PROTOCOL RV 397

Safety and Therapeutic Efficacy of the Broadly Neutralizing HIV-1 Specific Monoclonal Antibody VRC01 during Analytic Treatment Interruption in Patients who Initiated Antiretroviral Therapy During Early Acute HIV Infection

Study Agent Provided by
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Study Conducted By
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The Thai Red Cross AIDS Research Center, Bangkok, Thailand

In Collaboration with
Vaccine Research Center, NIAID, NIH

Study Sponsored By

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SCHEMA

Title

Safety and Therapeutic Efficacy of the Broadly Neutralizing HIV-1 Specific Monoclonal Antibody VRC01 during Analytic Treatment Interruption in Patients who Initiated Antiretroviral Therapy during Early Acute HIV Infection

Clinical Phase

Phase II

Study Duration

Study duration is up to 54 weeks.

Study Design

This is a placebo-controlled clinical trial of VRC01 administration and analytic treatment interruption (ATI) in adults who began antiretroviral therapy (ART) during early acute HIV infection (Fiebig stage I to III). Eligible volunteers will be randomized in a 3:1 ratio to either VRC01 or placebo, with randomization stratified by Fiebig stage. Volunteers who are receiving ART with a non-nucleoside reverse transcriptase inhibitor (NNRTI) will undergo 4 weeks of protease inhibitor (PI) substitution for their NNRTI prior to randomization. ATI will begin the day of the first dose of either VRC01 or placebo. Participants will be monitored closely for HIV viremia and other pre-defined criteria for ART resumption (see section 4.6). Administration of the study agent (VRC01) every three weeks will be discontinued after 24 weeks or if ART is resumed, whichever occurs first. Volunteers who are virally suppressed without laboratory or clinical indication for ART resumption at 24 weeks will continue intensive monitoring for ART resumption criteria for an additional 24 weeks, during which time no VRC01 or placebo will be administered.

Sample Size

Sample size is 24 participants

Participants

This study will recruit 24 adults aged 20-50 years in Bangkok, Thailand who were diagnosed during acute HIV infection (Fiebig stage I to III) and initiated on ART.

Intervention

The investigational agent, VRC-HIVMAB060-00-AB (VRC01), is a broadly neutralizing human mAb targeted against the HIV-1 CD4 binding site. It was developed by the Vaccine Research Center (VRC), National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) and manufactured for the VRC by the Vaccine Pilot Plant operated by Leidos Biomedical Research, Inc, formerly SAIC-Frederick, Inc., Frederick, MD. Vials are provided at 100 ± 10 mg/mL.

The placebo agent that will be used is normal saline (Sodium Chloride for Injection USP, 0.9%). Volunteers will receive either VRC01 or placebo administered intravenously every three weeks for a total duration of 24 weeks or until ART resumption criteria are met, whichever comes first.

Study Objectives

Primary

1. To evaluate the safety of VRC01 when administered during an ATI.
2. To evaluate the ability of VRC01 monotherapy to maintain virologic suppression at 24 weeks.

Secondary

1. To assess the impact of VRC01 on viral dynamics following ATI, including time to viral rebound and level of rebound viremia.
2. To assess the impact of VRC01 on CD4 count following ATI.
3. To assess the impact of VRC01 on HIV reservoir replenishment and expression following ATI.
4. To assess the impact of VRC01 on clinical characteristics of HIV infection following ATI.

Exploratory

1. To describe HIV-1 isolate neutralization sensitivity and genetic sequence, including sieve effect of VRC01.
2. To characterize the effect of VRC01 on host cellular and innate immune responses, including broad and HIV-specific immune responses.
3. To identify predictors of sustained virologic control, such as host genetic alleles, immune responses, and viral genetics.
4. To identify the presence or absence of anti-VRC01 antibodies after ATI and administration of VRC01.
5. To describe the impact of VRC01 on viral dynamics in multiple body compartments.
6. To assess the distribution of VRC01 into various body compartments.

LIST OF ABBREVIATIONS

TERM	DEFINITION
Ab	Antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse experience
AFRIMS	Armed Forces Research Institute of Medical Sciences
AHI	Acute HIV infection
AI	Associate Investigator
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT/AST	Alanine aminotranferase and aspartate aminotransferase liver enzymes
ART	Antiretroviral therapy
ATI	Analytic treatment interruption
BMA	Bangkok Metropolitan Authority
BRA	Behavioral risk assessment
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research (FDA)
CD4+	A functional subclass of T cells, helper T lymphocytes (Th) that are necessary for augmentation and coordination of innate and adaptive effector responses, humoral and cellular
CD8+	Cytotoxic T-Cells that destroy host cells, which have become infected by viruses or other intracellular pathogens
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CIOMS	Council of International Organization of Medical Sciences
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CSRC	Clinical Science Review Committee
CXR	Chest x-ray
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	U.S. Division of AIDS, NIAID, NIH
DCAC	Data Coordinating and Analysis Center
DNA	Deoxyribonucleic acid
DoD	United States Department of Defense
DTI	Diffusion tensor imaging
EAE	Expedited Adverse Events
EIA	Enzyme immunoassay
ELISA	Enzyme linked immunosorbent assay

ELISPOT	Enzyme-Linked Immunospot
EKG	Electocardiogram
ERC	Ethical Review Committee
FDA	U.S. Food and Drug Administration
GALT	Gut-associated lymphoid tissue
GCP	Good Clinical Practices
GCLP	Good Clinical and Laboratory Practices
GFR	Glomerular filtration rate
GLP	Good Laboratory Practices
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV and HIV-1	Human immunodeficiency virus, type 1
HLA	Human leukocyte antigen
HRPO	Human Research Protection Office, Office of Research Protection, USAMRMC
HSPB	Human Subjects Protection Branch, WRAIR
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
ICS	Intracellular cytokine staining
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous(ly)
LDL	Low-density lipoprotein
mAb	Monoclonal antibody
Mg	Milligram
MHA	Multi-region hybridization assay
MHRP	U.S. Military HIV Research Program
mL	Milliliter
Mm	Millimeter
MO	Medical Officer
MOP	Manual of Operations
MOPH	Ministry of Public Health, Royal Thai Government
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MSM	Men who have sex with men
NAAT	Nucleic acid amplification tests
Nab	Neutralizing antibody
NHP	Non-human primate

NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	“no observed adverse effect level”
NOEL	“no observed effect level”
OHRP	Office for Human Research Protection
ORP	Office of Research Protections, USAMRMC
ORTA	WRAIR Office of Research Technology and Applications
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PI	Principal investigator
PIR	post-injection reactogenicity
PK	Pharmacokinetics
PSRT	Protocol Safety Review Team
QA	Quality assurance
QVOA	Qualitative viral outgrowth assay
RAB	DAIDS Regulatory Affairs Branch
RBC	Red blood cell count
RSC	DAIDS Regulatory Support Center
SAE	Serious adverse experience
SBV	Small blood volume
SC	Subcutaneous injection
SEARCH	South East Asia Research Collaboration with Hawaii
SHIV	Simian-human immunodeficiency virus
SIV	Simian immunodeficiency virus
SOE	Schedule of Evaluations
TILDA	Tat/Rev induced limiting dilution assay
TRCAC	Thai Red Cross Anonymous Clinic
TRCARC	Thai Red Cross AIDS Research Centre
TULDA	Tat/Rev uninduced limiting dilution assay
U.S.	United States
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UPIRTSOs	Unanticipated problems related to the study and involving risk to subjects or others
USAMRMC	U.S. Army Medical Research and Materiel Command
VCT	Voluntary counseling and testing
VRC01	VRC-HIVMAB060-00-AB, a broadly neutralizing human monoclonal antibody targeted against the HIV-1 CD4 binding site
WBC	White blood cell count
WRAIR	Walter Reed Army Institute of Research

1.0 INTRODUCTION

1.1 BACKGROUND

Antiretroviral therapy (ART) is currently the cornerstone of HIV management. ART in the setting of chronic HIV reduces both morbidity and mortality [1-5]. There is a growing body of evidence that ART is also beneficial in the management of acute infection, wherein it may preserve immune function [6, 7], decrease viral evolution [8], and limit the viral reservoir [9-11]. Still, CDC estimates suggest that only 36% of persons living with HIV (PLWH) in the U.S. are currently prescribed ART and only 28% have achieved HIV suppression [12]. Barriers to the universal use of ART include the need for high-level and lifelong adherence, development of drug resistance, toxicities, and cost [13-16]. These barriers are intensified in resource-limited settings [17-19].

Treatment strategies that can confer durable virologic control and delay disease progression while minimizing ART exposure are highly desirable. Strategic interruption of ART has therefore been the focus of several large studies. In these studies involving patients chronically infected with HIV, interruption of ART was associated with worse clinical outcomes than continuous prescription of ART [20, 21]. Furthermore, peripheral blood HIV-1 RNA was seen to rapidly return to pre-ART levels upon discontinuation of therapy [21-23]. Inaccessible reservoirs of latently-infected resting memory CD4+ T cells, particularly in the gut-associated lymphoid tissue (GALT), are hypothesized to be the major source responsible for rebound viremia after discontinuation of ART [24-28].

In contrast to patients begun on ART late in the course of chronic HIV infection, some patients who begin ART at the time of acute infection demonstrate blunted or delayed rebound viremia after treatment interruption and 5-16% show sustained virologic control [9, 29-32]. Factors associated with successful virologic control include shorter duration from HIV onset to ART initiation, longer duration on ART and low peripheral blood mononuclear cell-associated HIV DNA. In the RV 254/SEARCH010 study in Thailand, early initiation of ART significantly restricted integration of HIV DNA in peripheral blood mononuclear cells, including central memory CD4+ T cells [33-35]. In this study, total HIV declines were also seen on serial sigmoid biopsies in several patients. Total blood HIV DNA at initiation of therapy predicted reservoir size after 24 weeks of aggressive ART, underscoring the importance of early initiation of ART. Prior evidence has shown that reservoir distribution in shorter-lived cells is associated with elite control status [36-38]. Patients in RV 254/SEARCH 010 demonstrated this favorable pattern of reservoir distribution. For multiple reasons, patients who have received ART early in acute HIV infection are ideal candidates for the evaluation of novel therapies that seek to achieve a functional cure of HIV.

VRC-HIVMAB060-00-AB (VRC01) is a broadly neutralizing human monoclonal antibody targeted against the HIV-1 CD4 binding site. VRC01 has shown promise in animal studies as a safe and potent therapy to both reduce HIV viremia in infected animals and prevent HIV acquisition in uninfected animals given a variety of challenges. Phase I studies have demonstrated safety in humans and elucidated pharmacokinetic parameters (see section 2.7).

This is a randomized clinical trial to explore the impact of VRC01 on both virus and host-specific parameters in adults who began ART during acute HIV infection.

2.0 STUDY AGENT

2.1 BACKGROUND

The study agent, VRC-HIVMAB060-00-AB, was manufactured for the VRC by the Vaccine Pilot Plant operated by Leidos Biomedical Research, Inc, formerly SAIC-Fredrick, Inc, Fredrick, MD. 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.

