the rebound probability will be (0.173,0.528).

Table 4: Confidence Intervals For Rebound Probability

0	5	10	15	20
0-0.116	0.056-0.347	0.173-0.528	0.313-0.687	0.472-0.827

The second row gives exact 95% confidence intervals for rebound probability given the observed number of rebounders in row 1 among the 30 patients.

Futility guidelines (Table 5) are based on the numbers of patients meeting virologic criteria to restart cART within the first 12 weeks of the study. We use Bayesian methodology whereby we quantify our prior opinion about the 42 day probability with monoclonal antibodies as roughly equivalent to having observed 4 people, 2 of whom meet virologic criteria to restart cART by 12 weeks . This translates to a beta (2,2) prior distribution for p, the probability of meeting virologic critera of failure by 12 weeks. Futility is declared if the posterior probability that p exceeds 0.70, given the observed results, is 90% or greater.

Table 5: Futility Guidelines

10	12	16	19	22
10	13	18	22	26

Row 2 shows the number of patients evaluated; futility is declared if the number meeting virologic criteria to restart by 12 weeks is at least as large as the number shown in row 1. That is, the futility boundary is crossed if the first 10 patients rebound by 12 weeks, or at least 12 of the first 13 meet virologic criteria by 12 weeks or at least 16 of the first 18 rebound by 12 weeks , etc.

The probabilities of crossing this futility boundary are shown in Table 6 for different true 12 week probabilities.

Table 6: Probability of Crossing Futility Boundary

0.50	0.60	0.70	0.80	0.90
0.002	0.021	0.126	0.466	0.913

Row 2 shows the probability of crossing the futility threshold if the true 12 week rebound probability is as shown in row 1. For instance, if the true 12 week probability of having plasma viral level >5,000 is 0.50, the probability of crossing the futility boundary is only 0.002. On the other hand, if the true 12 week rebound probability is 0.90, the probability of crossing the futility boundary is 0.913.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 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 on-going 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.

14.1.1 Non-English–Speaking Participants

If a non-English speaking participant is eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English Speaking Research Participants in the participant's native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and 45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record (CRIMSON), including the name of the interpreter. Further, 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 Participants

As the majority of the patient populations from which the study participants 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 participants as consistent with NIH MAS Policy M77-2 without separate IRB approval for each specific use. At Continuing Reviews, the NIAID IRB will be informed of the number of illiterate participants who provided consent verbally.

14.2 Subject 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.

15 DATA HANDLING AND RECORD KEEPING

15.1 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.

15.2 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 two 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

OCRPRO/NIAID 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.

APPENDIX A: SCIENTIFIC REFERENCES

1. Chun TW, Fauci AS. HIV reservoirs: pathogenesis and obstacles to viral eradication and cure. AIDS. 2012;26(10):1261-8.
2. Chun TW, Stuyver L, Mizell SB, Ehler LA, Mican JA, Baseler M, et al. Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proc Natl Acad Sci U S A. 1997;94(24):13193-7.
3. Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science. 1997;278(5341):1295-300.
4. Wong JK, Hezareh M, Gunthard HF, Havlir DV, Ignacio CC, Spina CA, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. Science. 1997;278(5341):1291-5.
5. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, et al. A Blueprint for HIV Vaccine Discovery. Cell Host Microbe. 2012;12(4):396-407.
6. Fauci AS, Marston HD. Ending AIDS--is an HIV vaccine necessary N Engl J Med. 2014;370(6):495-8.
7. Moir S, Malaspina A, Fauci AS. Prospects for an HIV vaccine: leading B cells down the right path. Nat Struct Mol Biol. 2011;18(12):1317-21.
8. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature. 2011;477(7365):466-70.
9. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science. 2010;329(5993):811-7.
10. Barouch DH, Whitney JB, Moldt B, Klein F, Oliveira TY, Liu J, et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature. 2013;503(7475):224-8.
11. Klein F, Halper-Stromberg A, Horwitz JA, Gruell H, Scheid JF, Bournazos S, et al. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. Nature. 2012;492(7427):118-22.
12. Shingai M, Nishimura Y, Klein F, Mouquet H, Donau OK, Plishka R, et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. Nature. 2013;503(7475):277-80.
13. Malbec M, Porrot F, Rua R, Horwitz J, Klein F, Halper-Stromberg A, et al. Broadly neutralizing antibodies that inhibit HIV-1 cell to cell transmission. J Exp Med. 2013;210(13):2813-21.
14. Chun TW, Murray D, Justement JS, Blazkova J, Hallahan CW, Fankuchen O, et al. Broadly neutralizing antibodies suppress HIV in the persistent viral reservoir. Proc Natl Acad Sci U S A. 2014;111(36):13151-6.
15. Garcia F, Climent N, Guardo AC, Gil C, Leon A, Autran B, et al. A Dendritic Cell-Based Vaccine Elicits T Cell Responses Associated with Control of HIV-1 Replication. Sci Transl Med. 2013;5(166):166ra2.
16. Jacobson JM, Pat Bucy R, Spritzler J, Saag MS, Eron JJ, Jr., Coombs RW, et al. Evidence that intermittent structured treatment interruption, but not immunization with ALVAC-HIV vCP1452, promotes host control of HIV replication: the results of AIDS Clinical Trials Group 5068. J Infect Dis. 2006;194(5):623-32.