2.2 DESCRIPTION OF STUDY AGENT VRC-HIVMAB060-00-AB (VRC01)

VRC-HIVMAB060-00-AB (VRC01) is a broadly neutralizing human mAb targeted against the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH. VRC01 is of the IgG1 subtype and is highly somatically mutated from its 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 CHO cell line developed by Lonza Biologics (Slough, UK) was used to produce the VRC01 mAb. The methods by which VRC01 was isolated and produced have been described previously in detail. Briefly, PBMCs from HIV-1 infected adults stained with specific antigenic probes and passed through a flourescence activated cell sorter (FACS) through which single B lymphoctyes were isolated. Heavy and light chain variable regions of single B cell receptors were amplified by polymerase chain reaction (PCR) and sequenced. Heavy and light chains were initially expressed in an HEK 293 suspension cell culture.

The bulk lot of the mAb, however, was manufactured under cGMP using a stably transfected CHO cell line. The product was then purified and labeled at the VRC Vaccine Pilot Plant (Frederick, MD), operated by Leidos Biomedical Research, Inc., Frederick, MD.

More details on the VRC-HIVMAB060-00-AB composition and manufacturing can be found in the IB [39].

2.3 RATIONALE FOR VRC01 AS A STUDY AGENT

Administration of broadly neutralizing mAb has the potential to treat HIV infection by preventing viral spread (as with ART), and also by facilitating clearance of virus particles and mediating destruction of virus-producing cells, decreasing the viral reservoir and limiting immune activation. Several studies have demonstrated in non-human primate and humanized mouse models that therapy with broadly neutralizing monoclonal antibodies (mAbs) can control HIV viremia and reduce the HIV-1 reservoir in infected animals in the absence of ART [40-42].

The VRC, NIAID, NIH developed the VRC01 study agent. This mAb was originally discovered in a subject infected with HIV-1 for more than 15 years who maintained viral control without ART

[43]. Using novel methods to isolate and screen memory B lymphocytes from the peripheral blood mononuclear cells (PBMCs) of HIV infected donors, investigators at the VRC were able to clone out this antibody that neutralized more than 90% of genetically diverse heterologous strains of HIV-1[44]. Since the initial isolation and characterization of the VRC01 mAb, subsequent investigations on longitudinal serum samples from HIV-1 infected individuals have shown that VRC01-like epitopes are induced during HIV-1 infection in a subset of HIV-infected individuals, but may take years to develop [45].

In vitro, VRC01 demonstrates potent and broad neutralization capabilities, with a half-maximal inhibitory concentration (IC_{50}) of <50 mcg/mL against 91% of primary isolates of various HIV-1 clades and <1 mcg/mL against 72% of these HIV-1 clades [44]. Several proof-of concept studies have been conducted to determine whether the in vitro neutralization capabilities of VRC01 translate into protecting NHPs from challenge with virulent chimeric simian-human immunodeficiency virus (SHIV), which contains the HIV envelope in a simian immunodeficiency virus (SIV) background. Rhesus macaques that received a single dose of IV VRC01 at 20mg/kg were fully protected against single high-dose rectal and vaginal challenges of SHIV-SF162P3 (a CCR5 tropic strain of HIV). VRC01 at the same dose also protected infant macaques from oral SHIV challenge [39].

Additional NHP work with VRC01 is exploring the impact of the mAb on viremia and the latent reservoir in acute SHIV infection. Rhesus macaques were challenged intravenously with SHIVSF162P3 and subsequently administered a single dose of VRC01 40 mg/kg or started on a daily antiretroviral drug regimen, ten days following challenge. A control group was left untreated. Both VRC01 and ARV groups demonstrated a substantial antiviral effect compared to the control group, with reduced peak viremia [39].

2.4 PRECLINICAL GLP TOXICOLOGY STUDY

A single-dose pharmacokinetics (PK) study and repeat-dose toxicity study of IV and subcutaneous (SC) administration of VRC-HIVMAB060-00-AB (VRC01) was performed by SRI International (Menlo Park, CA) in male and female Sprague-Dawley rats according to U.S. 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 a smaller scale using a purification process similar to that of the GMP clinical-grade drug product.

For the safety assessment, vehicle control, 4 mg/kg VRC01, 40 mg/kg VRC01, and 400 mg/kg of VRC01 were administered by tail vein injection on Days 1 and 8 to Groups 1 through 4, respectively. The vehicle consisted of the VRC01 formulation buffer containing 25mM sodium citrate, 50mM sodium chloride and 150mM L-arginine-HCl at pH 5.8. 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 of each sex were sacrificed on Day 9, one day after the second administration; 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 general clinical condition, body weight, food consumption, body temperature, injection site irritation, organ weight or in hematologic or coagulation factor measurements that could be attributed to

VRC01. However, 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 by enzyme-linked immunosorbent assay (ELISA) on pre-dose samples collected from each animal. Untreated control samples were collected from and tested on an additional 3 males and 3 females. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following post-dose time points: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life ($t_{1/2}$) was about 10 days, with clearance (Cl) of approximately 20 ml/day/kg and volume of distribution (Vd) that was about 0.28 l/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly.

2.5 TISSUE CROSS-REACTIVITY GLP STUDY OF VRC01 WITH HUMAN TISSUES *IN VITRO*

A tissue cross-reactivity study of VRC-HIVMAB060-00-AB (VRC01) using normal adult and neonatal human tissues *in vitro* (Testing Facility Study No. A255-12) was performed by Charles River Laboratories (Reno, NV) in accordance with U.S. FDA "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies." The tissue panels used as the test system for this *in vitro* cross-reactivity study included all of the tissues on the "Suggested list of human tissues to be used for immunohistochemical or cytochemical investigations of cross reactivity of monoclonal antibodies" in Annex I of the "European Medicines Agency Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use (CHMP) on December 18, 2008" and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research (CBER) "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997)."

To determine the cross-reactivity of VRC01 binding, VRC01 was applied to cryosections from a full panel of tissues from normal human adults and a limited panel of human neonatal tissues, immunohistochemically detected using a biotinylated rabbit anti-human immunoglobulin G (IgG) secondary antibody and binding visualized with a streptavidin-horseradish peroxidase complex and a diaminobenzidine chromogen substrate. VRC01 binding was evaluated at concentrations of 5 and 50 mcg/mL.

Specific VRC01 staining was not observed in any normal adult human or neonatal human tissues evaluated. Therefore, *in vitro* evaluation of cross-reactivity in tissue specimens did not identify potential tissue sites or organ systems to more thoroughly evaluate in subsequent preclinical studies, thus supporting the use of VRC01 in humans.

2.6 NONHUMAN PRIMATE (NHP) STUDIES OF VRC01

Several non-GLP preclinical studies of VRC01 have been completed in nonhuman primates (NHP), suggesting potential *in vivo* efficacy of this agent in the prevention of HIV infection. Table 1 is a brief summary of the studies performed [39].

Table 1: Pre-Clinical Non-Human Primate Studies of VRC01

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	The administration of VRC01 (40 mg/kg IV) during the acute phase of infection led to a reduction of peak viremia and control of viremia during the chronic phase of infection.

2.7 PHASE 1 CLINICAL TRIALS OF VRC01

Evaluation of VRC01 as an investigational drug began in humans with the initiation of the VRC 601 study in September 2013. Initial development of VRC01 was based on an intended indication for the prevention of HIV-1 infection in infants at risk for HIV-1 infection through maternal

transmission at birth or during breastfeeding. Further evaluation of VRC01 in adults will continue towards possible therapeutic and preventive indications.

This summary represents experience in human clinical trials with VRC01 mAb from September 30, 2013 to May 22, 2014. VRC 601 and VRC 602 are Phase 1, dose-escalation studies to examine safety, tolerability, dose, and pharmacokinetics (PK) of VRC-HIVMAB060-00-AB (VRC01) when it is administered to HIV-infected and healthy adults, respectively. Both the intravenous (IV) or subcutaneous (SC) routes of administration are being evaluated. The dose groups in these studies are as shown in Table 2.

Table 2: Dose Groups in Human Clinical Trials of VRC01

Group	VRC 601	VRC 602
1	1 mg/kg IV	5 mg/kg IV
2	5 mg/kg IV	20 mg/kg IV
3	5 mg/kg SC	40 mg/kg IV
4	20 mg/kg IV	5 mg/kg or placebo SC
5	40 mg/kg IV	

Both 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 serious adverse events.

As of May 22, 2014, cumulatively, 35 subjects had begun product administration: 30 had completed a second dose; 2 had withdrawn prior to second dose and 3 remained on the schedule for a second dose. There have been no discontinuations due to an adverse event.

The 65 product administrations to date were distributed among the dose schedules as follows:

- 6 administrations at 1 mg/kg IV
- 14 administrations at 5 mg/kg IV
- 13 administrations at 20 mg/kg IV
- 10 administrations at 40 mg/kg IV
- 22 administrations at 5 mg/kg (or placebo) SC; of these, the estimate is 8 administrations in VRC 602 are placebo. The method of SC administration has been by SC infusion pump into a single site in the abdomen for 15 SC administrations and by direct needle and syringe injection divided into two sites in abdomen or thigh for 7 SC administrations.

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 [39].

2.7.1 Adverse Events

There have been no serious adverse events, safety pauses or unsolicited adverse events greater than grade 2 in severity. No systemic or local reactions have been reported during the IV infusions administered to date. No systemic reactions have been reported during SC product administration to date. The SC product administrations are sometimes associated with mild local reactions during

the infusions that may include some pruritus (itchiness), redness and swelling, which resolves within a few minutes to a few hours after the administration is completed. The largest diameter for those erythema or swelling events that were observed during infusions ranged from about 2 to 5 cm. During the period of solicited adverse events for 3 to 7 days following product administration, reported local and systemic reactions have been no more than mild in severity. All product administrations to date have been well tolerated.

2.8 SUMMARY STATEMENT ON SAFETY OF STUDY AGENT

VRC01 displays several unusual structural features. It is highly affinity-matured, has a disulfide link between complementarity-determining regions (CDR) H1 and H3 and has a glycan in the variable (V) region of the light chain [46]. Unlike some HIV-1 neutralizing antibodies, VRC01 does not have an unusually long CDR-H3 region, it is not self- or poly-reactive, and it lacks anti-phospholipid antibody activity [47]. These features suggest that VRC01 is safe for human administration.

Toxicology studies in rat models have demonstrated a "no observed adverse effect level" (NOAEL) for VRC01 by the intravenous route of administration of 400 mg/kg, the highest dose used in the study, and by the subcutaneous route of administration of 40 mg/kg, the only SC dose examined. VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life ($t_{1/2}$) was about 10 days, with clearance (Cl) of approximately 20 mL/day/kg and volume of distribution (Vd) of about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly.

Tissue cross-reactivity studies using normal adult and neonatal human tissues did not identify any potential tissue sites or organ systems that required further evaluation in preclinical studies, again suggesting that VRC01 is safe for human administration.

Phase I clinical trials are currently underway in both HIV-infected and uninfected adults. Accrual into VRC 601 was initiated in September 2013 with the first infusion at 1 mg/kg IV administered on September 30, 2013. Accrual into VRC 602 was initiated in December 2013 with the first infusion at 5 mg/kg IV administered on December 9, 2013. Both 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 serious adverse events. All IV and SC infusions have been well-tolerated with no SAEs or dose limiting toxicity.

3.0 STUDY OBJECTIVES, ENDPOINTS AND RATIONALE

3.1 STUDY OBJECTIVES

3.1.1 Primary

1. To evaluate the safety of VRC01 when administered during an ATI.
2. To evaluate the ability of VRC01 monotherapy to maintain virologic suppression at 24 weeks.

3.1.2 Secondary

1. To assess the impact of VRC01 on viral dynamics following ATI, including time to viral rebound and level of rebound viremia.
2. To assess the impact of VRC01 on CD4 count following ATI.
3. To assess the impact of VRC01 on HIV reservoir replenishment and expression following ATI.
4. To assess the impact of VRC01 on clinical characteristics of HIV infection following ATI.

3.1.3 Exploratory

1. To describe HIV-1 isolate neutralization sensitivity and genetic sequence, including sieve effect of VRC01.
2. To characterize the effect of VRC01 on host cellular and innate immune responses, including broad and HIV-specific immune responses.
3. To identify predictors of sustained virologic control, such as host genetic alleles, immune responses, and viral genetics.
4. To identify the presence or absence of anti-VRC01 antibodies after ATI and administration of VRC01.
5. To describe the impact of VRC01 on viral dynamics in multiple body compartments.
6. To assess the distribution of VRC01 into various body compartments.

3.2 STUDY ENDPOINTS

3.2.1 Primary

1. Serious adverse event at any time up to 10 weeks after the last infusion of VRC01 or placebo.
2. Sustained virologic suppression, without indication for ART resumption, at 24 weeks.

3.2.2 Secondary

1. Time to viral rebound and level of rebound viremia after cessation of ART.
2. Time to ART resumption for any reason after cessation of ART.
3. Detectable HIV RNA via single copy assay at various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.
4. CD4+ T cell count various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.
5. Cell-associated HIV RNA and DNA in the peripheral compartment various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.
6. Neuropsychological battery performance at weeks 24 and 48, as compared to baseline at week 0.
7. Control and attention testing performance at various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.
8. Frequency of hospitalization and incidence of non-AIDS related conditions.

3.2.3 Exploratory

1. Viral sequence evolution and the development of VRC01 escape mutations.
2. Neutralization sensitivity of virus isolates, including sensitivity to VRC01.
3. Measures of cellular immune responses, such as percentage of peptide specific T cell responses as measured by enzyme-linked immunospot (ELISPOT), breadth and magnitude of epitope-specific T cell responses, and polyfunctionality of cellular responses.
4. Measures of innate immune response such as natural killer cell activity.
5. HIV RNA quantification in the CSF and mucosal compartments, including single copy assays, in volunteers consenting to the necessary optional procedures.
6. Cell-associated HIV RNA and DNA in the CSF, mucosal and tissue compartments, in volunteers consenting to the necessary optional procedures.
7. Correlation of HIV RNA and DNA measurements across biologic compartments that include the peripheral blood, CSF, mucosal, and tissue compartments, in volunteers consenting to the necessary optional procedures.
8. HIV RNA and DNA in sorted memory CD4+ T cell subsets, in volunteers with sufficient PBMC collections.
9. Viral outgrowth in total CD4+ T cells and sorted memory CD4+ T cell subsets, in volunteers with sufficient PBMC collections.

10. Host genetic determinants of virologic suppression.

11. Presence of anti-VRC01 antibody.

12. Binding and neutralizing activities of elicited antibodies.

13. Biomarkers of immune activation, such as soluble markers, cellular markers, and gene expression.

14. Non-neutralizing antibody functional assays including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), antibody-dependent cell-mediated viral inhibition (ADCVI), and viral capture.

15. VRC01 levels across biologic compartments that include the CSF and mucosal secretions, in volunteers consenting to the necessary optional procedures.

3.3 HYPOTHESES

We hypothesize that patients receiving VRC01 will have a significantly higher rate of HIV viral suppression at 24 weeks following ATI as compared to patients receiving placebo.

3.4 RATIONALE FOR STUDY TIMING

This substudy of RV 254 will begin enrolling participants after the initiation of another substudy of RV 254 that also includes an analytic treatment interruption, "RV 411: Viral Suppression after Analytic Treatment Interruption in Thai Patients who Initiated Highly Active Antiretroviral Therapy during Acute HIV Infection." RV 411 may or may not be completed by the time that the currently proposed investigation begins, but early results from that study will be made available for review by the Data Safety and Monitoring Board for this study in case any new data has emerged that might impact participant safety.

The currently proposed study differs from RV 411 in that this study will recruit participants who initiated therapy during Fiebig stages I through III, whereas the previously described study only enrolls patients started on therapy during Fiebig stage I. It is not known how Fiebig stage may impact rebound viremia during ATI in these patients. Patients who start therapy during Fiebig stage I or II demonstrate lower total HIV DNA and more robust gut CD4 reconstitution than patients started on therapy later in infection [33]. However, patients who start therapy during Fiebig stage III have mounted HIV-specific immune responses that are not detectable in patients started at earlier stages of infection [48, 49].

RV 411 is designed with 85% power to detect a rate of sustained virologic control of 30%, so there is a 15% chance of missing a true rate of 30%. There is an even greater chance of missing a true rate that is greater than 0 but less than 30%. Whatever success rate is observed in RV 411 cannot be assumed to apply across Fiebig stages. The results of the currently proposed study will remain relevant regardless of the outcome of RV 411, although amendments to this protocol may be considered based on early results from that study.

3.5 RATIONALE FOR INCLUSION OF PLACEBO ARM

Since little is known about the clinical course of HIV during ATI in patients who were started on antiretroviral therapy during early acute infection, it is essential that a placebo arm be included as an appropriate comparator group in order to characterize the impact of VRC01 administration. No existing cohort of patients could serve this purpose.

Subjects enrolled in this study have received ART during acute HIV infection and have achieved an undetectable integrated HIV DNA. Therefore, these participants have a likelihood of achieving virologic control during treatment interruption even without any specific intervention [32]. Inclusion of the placebo control group is essential to assess whether any observed sustained virologic control might be due to VRC01. Since differences in HIV-specific immune responses among patients started on ART during different Fiebig stages may influence the endpoint of sustained virologic control, it is important that the comparator group in this study include the same spectrum of Fiebig stages (I-III) that is represented in the VRC01 arm [48, 49]. RV 411 may not run contemporaneously with this study and enrolls only participants started on ART during Fiebig stage I. Therefore, participants in RV 411 cannot serve as a control group for this study. Participants in this study, including those randomly assigned to the placebo arm, will be monitored closely for clinical and laboratory indications to resume ART. These criteria are designed to protect the subjects from any possible clinical, immunological, or virological adverse effects of study participation while maintaining the scientific validity of study.

4.0 STUDY DESIGN AND POPULATION

4.1 GENERAL DESIGN

This is a placebo-controlled clinical trial of VRC01 administration and ATI in adults who began ART during early acute HIV infection (Fiebig stage I to III). Eligible volunteers will be randomized in a 3:1 ratio to either VRC01 or placebo. Participants will undergo randomization stratified by Fiebig stage. Volunteers who are receiving ART with an NNRTI will undergo 4 weeks of PI substitution prior to randomization. ATI will begin the day of the first dose of either VRC01 or placebo. Participants will be monitored closely for HIV viremia and other pre-defined criteria for ART resumption (see section 4.6). Administration of the study agent (VRC01) every 3 weeks will be discontinued after 24 weeks or at the time ART resumed, whichever occurs first. Volunteers who are virally suppressed without laboratory or clinical indication for ART resumption at 24 weeks will continue intensive monitoring for ART resumption criteria for an additional 24 weeks, during which time no VRC01 or placebo will be administered. Clinical study visits will take place at the Thai Red Cross AIDS Research Centre, and the optional procedures may occur at the King Chulalongkorn Memorial Hospital.

4.2 PARTICIPANTS

This study will recruit 24 adults aged 20-50 years who were diagnosed during acute HIV infection (Fiebig stage I to III) and initiated on ART in Bangkok, Thailand. Participants will be recruited from protocol RV 254 (SEARCH 010, WRAIR 1494). This ongoing parent study cohort enrolls participants with documented acute HIV infection at the Thai Red Cross AIDS Research Center in Bangkok, Thailand. All participants in RV 254 are offered ART at the time of enrollment through a separately funded protocol.

4.3 PROTEASE INHIBITOR SUBSTITUTION

Subjects prescribed an ART regimen that contains a non-nucleoside reverse transcriptase inhibitor (NNRTI) at study enrollment will be switched to a regimen that replaces the NNRTI with a protease inhibitor (PI) such as lopinavir/ritonavir, atazanavir/ritonavir, or darunavir/ritonavir for four weeks prior to ATI. This will minimize the risk of developing NNRTI resistance mutations. Post-hoc analysis of the SMART trial suggests that this strategy is associated with the lowest risk for the development of drug resistance mutations as compared to staggered interruption or simultaneous discontinuation of all antiretroviral agents. None of the 13 volunteers in the SMART study who replaced efavirenz with a protease inhibitor prior to treatment interruption developed NNRTI resistance mutations [50]. Subjects on other ART regimens that do not contain an NNRTI will continue their usual regimen until ATI.

Data from Thai children enrolled in the PENTA 11 trial showed that the majority of children had no efavirenz level detected by day 14 after cessation and none developed NNRTI resistance mutations [51]. Since a small minority did demonstrate detectable NNRTI plasma levels at the 14-day mark, this study will conservatively extend the period off NNRTIs to 28 days prior to ATI and administration of VRC01 or placebo. Since pharmacokinetic parameters of NNRTIs in this population in the setting of PI co-administration are not clearly defined, plasma NNRTI level will be monitored at the time of NNRTI discontinuation, and 2 and 4 weeks following discontinuation.

Results of this testing will be available within 2-3 weeks and will be evaluated in aggregate as they become available. The study protocol may be modified based on these results if needed for patient safety. If rebound viremia occurs in any patient, the investigators will perform resistance testing at the time of ART resumption. The results will be available in 7 days, and results will be made available to the treating physician for treatment modification considerations.

4.4 INTERVENTION

4.4.1 Study Agent

VRC-HIVMAB01060-00-AB (VRC01) is a monoclonal antibody directed towards the site of CD4 attachment on the HIV-1 gp120 envelope (Env) glycoprotein. Vials contain an isotonic, sterile solution that is a colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. 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 do not contain a preservative. Vials with visible particles at the end of the thaw procedure should not be used for infusion.

VRC01 will be administered at a dose of 40 mg/kg intravenously every three weeks to participants assigned to the intervention arm of the trial for a total duration of 24 weeks or until ART resumption criteria are met, whichever comes first.

The first dose of VRC01 will be administered on the same day that ART is interrupted. In the simian model, VRC01 administered intravenously achieved peak serum levels within one hour of infusion and was slowly metabolized with an average half-life of 7.61 days. All animals had detectable VRC01 levels 28 days after infusion. Preliminary human data suggest a mean half-life of 13.6 days (range 6.76-21.3 days). These pharmacokinetic parameters suggest that serum levels will remain above the target level of >50 micrograms/mL throughout the dosing interval. Furthermore, the evidence suggests that the mAb will be well-distributed by the expected time of highest risk for rebound viremia at 2-6 weeks after treatment interruption [31, 52]. The second infusion of VRC01 will occur at the midpoint of this highest risk period.