17. Rosenberg ES, Graham BS, Chan ES, Bosch RJ, Stocker V, Maenza J, et al. Safety and immunogenicity of therapeutic DNA vaccination in individuals treated with antiretroviral therapy during acute/early HIV-1 infection. PloS One. 2010;5(5):e10555.
18. Schooley RT, Spritzler J, Wang H, Lederman MM, Havlir D, Kuritzkes DR, et al. AIDS clinical trials group 5197: a placebo-controlled trial of immunization of HIV-1-infected persons with a replication-deficient adenovirus type 5 vaccine expressing the HIV-1 core protein. J Infect Dis. 2010;202(5):705-16.
19. Routy JP, Boulassel MR, Nicolette CA, Jacobson JM. Assessing risk of a short-term antiretroviral therapy discontinuation as a read-out of viral control in immune-based therapy. J Med Virol. 2012;84(6):885-9.
20. Davey RT, Jr., Bhat N, Yoder C, Chun TW, Metcalf JA, Dewar R, et al. HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. Proc Natl Acad Sci U S A. 1999;96(26):15109-14.
21. Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;355(22):2283-96.
22. Investigators ST, Fidler S, Porter K, Ewings F, Frater J, Ramjee G, et al. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med. 2013;368(3):207-17.

APPENDIX B: SCHEDULE OF PROCEDURES/EVALUATIONS

	Screening and Baseline		**Treatment Phase**														
Study time point	Screen	Enrollment/ Baseline	Day 3	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Repeat Visit for End ATI Criteria
ASSESSMENTS																		
H & P	X	X			X		X		X		X		X		X		X	X-PRN
HIV Counseling		X			X		X		X		X		X		X		X	
Vital Signs	X	X			X		X		X		X		X		X		X	
MEDICATIONS																		
Last Dose of cART			STOP															
Re-Start cART**																		START-PRN
Infusion		X			X		X		X		X		X		X		X	
PROCEDURES																		
EKG	X																	
Leukapheresis		X-OPT															X-OPT	
CLINICAL LABS																		
CBC/Diff	X	X					X		X		X		X		X		X	

aPTT/PT	X																	
Chemistries	X	X					X		X		X		X		X		X	
Urinalysis	X																	
Pregnancy Test***	X	X			X		X		X		X		X		X		X	
HBsAg, Anti-HCV, HCV RNA Quant	X																	
HLA Typing*		X																
RESEARCH LABS																		
ELISA/WB*	X																	
HIV-1-RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X-PRN
Flow cytometry	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X-PRN
Plasma Storage	X-PRN	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Storage	X-PRN	X					X		X		X		X		X		X	
PBMC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PBL Storage $		X															X	

* Do not repeat if previously on file
** If meets criteria for ending ATI (Section 6.3)
*** For females of childbearing potential
$ If not able to complete apheresis