4.4.2 Placebo

Normal saline (Sodium Chloride for Injection USP, 0.9%) will be administered intravenously every three weeks to participants assigned to the placebo arm of the trial for a total duration of 24 weeks or until ART resumption criteria are met, whichever comes first.

4.5 ANALYTIC TREATMENT INTERRUPTION (ATI)

Analytic treatment interruption will begin on the day of administration of the first dose of either VRC01 or placebo. During the ATI, participants will be monitored closely for clinical and laboratory indications to resume ART (see Section 4.6). These criteria are designed to protect the subjects from clinical, immunological, or virological adverse effects during the ATI.

Because several vaccinations have been associated with induction of HIV-1 replication in the absence of ART [53-59], participants will be counseled to avoid non-essential vaccination during

the period of ATI and any essential vaccinations, such as seasonal influenza, will be administered outside of weeks 2-6 and 26-30, when the risk of rebound viremia is considered to be highest (2-6 weeks after stopping ART and 2-6 weeks after plasma VRC01 is expected to drop below therapeutic levels). Volunteers are generally expected to have received routine vaccinations against viral hepatitis through their prior participation in the RV 254 cohort.

Prior data from RV 254 demonstrated that Fiebig I patients in the cohort had a median (range) HIV-1 RNA of 4.8 (2.8-5.7) $\log_{10}$copies/mL, at a median (range) of 12 (4-40) days after exposure to HIV, prior to initiation of antiretroviral therapy (ART) and have therefore already been exposed to high levels of plasma virus during acute infection [60]. Despite this previous exposure, our data to this point indicate that these patients have very small or no HIV viral reservoirs, as assessed by integrated HIV DNA levels in PBMCs, CD4+ T cells, and CD8+ T cells. In the proposed protocol, participants will have very frequent monitoring for viral rebound; detection of HIV viremia via qualitative or quantitative assessments will prompt repeat testing via PCR every three days until either (1) the PCR reverts to undetectable or (2) criteria for resumption of ART are met. ART may be resumed for multiple reasons, including a swift rise in HIV-1 RNA of ≥ 0.5 $\log_{10}$copies/ml per day provided that the last HIV-1 RNA is above 1000 copies/mL or a sustained HIV-1 RNA above 1,000 copies/mL for a period of 3 days or more (see Section 4.6 for a full list of criteria for resumption of ART). This level of viremia is lower than that already experienced by virtually all subjects in the cohort. Therefore, we believe that the protocol poses little additional risk for establishment or increase of an HIV reservoir in these subjects. The HIV reservoir will be measured both before treatment interruption (in this protocol) and after ART resumption (in RV 412).

Prior investigation of subjects undergoing ATI has shown that some may develop similar transient viremias <1,000 copies/mL and that these reversible viremias do not always indicate viral rebound [32]. In the setting of acute HIV infection, this low-level viremia is associated with Fiebig stage I, which appears to have little or no impact on the HIV reservoir. We have previously demonstrated that even patients started on therapy at Fiebig stage III, with much higher viral loads (median 5.9, IQR 5.6-6.9 $\log_{10}$copies/ml), have comparable virologic and reservoir outcomes as patients started at lower viral loads associated with Fiebig stage I after 48 weeks of ART.

The viral load threshold selected as an indication for ART resumption in this protocol is an evidence-based threshold chosen to maximize study subject safety while also providing subjects an opportunity to demonstrate subsequent virologic control. Additional virologic, CD4 and clinical criteria for ART resumption are included to further enhance participants' safety.

4.6 CRITERIA FOR RESUMPTION OF ART

ART will be resumed in study participants demonstrating any one of the following criteria during ATI:

- HIV-1 RNA above 1,000 copies/mL on 2 consecutive determinations at least 3 days apart.
- HIV-1 RNA rise of ≥ 0.5 $\log_{10}$copies/ml per day provided that the last HIV-1 RNA is above 1000 copies/mL.

- A single HIV-1 RNA above 10,000 copies/mL.
- CD4+ T-cell counts below 350 cells/mm^3 on 2 consecutive determinations at least 2 weeks apart.
- CD4+ T-cell count decline of > 50% from baseline prior to ATI.
- Clinical progression to CDC Category B or C disease.
- Diagnosis of acute retroviral syndrome (ARS) (Appendix I).
- Pregnancy.
- Participant request for re-initiation of ART.

If new information becomes available during the course of the study suggesting that additional ART resumption criteria should be employed or that earlier resumption of ART may be beneficial to volunteers, the protocol and guidance for study participants will be modified to reflect this.

HIV-1 RNA will be measured frequently throughout the study period, including twice weekly assessments during weeks 2-6 and 26-30. HIV-1 RNA will be measured either quantitatively using a venous blood sample (3mL) or qualitatively using a small blood volume collection (0.6mL). The latter may be performed either via finger stick or venous sampling.

4.7 MANAGEMENT OF SUBJECTS AFTER COMPLETION OF PROTOCOL

Due to the exploratory nature and unknown risks of ATI, an individualized treatment plan will be developed on exit from the study for all subjects, regardless of the reason or reasons for exiting the study. The treatment plan will be developed by the study physician in consultation with the subject and any other physicians involved in the subject's medical care. Treatment plans will take account of the subject's specific medical needs, as well as their status at the end of study participation.

4.8 MANAGEMENT OF SUBJECTS AFTER RESUMPTION OF ART

If the decision is made to reinitiate ART for any reason, then procedures scheduled for study end at week 48 will instead be conducted at the study visit before ART resumption. If this occurs within 10 weeks of a volunteer's last infusion of VRC01, that volunteer will continue to be followed for safety evaluations only under this protocol until 10 weeks after the last infusion of VRC01 and will be offered co-enrollment in RV 412: Safety and Virologic Outcomes after Analytic Treatment Interruption in Thai Patients who Initiated Antiretroviral Therapy During Early Acute HIV Infection. Evaluations that are listed under both protocols will not be duplicated in volunteers who are co-enrolled. Volunteers who have met criteria for resumption of ART more than 10 weeks after their last infusion of VRC01 will no longer be considered enrolled in this protocol and will be offered enrollment in RV 412. Volunteers who have met the criteria for resumption of ART under

this protocol will resume ART at the time of enrollment or co-enrollment in RV 412 and will be monitored closely for viral suppression. If ART is reinitiated due to rebound viremia with peripheral HIV-1 RNA sufficient to allow amplification, then HIV genotype testing will be performed at the time of ART resumption. The results of genotype testing will be available in seven days and may be used to guide ART selection. The final regimen will be determined by discussion between the subject and the study physician. ART is available through the Thai national treatment program or through co-enrolled research protocols.

In RV 412, volunteers will undergo quantitative HIV-1 RNA testing every two weeks for the first four weeks and then every four weeks for up to 48 weeks. Safety monitoring to include CD4/CD8 counts, complete blood counts, renal function testing, liver function testing, lipid profile, and urine pregnancy testing will also be performed routinely. Participation in RV 412 will end when volunteers demonstrate two consecutive HIV-1 RNA measurements <50 copies/mL or when 48 weeks of follow-up has been completed, after which time volunteers will return to routine follow-up in the parent RV 254 cohort every 12 weeks and as needed.

4.9 MANAGEMENT OF SUBJECTS WITH SUSTAINED VIROLOGIC CONTROL AT END OF STUDY

Volunteers who demonstrate sustained virologic control at the end of this study will be offered enrollment in RV 412 for continued observation. This continued monitoring will help to ensure the safety of study participants and will also allow further assessment of host and virus parameters that can improve our understanding of HIV pathogenesis and inform future efforts to achieve a functional cure of HIV. For volunteers not on ART, the RV 412 protocol includes HIV-1 RNA testing every two weeks for 12 weeks, every 4 weeks for the subsequent 28 weeks, and every 8 weeks for the remaining 56 weeks for a total of 96 weeks of aggressive monitoring off of ART. Volunteers who meet criteria for resumption of ART (which are the same in RV 412 as in RV 397) at any time will be offered therapy using either the subject's last known ART regimen or another empiric regimen as determined by discussion with the subject's medical provider. Patient preference will always be considered an indication to resume ART. If peripheral HIV-1 RNA is sufficient to allow amplification at the time of ART resumption, an HIV genotype will be checked. Results of genotype testing will be available in seven days and will inform any potential adjustment to the ART regimen. Volunteers who complete 96 weeks of observation without an indication for ART will return to routine follow-up every 12 weeks in the parent RV 254 cohort.

4.10 MANAGEMENT OF SUBJECTS WHO BECOME PREGNANT

Volunteers who become pregnant during the study period will complete all procedures scheduled for study end at the time the pregnancy is diagnosed. If the volunteer was scheduled to receive infusions of VRC01 or placebo, these will not be administered after pregnancy has been diagnosed. Procedures scheduled for study end at week 48 will instead be conducted at the visit at which pregnancy is diagnosed or immediately following the diagnosis (if diagnosed outside the study). If pregnancy occurs within 10 weeks of a volunteer's last infusion of VRC01, that volunteer will continue to be followed for safety evaluations only under this protocol until 10 weeks after the last infusion of VRC01. All pregnant volunteers will be offered enrollment or co-enrollment in RV 412 for continued observation and initiation of ART. Evaluations that are listed under both

protocols will not be duplicated in volunteers who are co-enrolled. Participation in RV 412 will require separate informed consent. If the volunteer completes participation in RV 412 before the pregnancy is completed, she will subsequently return to the RV 254 parent study. Pregnant volunteers will also be enrolled in the antiretroviral pregnancy registry (http://www.apregistry.com/who.htm).

The site PI or designated associate investigator will be responsible for reporting any pregnancy to the PSRT. This information will be reviewed by the PSRT weekly in aggregate with other safety data. The PSRT will forward notification as necessary to IRBs, study sponsors, and regulatory agencies.

Pregnancy outcomes will be recorded via a standardized case report form. Information documented on this form will include date of last menstrual period, date pregnancy confirmed, history of complications during prior pregnancies (such as congenital abnormalities or spontaneous abortions), and the outcome of the pregnancy including date of termination or delivery, any complications of pregnancy, and the status of the child. A separate case report form will be completed for the delivered child to document date of delivery, gender, weight, presence of any congenital abnormalities, APGAR score, HIV status, and any other complication of delivery.

5.0 STUDY PROCEDURES

5.1 ELIGIBILITY

5.1.1 Inclusion Criteria

1. Able and willing to provide written informed consent or, in the case of illiteracy, witnessed verbal informed consent with documentation of a thumbprint in lieu of a signature.
2. Passes Test of Understanding
3. Man or woman aged 20-50 years.
4. Initiated on ART during acute HIV infection (Fiebig Stage I to III at RV 254 enrollment).
5. Prescribed ART for at least 24 months prior to enrollment.
6. HIV-1 RNA < 50 copies/mL on at least three consecutive measurements within the past 12 months.
7. Integrated HIV DNA in PBMCs below the level of detection (1 copy/10^5 PBMCs) within 6 months prior to enrollment.
8. Last documented peripheral blood CD4 >400 cells/mm^3 within 3 months prior to enrollment.
9. No HIV-related or AIDS-defining illness within 6 months prior to enrollment.
10. In general, good health
11. Able to participate in study visits.

Female-specific Criteria:

12. Agrees not to become pregnant from the time of study enrollment until the last study visit. If a woman is sexually active and has no history of hysterectomy or tubal ligation or menopause, she must agree to use a prescription birth control method or a barrier birth control method.
13. Negative β-HCG (human chorionic gonadotropin) pregnancy test (urine or serum) on day of enrollment for any women unless she is post-menopause for 24 consecutive months or has undergone a surgical procedure that precludes pregnancy

5.1.2 Exclusion Criteria

1. Previous receipt of humanized or human monoclonal antibody whether licensed or investigational.
2. Ongoing AIDS-related opportunistic infection (including oral thrush).
3. Active injection drug use within previous 12 months.
4. History of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis in the 2 years prior to enrollment.

5. History of chronic urticaria requiring daily treatment.
6. Physical finding on examination considered indicative of significant disease such as murmur (other than functional), hepatosplenomegaly, or focal neurologic deficit.
7. Hypertension that is not well controlled by medication.
8. Hepatitis B surface antigen positive at any time in the past.
9. Hepatitis C antibody positive at any time in the past.
10. Untreated syphilis
11. Estimated GFR < 50 ml/min within the past 90 days.
12. Pregnant or breast-feeding.
13. Receipt of licensed vaccine or other investigational study agent within 28 days prior to enrollment or past participation in an investigational HIV vaccine study with receipt of active product.
14. Current or planned participation in another interventional clinical trial during the study period.
15. Chronic or recurrent use of medications that modify host immune response, e.g., oral or parenteral steroids, cancer chemotherapy.
16. Any other chronic or clinically significant medical condition that in the opinion of investigator would jeopardize the safety or rights of the volunteer. Including, but not limited to: diabetes mellitus type I, chronic hepatitis, renal failure; OR clinically significant forms of: drug or alcohol abuse, mental illness, severe asthma, autoimmune disease, psychiatric disorders, heart disease, or cancer.
17. Study site employee.

5.2 RATIONALE FOR ELIGIBILITY CRITERIA

Eligibility criteria for this study largely reflect criteria already being used for enrollment in the ongoing prospective cohort study of Thai patients with acute HIV infection, RV 254, also being conducted at the Thai Red Cross AIDS Research Center in Bangkok, Thailand.

These criteria were selected to ensure that participants enrolled in the study satisfy the demographic characteristics of the study's target population, demonstrate laboratory characteristics suggesting a high likelihood of achieving the study endpoint of sustained HIV suppression at 24 weeks after ATI, and lack clinical or laboratory indicators that might suggest a heightened risk of adverse outcome as a result of study participation.

These eligibility criteria ensure that participants in this study have demonstrated sustained HIV suppression below the limit of detection by conventional clinical assays for HIV RNA via PCR (<50 copies/mL) and are immunologically intact according to both CD4 and clinical criteria. Furthermore, participants must demonstrate undetectable HIV DNA in peripheral blood mononuclear cells (PBMCs) within 6 months of enrollment. Integrated HIV DNA in PBMCs is thought to be the most relevant measure of the size of the latent and inducible HIV reservoir, since non-integrated HIV DNA molecules are unlikely to produce viral particles upon stimulation [61,

62]. Importantly, the measurement of integrated HIV DNA in PBMCs is the only assay that correlates with the Quantitative Viral Outgrowth Assay (QVOA) [63]. Quantifications of integrated DNA in PBMCs from RV 254 subjects treated during Fiebig I to III indicate that almost all subjects display undetectable levels of integrated HIV DNA by week 24 of ART. As a marker of little or no inducible HIV reservoir, an undetectable HIV DNA suggests that a volunteer may be a good candidate for achieving the primary study endpoint. If sustained HIV suppression is not achieved and rebound viremia does occur, the proposed research includes processes for intensive monitoring and resumption of ART via a companion study (RV 412). These processes are designed to prevent full evolution of acute viremia. Even at Fiebig stage III, we have previously shown that reservoir status can be restored to that seen at Fiebig stage I with 48 weeks of ART.

Participants are excluded from this study for reasons that would interfere with the safety or feasibility of adhering to the study protocol. Pregnancy is considered an exclusion criterion for multiple reasons, including lack of data on the safety and pharmacokinetics of VRC01. Furthermore, pregnancy is considered an indication for ART in HIV-positive women. Women of child-bearing potential who enroll in this study will be required to use contraception during the entirety of the study, including the 24 weeks during which VRC01 or placebo is administered and the subsequent 24 weeks of observation off all therapy for HIV. The mean half-life of intravenous VRC01 in human studies is 13.6 days with a range of 6.76 to 21.3 days. The requirement for contraceptive use minimizes the risk for potential harm to study participants or the fetus due to either VRC01 administration or transient HIV viremia.

5.3 SCHEDULE OF EVALUATIONS

5.3.1 Week -6

All screening, enrollment, and consent procedures will be completed, including screening laboratory and clinical evaluations.

5.3.2 Week -4

Subjects prescribed an ART regimen that contains an NNRTI drug will be switched to a regimen that substitutes a boosted PI for the NNRTI. Subjects on other ART regimens that do not contain an NNRTI will continue their usual ART medications until ATI at week 0.

5.3.3 Week 0

Subjects will be randomized in a 3:1 ratio to receive an intravenous infusion of either VRC01 or placebo, with randomization stratified by Fiebig stage. All women of child-bearing potential will need to have a negative pregnancy test prior to the infusion. All antiretroviral medications will be stopped. Baseline laboratory studies (fasted blood collection) for safety parameters will be performed.

5.3.4 Weeks 1-24

Subjects will continue to receive intravenous infusions of either VRC01 or placebo every three weeks until week 24 or until criteria for resumption of ART are met. Women of child-bearing potential will have a negative pregnancy test result prior to each infusion of study drug. Subjects will be observed for 1 hours after receiving intravenous infusions. Clinical and laboratory monitoring will follow the schedule in Appendix II, which includes qualitative or quantitative assessments for HIV-1 RNA weekly until week 2, then twice weekly until week 6, and then HIV-1 RNA testing via quantitative or qualitative assessments weekly until resumption of ART or the end of this study period. Willing participants may continue twice weekly assessments for HIV-1 RNA during this period, though this will not be required. Any positive qualitative assessment for HIV-1 RNA will be immediately followed by quantitative HIV-1 RNA testing via PCR. Any positive HIV-1 RNA PCR will prompt repeat testing via PCR every three days until either (1) the PCR reverts to undetectable or (2) criteria for resumption of ART are met, as described in Section 4.6. In subjects who meet criteria for resumption of ART, the study visit prior to resumption of ART will be considered the final study visit and will follow the data and specimen collection schedule for end of study. ART blood levels may be checked during this period at investigator discretion in order to monitor for surreptitious ART use.

5.3.5 Weeks 25-47

Subjects will no longer receive intravenous infusions of VRC01 or placebo. Subjects who are virally suppressed and without clinical or laboratory indication for resumption of ART will continue laboratory monitoring every week until week 26, then twice weekly until week 30, then weekly until week 32, then every 2 weeks until end of study, as described in the SOE. Willing participants may continue twice weekly assessments for HIV-1 RNA during this period, though this will not be required. To reduce participants' discomfort due to frequent assessments, qualitative HIV-1 RNA (Aptima) may be performed using small blood volume collection via finger stick or venous sampling, which has a lower bound 95% confidence interval that exceeds 95% detection at 30 copies/mL. ART blood levels may be checked during this period at investigator discretion in order to monitor for surreptitious ART use.

5.3.6 Week 48/End of Study

Subjects will undergo final clinical and laboratory evaluation as described in the SOE (Appendix II). The procedures for week 48 will be performed earlier in the event that study participation ends early due to resumption of ART. After completing this study, the participants will be offered enrollment into the RV412 substudy of RV254 for close monitoring during either resumption of ART or continued treatment interruption. Participants will also continue to be enrolled in RV254, where a maximum follow-up time of eight years is anticipated.

5.4 MANAGEMENT OF INDIVIDUAL RESEARCH RESULTS

Results of clinical testing (CD4, HIV RNA, safety tests) will be placed in the patient medical record and will be available to both the treating physicians and to study participants. For other incidental findings of known clinical significance but not related to participation in the study, research physicians will refer the subject to the appropriate facility for treatment and will ensure

that the subject receives appropriate care. National health insurance programs cover all Thai people and include treatment for any HIV-related events. No human leukocyte antigen (HLA) testing will be performed as part of this study.

Research testing results for which clinical significance is unknown will not be shared with study participants. In this study, such tests include but are not limited to, integrated HIV DNA, total HIV DNA, 2LTR circles, qualitative viral outgrowth assay (QVOA), Tat/Rev Induced Limiting Dilution Assay (TILDA), and TULDA.

5.5 NEUROPSYCHOLOGICAL TESTING

Visits at week 0, 24, and 48/End of Study, testing conducted at TRCARC will include neuropsychological (NP) testing consisting of a set of memory and thinking tests, questions about mood, and questions about ability to function in day-to-day activities. Volunteers will be asked to remember things, do easy tasks as fast as possible (such as put pegs in holes), and draw objects. Mood and anxiety measures are necessary for the accurate interpretation of the neuropsychological measures and will be captured as covariates, as will information about recentsleep patterns and use of intoxicants. We will also capture a brief assessment of quality of life and stress as it may be impacted by treatment.

A trained psychometrist completes this cognitive testing using a modification of published international neuropsychological battery [64]. For this study a brief NP battery will be used, Non-Dominant Hand Grooved Pegboard Test, Trails A Test, and Color Trails 1 and 2. To assess stress and depression the following tools will be used: the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire-9 (PHQ-9), the World Health Organization-Quality of Life (WHO-QOL), and the Distress Thermometer.

5.6 CONTROL AND ATTENTION TESTING

The Control and Attention task (i.e., Flanker Task) is a computerized test of cognition developed and managed by the National Institutes of Health. The test requires the participant to focus on a stimulus presented on a computer screen while inhibiting attention to arrows adjacent to the stimulus (the flankers). On some trials the middle stimulus points in the same direction as the flanker and on other trials the middle stimulus points in the opposite direction. The test is scored based on a combination of accuracy and reaction time. The test requires approximately 3 minutes to complete. It is a valid and reliable measure of attention and mental control across a broad age range. This will be performed upon enrollment and repeated at weeks 0, 1, 4, 12, 24, and 48/EOS.

5.7 THERAPEUTIC DRUG MONITORING

For patients on NNRTI prior to ATI, substitution of the NNRTI with a PI drug will be done at week -4 in order to minimize the possibility of developing resistance to the NNRTI during ATI. Plasma drug levels of the NNRTI will be tested at weeks -4, - 2, and 0 to assess the pharmacodynamics effects of this schedule.

Plasma drug levels of NNRTI and/or other antiretroviral medications will be checked on all subjects who are virologically suppressed at week 24 in order to monitor for possible ART use. ART blood levels may be performed at other time points at investigator discretion.

5.8 OPTIONAL PROCEDURES

Volunteers will have the option of participating in separately consented collections and procedures to characterize the impact of VRC01 in addition to early ART on the HIV-1 reservoir and pathogenesis. These will be offered to volunteers at the discretion of investigators at specific timepoints as described in the SOE (Appendix II).

Little is known about the distribution of VRC01 in body tissues. Among other things, these optional procedures will include assessments of penetration into some body compartments, such as the cerebrospinal fluid. The observation that peak serum levels of VRC01 are followed by a decline over several hours suggests that equilibrium across body compartments occurs quickly. It is possible, however, that VRC01 will not distribute uniformly into all body compartments and potential HIV reservoir sites. Similarly, various antiretroviral drugs have differing penetration into body sites, such as the gut associated lymphoid tissue, lymph nodes, and central nervous system [65-68]. The clinical relevance of distribution into these sites is uncertain, but may theoretically contribute to HIV persistence despite ART, rebound after ART, and even selection of resistance [69].

5.8.1 Genital Secretion Collection

Genital secretion collection will be performed on a subset of consenting individuals. Consenting women will be instructed on how to use a Softcup device to collect cervical and vaginal secretions. The cup will remain in place for 4 -12 hours. Pregnant women and those with a history of toxic shock syndrome will be excluded. Collection will not take place if the woman is menstruating or has symptoms of active inflammation or infection of the vagina or cervix. Date of last menstrual period will be recorded at each collection visit and blood samples for hormone levels will be drawn. If, during the course of the study, a woman becomes pregnant, she will be excluded from further genital secretion collections.

Consenting men will be asked to ejaculate into a sterile container. Additionally, rectal sponge secretions will be collected from volunteers who are men who have sex with men. Semen and rectal sponge collections will be deferred from men if there are signs or symptoms of urethral or perianal inflammation, respectively. The anal rectal sponge used for this procedure is the Medtronic Merocel sponge, which is approved for use in nasal and ear packing and as an ear wick. According to the package insert, the product is “non-toxic and is considered safe to pass once it is completely in the alimentary tract.” There is no maximum time for product insertion. In this study, the Merocel sponge is used only as a specimen collection tool for rectal secretions, will be inserted and removed by trained medical staff, and will be placed in the rectum for a maximum of 5 minutes. For all genital secretion specimen collections, volunteers are requested to refrain from sexual intercourse or insertion of foreign objects into the vagina or rectum for 3 days and, for semen collection, to refrain from ejaculation for 48 hours prior to specimen collection. Examination and specimen collections take up to 30 minutes to complete.

Genital secretion samples will be assayed for HIV RNA PCR using the Roche Amplicor® 2.0 kit or other nucleic acid amplification method. Left over samples will be stored at –80˚C and will be used to isolate and sequence HIV, to assay cytokines and inflammatory markers, and to detect sexually transmitted infections. Other HIV-specific immune responses may also be evaluated.

5.8.2 Colon Biopsy

Colon biopsy will also be performed on a subset of consenting individuals. Sigmoidoscopy will be performed by a gastroenterologist at King Chulalongkorn Memorial Hospital following standard procedures. The procedure lasts about 90 minutes, including preparation just prior to the procedure. In addition, observation and recovery from the procedure take approximately 3 hours. Biopsy specimens will be cryo-preserved for reservoir and transcriptional analysis and immunohistochemistry and collected in RPMI medium 1640 (Invitrogen) for flow cytometric analysis.

As HIV preferentially infects the gut, the infection density in the gut is usually higher than in the peripheral blood and this tissue infection may be responsible for viral rebound when ART is interrupted [26, 27]. In addition, the majority of CD4+ T cells resides in the gut and may play a critical role in anti-HIV defense following ATI. Therefore, it is critical to characterize the HIV-specific immune responses and reservoir in the gut before and after ATI, as well as to characterize the influence of VRC01 on these parameters.

5.8.3 Inguinal Lymph Node Biopsy

Inguinal lymph node biopsy will be performed at King Chulalongkorn Memorial Hospital by a qualified surgeon. The procedure itself will be performed under local anesthesia and last approximately 30-40 minutes, however, subjects will also be asked to rest under observation for approximately another 4 hours. An inguinal lymph node will be removed via a surgical incision and divided to be sent for immuno-fluorescence confocal microscopy, flow cytometry, gene expression/whole transcriptome analysis and, if sufficient, cytokine production assays. Other HIV-specific immune responses may also be evaluated. Subjects agreeing to inguinal lymph node biopsy may be asked to undergo photography of the biopsy wound immediately after the procedure and again six months later in order to provide an objective reference for assessment of wound healing and for possible use as volunteers' educational material. Subjects are free to refuse photography of their wound at any point should they not be amenable for any reason.

Similar to the gut, HIV preferentially infects cells in the lymph nodes in acute HIV infection and destroys lymph node architecture leading to fibrosis and CD4+ T cell loss [70, 71]. The function of T follicular helper cells is negatively affected by HIV and results in dysfunctional humoral immune responses against HIV [72]. In treated chronic HIV infection, the lymph nodes continue to harbor latently infected cells despite prolong periods of viral suppression, and contribute to the rapid return of viremia if ART is interrupted [73]. It will therefore be critical to understand the reservoir characteristics and the HIV-specific immune responses before and after ATI, as well as to characterize the influence of VRC01 on these parameters. Such investigations may allow for the identification of correlates to viremic control post ATI.

5.8.4 Leukapheresis

Leukapheresis also requires separate consent. At specific study visits identified in the SOE, volunteers will have the option of undergoing apheresis in lieu of peripheral blood phlebotomy to collect PBMC and plasma. Each occurrence of this procedure is associated with a maximum blood loss of 50 mL.

Leukapheresis will be performed in the Blood Bank Unit at King Chulalongkorn Memorial Hospital, and procedures will be scheduled by study staff according to the SOE. Leukocytes and plasma for *in vitro* investigation will be obtained using automated apheresis techniques conducted by a qualified apheresis nurse/technician. During apheresis, whole blood is withdrawn through a catheter placed in an antecubital vein and channeled into a cell separator where cellular and plasma fractions are separated by centrifugation. The component to be harvested, e.g. leukocytes, is directed into a collection bag and the red cells, platelets, and plasma are returned to the donor. The return is accomplished through a second needle placed at another site, usually in the other antecubital vein. The cells collected will allow for detailed examination of the HIV reservoir including QVOA and HIV-specific immune responses.

5.8.5 Lumbar Puncture

Lumbar puncture for CSF collection (20ml) will be done at the TRCARC by the study investigator or other trained personnel in volunteers who give consent for this procedure regardless of neurological symptoms, provided that the procedure is deemed safe by the study investigator or other qualified study physician. Procedures will be performed according to the SOE. CSF will be assayed for HIV RNA PCR using the Roche Amplicor® 2.0 kit or another nucleic acid amplification method. CSF cell count, glucose and protein quantification will be performed. Left over CSF will be spun and stored at –80˚C and will be used to isolate and sequence HIV, and for cytokine/chemokine and biomarker assays (such as MCP-1, neopterin, IL6, T-tau, P-tau, Abeta42, sAPPalpha, sAPPbeta, neurofilament light and other biomarkers relevant to immune response to HIV) (at the Retrovirology laboratory at WRAIR and/or laboratory at Yale, and/or University of Gothenburg). To facilitate interpretation of CSF data, blood glucose, protein and HIV RNA will also be measured at the time of lumbar puncture.

5.8.6 Brain MRI/MRS/DTI

Brain MRI may be performed at King Chulalongkorn Memorial Hospital (which is 100 meters from the TRCARC in Bangkok) or at the Pattaya Memorial Hospital-affiliated radiology facility, according to patient convenience and availability. The procedure lasts approximately 60 minutes. Brain MRS and DTI will be performed at King Chulalongkorn Memorial Hospital only. No preparations or precautions are needed. MRI/MRS/DTI is a standard medical procedure and MRI/MRS for this study follows the standard hospital protocol.

5.9 CONCOMITANT MEDICATIONS

Concomitant medications will be recorded for the time period beginning 45 days prior to study enrollment and at every study visit. This will include documentation of prescription and over-

the-counter drugs as well as vitamin and mineral supplements. Study participants can receive medications such as acetaminophen, NSAIDs, or antihistamines as required; although they must be documented. No medications will be prohibited during study participation. Participants will be counseled to avoid non-essential vaccination during the period of ATI and any essential vaccinations, such as seasonal influenza, will be administered outside of weeks 2-6 and weeks 26-30, when the risk of rebound viremia is considered to be highest.

5.10 SOLICITED ADVERSE EVENTS

Temperature and solicited systemic symptoms will be recorded in the clinic prior to each infusion of either VRC01 or placebo, at a minimum of 60 minutes after the infusion, and then daily by the participant for 7 days after infusion. All participants will be given a thermometer, trained in its use, and provided a diary card for the purpose of recording these data after each infusion. The diary card may be used as a source document.

For this study, solicited adverse events occurring during the 7 days after receipt of study agent will include: unusually tired/feeling unwell, muscles aches, headache, chills, nausea, rash and joint pain. Subjects will also record daily measured temperature. The diary cards are reviewed for completeness at follow-up visits and are recorded without an attribution assessment (unless they are Grade 3 or higher in severity in order to assess whether the event is relevant to the study pause criteria). Severity will be graded by the study team at the time of diary card review. Clinicians will collect resolution information for any systemic symptoms that are not resolved after 3 days.

Clinician assessment of the local IV administration site will be conducted on day of study agent administration and during the scheduled follow-up timepoints on days 1, 3 and 7 after administration.

At every visit, all participants will be asked about other adverse experiences, which will be recorded and entered the same day into the study database. The PI will assess the relationship of the study products to the events.

5.11 STUDY DISCONTINUATION

5.11.1 Early Discontinuation or Withdrawal of Study Participants

A participant may be removed from the study entirely for any of the following reasons:

1. Repeated failure to comply with protocol requirements.
2. Decision by DAIDS, the PI, Walter Reed Army Institute of Research Institutional Review Board (IRB), U.S. FDA, and the Office for Human Research Protection (OHRP), or local regulatory authorities and local IRB(s) to stop or cancel the study.
3. Participant request.
4. Pregnancy (with subsequent offer to enroll in RV 412)

Each subject has the right to withdraw from the study at any time for any reason without affecting the right to treatment. The investigators will attempt to contact subjects who do not return for scheduled visits or follow-up. Although the subject is not obliged to give the reason(s) for

withdrawing prematurely, the investigators will make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

For those subjects who are unable to continue participation in the study, but who do not withdraw consent, an exit visit will be conducted (refer to SOE, Appendix II, for list of procedures to be conducted). Any subject who withdraws consent will not have any further data collected after consent has been withdrawn. Data that were collected prior to withdrawal of consent will remain a part of the research database and will be included in data analysis. Stored specimens will remain available for the conduct of IRB-approved non-human research.

The investigator also has the right to withdraw a subject, e.g., because of worsening health status, intercurrent illness, or AEs.

If a subject withdraws from the study before the first infusion of VRC01 or placebo, the next available participant will be placed in the vacated randomization slot. Replacements for participants who withdraw from the study before the first infusion will only be permitted while enrollment is open. Subjects will not be replaced if withdrawal from the study occurs after the first infusion of VRC01 or placebo. To minimize bias, only the study pharmacist will know whether the replacement has been assigned to placebo or VRC01 and the study staff and all volunteers will be blinded to assignment.

5.11.2 Premature Termination of the Study

Walter Reed Army Institute of Research IRB, DAIDS, the U.S. FDA, and OHRP reserve the right to terminate the study. The investigator will notify reviewing IRBs in writing of the study's completion or early termination.

6.0 STUDY TREATMENT

Study treatment is defined as VRC-HIVMAB060-00-AB (VRC01) or placebo for VRC01.

6.1 STUDY TREATMENT REGIMENS, ADMINISTRATION, AND DURATION

6.1.1 Regimens

Twenty-four men and women aged 20-50 years who began ART during early acute HIV infection (Fiebig stage I to III) will be randomized in a 3:1 ratio to either VRC01 or placebo, with randomization stratified by Fiebig stage.

VRC01 will be dosed at 40 mg/kg and administered intravenously in 100 ml of normal saline every three weeks for a total of up to 24 weeks.

Placebo for VRC01 will be normal saline (0.9% sodium chloride for injection, USP) administered intravenously at a volume of 100 mL every three weeks for a total of up to 24 weeks.

6.1.2 Administration

VRC01 or placebo for VRC01 will be administered as an intravenous infusion about 30-60 minutes using a volumetric pump. The 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 participant tolerance. Infusion access should be maintained and the participant observed for a minimum of 1 hour following completion of the infusion. There is currently very little data concerning administering the study drug over 30 min.

6.1.3 Duration

Study agents will be administered for up to 24 weeks, or until criteria for ART resumption are met (see Section 4.6), whichever comes first. Participants will be followed for up to 48 weeks after the first dose of a study agent.

6.2 STUDY PRODUCT FORMULATION AND PREPARATION

6.2.1 Formulation

VRC01 (labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB) is supplied at a concentration of 100 ± 10 mg/mL in an isotonic, sterile solution. Two fill volumes are available: 10 mL glass vials with a 6.25 ± 0.10 mL fill volume and 3 mL glass vials with a 2.25 ± 0.10 mL fill volume. The vials contain a clear, colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. 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 do not contain a preservative. All dose calculations should be based on a concentration of VRC01 of 100 mg/mL.

Placebo for VRC01 will be sodium chloride for injection 0.9%, USP.

6.2.2 Preparation for Intravenous Administration

A new prescription must be sent to the pharmacy after the participant is weighed on the day of each visit during which study product will be administered. Participants' screening weight or entry weight or last obtained weight may be used for calculation of the dose to thaw vials, but actual weight on the day of dosing will be used for calculating the final dose of study product to be infused. The prescription must contain the participants' weight and dose prior to being sent to the pharmacy (verbal orders are not permitted).

The pharmacist must verify the dose prior to preparing the study product.

Thawing Instructions:
Thaw vials of VRC01 at controlled room temperature 15°C to 25°C (59°F to 77°F) for a minimum of one hour up to a maximum of 24 hours. Continue to thaw the vials until the solution is clear, colorless to yellow with no visible particles. Prior to 24 hours at room temperature, the vials of VRC01 must either be used to prepare an infusion or may be placed in a refrigerator and stored up to 4 weeks at 2-8^{0}C (36°F to 46°F).

VRC01 may not be stored in direct sunlight at anytime.

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. Particles have been observed in 1-3% of the vials and generally disappear over a few hours at room temperature and may continue to dissipate at 2-8^{0}C.

Vials of VRC01 containing particles should be placed in the refrigerator as particles may continue to dissipate at 2-8^{0}C. Vials of VRC01 that previously contained particles but are now clear of particles may be used. Vials that continue to have visible particles after a maximum of 24 hours at controlled room temperature and up to 4 weeks at 2°C to 8°C (36°F to 46°F) are not to be used and will be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy. Report to the protocol pharmacist the quantity and the reason why for the disposal of any unused vials.

After removal from 2-8^{0}C, vials of VRC01 should be equilibrated to controlled room temperature 15°C to 25°C (59°F to 77°F) for a minimum of 30 minutes prior to preparing IV infusions. The maximum length of time that VRC01 in the vial may be held at controlled room temperature 15°C to 25°C (59°F to 77°F) prior to product preparation is 8 hours after removal from the refrigerator.

After thawing, the vials should be gently swirled for 30 seconds to avoid foaming. Vials must not be shaken. DO NOT SHAKE THE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vial during inspection. Observe vials for particles. If particles are observed follow the instructions above.

divided Calculate the total milligrams of VRC01 required based on the participants weight and 40mg/kg dose and total number of vials required based on a 6 mL withdrawal volume containing 600 mg of VRC01 or 2 ml withdrawal volume containing 200 mg of VRC01.

The calculated total milligrams needed of VRC01 should be added to a 100 mL bag of 0.9% sodium chloride for injection, USP, using aseptic technique to maintain sterility in a clean room with limited access using either an isolator, laminar flow hood, or biological safety cabinet. The 0.9% Sodium Chloride Injection, USP, 100 mL bag will accommodate the additional volume required for the dose of VRC01 to be used in this study. Do not withdraw fluid from the 0.9% Sodium Chloride Injection, USP, 100 mL bag to make room for the volume of study product to be added. A total of up to 50 mL of VRC01 may be added to a 100 mL bag of sodium chloride.. Please note: The prepared infusion bag must include expiration time of 7 days from the time of preparation when stored at room temperature (maximum 32°C) or 2°C to 8°C. When prepared IV bags are held at 2°C to 8°C the IV bags should be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be additionally held at room temperature for up to 24 hours prior to and during product administration. The IV bag should then be labeled to maintain blinding

Any unused portion of a VRC01 vial will not be used for another subject.

Placebo for VRC01 will be 0.9% sodium chloride for injection, USP and should be added to a 100 mL bag of 0.9% sodium chloride for injection, USP, using aseptic technique. The volume of placebo to be infused will be approximately 100 mL plus 0.4 mL/kg to be consistent with the volume infused in the active VRC01 arms. Do not withdraw fluid from the 0.9% Sodium Chloride Injection, USP, 100 mL bag to make room for the volume of placebo to be added. The IV bag should then be covered with an amber bag and labeled to maintain blinding.

6.2.3 Storage

VRC01 should be stored in a qualified, continuously monitored, temperature-controlled freezer at -35°C to -15°C (-31°F to 5°F). Freezer temperature from -45°C to -10°C (-49°F to 14°F) is acceptable.

The site pharmacist must promptly report any storage temperature excursions outside of the normal allowance for the freezer to the NIAID Clinical Research Products Management Center (CRPMC). The product must be quarantined in a separate area. The NIAID CRPMC will notify the site pharmacist if continued clinical use of the product is acceptable.

Placebo for VRC01 (0.9% sodium chloride for injection, USP) should be stored according to manufacturer recommendations.

6.3 PHARMACY: PRODUCT SUPPLY, DISTRIBUTION, AND ACCOUNTABILITY

6.3.1 Study Product Acquisition and Distribution

VRC01 is manufactured by the VRC and will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the VRC01 product(s) for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

The placebo for VRC01 (0.9% sodium chloride for injection, USP) will not be provided through the study and must be obtained locally.

Sodium chloride for injection 0.9%, USP, 100 ml bags required to prepare the dose for VRC01 and placebo for VRC01, will not be provided through the study and must be obtained locally.

6.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC or destroyed (as directed by the sponsor, DAIDS) after the study is completed or terminated. The procedures to be followed are in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

6.4 DISPOSITION

The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved. Any unopened vials that remain will be returned to the production facility or discarded at the discretion of DAIDS in accordance with policies that apply to investigational agents. Partially used vials will not be administered to other subjects or used for *in vitro* experimental studies. They will be disposed of in accordance with institutional or pharmacy policy.

Vials or IV infusion bags of VRC01 with particles should be quarantined and stored at 2-8^{0}C. Contact the protocol pharmacist for further instructions regarding management of VRC01 vials or infusion bags VRC01 with particles.

7.0 PHARMACOVIGILENCE, SAFETY, AND ADVERSE EXPERIENCE REPORTING

7.1 DEFINITIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (International Conference on Harmonization (ICH) E6) (Synonym: Adverse Experience).

A serious adverse event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

“Life-threatening” refers to an adverse event that at occurrence represents an immediate risk of death to the subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered an SAE.

7.2 ADVERSE EVENT GRADING AND RECORDING

Recording of all AEs will occur during the period from the first study agent administration through 175 days after the last study agent administration. After this and through completion of study participation, only SAEs and new chronic medical conditions that require ongoing medical management will be recorded as AEs in the study database.

All recorded AE and lab data will be coded for severity using the current version of the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), included as Attachment III and found on the website http://rsc.tech-res.com/safetyandpharmacovigilance/.

For adverse events not identified in the grading table, the following guidelines in Table 3 will be applied:

Table 3. Additional Categories for Grading of Adverse Events

Category	Grade	Description
Mild	Grade 1	Symptoms causing no or minimal interference with usual social & functional activities
Moderate	Grade 2	Symptoms causing greater than minimal interference with usual social & functional activities
Severe	Grade 3	Symptoms causing inability to perform usual social & functional activities
Potentially Life-Threatening	Grade 4	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability or death
Death	Grade 5	Symptoms resulting in fatal outcome

The site clinical research team will ascertain accurate recording of AEs during the study. AE case report forms (CRFs) will be completed by the research staff on a daily basis as the data become available from the clinic or laboratory.

The clinical investigators will monitor and analyze study data including all AE and lab data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study product. To insure that all AEs are captured in a timely manner, CRFs will be entered in real-time and also subjected to analysis to identify AEs that may invoke study pause rules.

Although post injection reactogenicity (PIR)/Solicited AEs are documented separately from unsolicited AEs, they are reported to DAIDS if they meet SAE or study pause rule definitions as noted below. Therefore, the PI or designee must review both PIR and AE CRFs to insure prompt and complete identification of all events that require expedited reporting as SAEs, study pause rules or other serious and unexpected events.

Study related AEs will be followed by the clinical research team through resolution. Non-study related AEs will be followed to resolution or study completion, whichever occurs first.

7.3 PROTOCOL SAFETY REVIEW TEAM (PSRT) AND PSRT REVIEWS

The PSRT will review all AEs (including reportable AEs) on a regular and expedited basis as needed. In addition, the PSRT will review aggregate safety data reports from all sites on a weekly basis. This team includes the following: Study Chair, Site PI, a DoD research monitor, and the DAIDS medical officer or their designees. Additional participants could include associate investigators, and senior clinical research nursing staff. A quorum is established with the Protocol Chair, site PI and the DAIDS medical officer (MO) or their designee.

7.4 SAFETY MONITORING COMMITTEE (SMC) REVIEWS

The SMC for this study will be comprised of an independent group of experts established with consultation of DAIDS to review safety data during the clinical trial. The Protocol Chair (or designee) will submit written recommendations and cumulative safety data, grouped according to treatment group, to the SMC Executive Secretary after the first enrollee has completed 90 days of the study. Subsequently, the SMC will convene every six months to review the completeness of the study data collected, the adherence to the protocol, and the Protocol Chair's review summaries. The SMC will also meet as needed to deliberate upon the initial interim safety data, the disposition of study pauses, and/or to provide other recommendations regarding the safe conduct of the study as requested by the Protocol Chair, Principal Investigator and/or DAIDS Medical Officer. The SMC Executive Secretary will provide the Protocol Chair and DAIDS Medical Officer with SMC recommendations, and the Protocol Chair and site PI will inform IRBs and regulatory authorities as appropriate.

7.5 CRITERIA FOR STUDY PAUSE OR TERMINATION

If the trial is placed on safety pause, all enrollment and infusions will be suspended until further notice. Study visits will continue. Enrollment and infusions will resume if and when safety is ensured. Study pauses should not delay the initiation of ART according to the study schedule.

Table 4 summarizes the AEs, which when experienced by at least one participant will lead to a safety pause or prompt PSRT AE review. For any AE where the outcome is death, the severity of the AE is classified as Grade 5. Related AEs refer to AEs deemed to be definitely, probably, or possibly related to the study; Not related AEs refer to AEs deemed to be unlikely related or not related to the study.

Grade 5 or 4 events that are judged related to study product administration should be reported immediately (within hours of the site learning of the event). These events require immediate pause.

Grade 3 events that are judged related to study product administration should be reported promptly i.e., within 24 hours. These events require prompt review by the PSRT.

All events that are related to study product administration and are similar grade 2 AEs in two or more participants will be routinely reviewed by the PSRT but will not necessarily prompt a pause. The PSRT may take that action after review.

When the administration of study products has been paused, VRC01 administration and enrollments would resume only if review of the triggering AEs by the PSRT (and where applicable, the SMC), result in a recommendation to permit further study product administration and study enrollments.

Table 4. Adverse Event Notification and Study Pausing Guidelines

Toxicity	Post-Injection Reactogenicity (PIR) and Study Treatment Related Adverse Events (AEs)	Action [1]
Grade 5/Grade 4 Related[2]	"Verified" [3] abnormal laboratory values, local or systemic reactogenicity, or related AEs (if fever, must persist for ≥ 48 hours)	Automatic pause Immediate reporting (Concurrent with observation or report)
Grade 3 Related[2]	"Verified"[3] abnormal laboratory values, fever for ≥ 48 hours, vomiting, or other clinical study mAb infusion related AEs (Except for subjective symptoms)	Consider pause Prompt reporting (within 24 hours of observation or report)

[1]Follow-Up and Resolution: All promptly or immediately reportable AEs are followed until resolution or condition is medically stable.

[2]Related AEs refer to AEs deemed to be definitely, probably, or possibly related to the study; Not related AEs refer to AEs deemed to be unlikely related or not related to the study

[3]If no evidence of disease is present other than the abnormal laboratory value, the test must be repeated at least one time in order to be considered "verified". The verification period will be a maximum of 48 hours after initial awareness of the abnormal laboratory value. When signs and symptoms are present, repeat test WILL NOT be needed

For events in the table above, the Site PI notifies the PSRT, which includes the Study Chair and DAIDS MO, within a few hours after the site observes, or is notified of, the AE. The PSRT will convene within one business day to review these adverse events. The PSRT will review and determine disposition (including whether the SMC needs to review the event). Any Grade 4 or Grade 5 AE will automatically trigger SMC review.

If a decision to resume study enrollment and study treatment administration is made, the PSRT and/or SMC will record its judgment in a memorandum to the study file and notify DAIDS, who will then forward the memorandum to the principal investigator and protocol chair. The protocol chair or designee will instruct the clinical site to resume activities upon receipt of written notification from DAIDS. As needed, the appropriate regulatory authorities will be informed in writing of the decision to resume or discontinue study activities. Site is responsible for notifying the Chulalongkorn IRB according to their standards and regulations, and the WRAIR IRB within 48 hours for awareness. The sponsor (DAIDS) is responsible for notifying the FDA.

7.6 EXPEDITED REPORTING TO IND SPONSOR (DAIDS)

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in the current version of the DAIDS Expedited Adverse Events (EAE) Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/. Reporting AEs to DAIDS will be conducted according to this Manual.

The SAE Reporting Category, as defined in the current version of the DAIDS EAE Manual, will be used for this study. All SAEs will be reported by the site PI or designee to the DAIDS RSC Safety Office.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

At the time of SAE submission, any supplemental forms as required by Chulalongkorn University and DoD IRBs must also be submitted to DAIDS RSC Outcomes of the SAE will need to be provided as updates through DAERS or on the EAE form until the adverse event is resolved, is stable, or chronicity has been established and documented.

For questions or other communication with RSC on SAEs, please note the following:

Website:	http://rsc.tech-res-intl.com
Office Phone*:	1-800-537-9979 (U.S. only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (U.S. only) or +1-301-897-1710
Office Email:	DAIDSRSCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (U.S. Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817
*Office phone and fax are accessible 24 hours per day	

7.6.1 Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS is the VRC01 MAb (VRC-HIVMAB060-00-AB) and placebo. In the event of an EAE, subject randomization will be unblinded as described in section 7.10 in order to meet reporting criteria.

7.6.2 Study Recording Period for SAEs

The protocol-defined expedited event reporting period for this protocol is 175 days after the last study agent administration until study completion or discontinuation of the subject from study

participation for any reason. After the end of the protocol-defined EAE Reporting Period stated above, the site must report serious, unexpected, suspected adverse drug reactions (SUSARS) if the study site becomes aware of the event on a passive basis (i.e, from publicly available information).

7.6.3 Timeframe for Expedited Reporting of Individual Adverse Events

The timeframe for expedited reporting of an individual AE begins when the site recognizes that an event fulfills reportable AE criteria. For SAEs sites must submit adverse events requiring expedited reporting to the DAIDS RSC Safety Office as soon as possible, but no later than 3 reporting days (as defined in the DAIDS EAE Manual), after the site's recognition that the event fulfills the criteria for SAE reporting. The RSC will submit written IND Safety Reports to the FDA in accordance with 21 CFR 312.32 as soon as possible and, in no event, later than 7 or 15 calendar days following receipt of reportable adverse event information.

For IND Safety Reports submitted to the FDA and received from DAIDS, COG will complete the necessary reporting to the WRAIR IRB by contacting them by phone or email within 48 hours, and submitting a written report within 10 working days of the initial safety report. The WRAIR HSPB will report IND Safety Reports to the USAMRMC ORP HRPO as per UWZ-C-636.

The necessary AE reporting documents and any study pauses will also be submitted to the WRAIR IRB and the USAMRMC ORP.

7.7 Reporting Serious and Unexpected Adverse Events to the DoD In Addition To DAIDS

All related serious adverse events (SAEs) and deaths should be reported to the WRAIR IRB within 48 hours by telephone, email or fax. A complete written report should follow the initial notification within 10 working days. All SAEs occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR IRB. The contact information for the WRAIR IRB is as follows:

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940
Fax: 301-319-9961
Email: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

The WRAIR HSPB will report SAEs to USAMRMC ORP HRPO as per SOP UWZ-C-636.

7.7.1 Social Harms Reporting

Unanticipated events and social harms may occur during the course of the study. When such events are related to study participation, the study staff, informed of these events, will inform the PI or his/her designee. The PI or designee will then prepare a narrative summary of the event and report to the Chulalongkorn University IRB, WRAIR IRB and PSRT including DAIDS Medical

Officer. The local medical monitor should also review the social harms and provide an independent assessment of these to the WRAIR IRB. The WRAIR HSPB will report these reports to the USAMRMC ORP HRPO as per UWZ-C-636. A summary of these reports should also be provided in the continuing review report.

7.7.2 Unanticipated Problems Reporting to WRAIR

Unanticipated problems involving risks to subjects or others (UPIRTSO) encompass a broader category of events than SAEs and may include issues such as problems with loss of control of subject data or the investigational product; adverse psychological reactions; or breach of confidentiality. Risks to others (e.g., program personnel) must also be reported.

Unanticipated problems involving risks to subjects or others (UPIRTSO) are any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms or nature, severity, or frequency) given (a) the procedures that are described in the protocol, investigators brochure or informed consent document; and (b) the characteristics of the subject population.
- Related or possibly related to a subject's participation in the study; and
- Suggests that the study places subjects or others at a greater risk of harm than was previously known or recognized.

All unanticipated problems related to the study and involving risk to subjects or others (UPIRTSO) should be promptly reported (48 hours) by telephone, email or fax to the WRAIR IRB. A complete written report should follow the initial notification within 10 working days. All unanticipated problems occurring within the reporting period should also be summarized in the continuing review reports submitted to the WRAIR IRB. The contact information for the WRAIR IRB is as follows:
Director, Human Subjects Protection HSPB
503 Robert Grant Ave.
Silver Spring, MD 20910-7500
Telephone: 301-319-9940
Fax: 301-319-9961
Email: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

The local medical monitor will also be responsible for reviewing the unanticipated problems and providing an independent assessment for all potential UPIRTSOs to the WRAIR IRB. A summary of all unanticipated problems will be included in the continuing review reports. The WRAIR HSPB will report unanticipated problems to the USAMRMC ORP HRPO as per UWZ-C-636. The report will be forwarded to the DAIDS.

7.8 REPORTING REQUIREMENTS TO THE LOCAL IRB

The site PI will be responsible for providing all Safety Reports and reporting all SAEs, study pauses, social harms, UPIRTSOs, and major deviations to the local regulatory authority, such as

the Chulalongkorn University IRB and any country-specific regulatory agencies, in a timely manner according to the institution's guidelines.

7.9 REPORTING REQUIREMENTS TO THE THAI FDA

Study investigators will inform the Thai FDA of adverse events in accordance with Thai regulations. It is the responsibility of the PI or designee to fulfill the reporting requirements.

A SUSAR resulting in death or which is life-threatening must be reported in an initial report within 7 days of awareness, followed by a full report within the following 8 days. Additional periodical reporting will be required if additional data emerges.

A SUSAR not leading to death and not life-threatening must be reported within 15 days of awareness. Any unexpected adverse reaction arising after the volunteer has left the research or after research is completed must also be reported within 15 days of awareness. A periodical report is also required if additional data emerge after the filing of the initial report.

An Annual Safety Report will be submitted to the Thai FDA of all AEs and SAEs, regardless of whether they were related to study agents and regardless of intensity. The Thai FDA wishes to receive any safety reporting, including from animal studies, that may change the evaluation of risk of the study products under investigation, the method of study product administration, or the overall conduct of the study.

Any reporting will use Thai FDA specific forms to be sent to the Health Product Vigilance Centre at http://thaihpvc.fda.moph.go.th. In case the system is not ready for use or develops technical problems, the report shall be sent to the Pre-Marketing Drug Supervision Group, Bureau of Drug Control, Thai Food and Drug Administration.

Thai FDA	Health Product Vigilance Centre Pre-Marketing Drug Supervision Group Bureau of Drug Control, Food and Drug Administration Ministry of Public Health Tiwanon Road, Nonthaburi 11000 Tel: +66- 2590-7160, +66- 2590-7171 Fax: +66-2591-8390, +66-2591-8489, +66-2590-7170 e-mail:drug@fda.moph.go.th Electronic submission at: http://thaihpvc.fda.moph.go.th

7.10 UNBLINDING

A request for unblinding, with its rationale, should be forwarded through the PI. The PI will evaluate the request and notify the DoD Research Monitor. The DoD Research Monitor will evaluate the request and advise the Sponsor regarding the course of action. The Sponsor will decide whether to approve the request for unblinding. In the case of the former, the Sponsor will authorize the independent statistician to provide this information to the PI. It should be noted that there are very few circumstances in which unblinding will be essential to the medical management

of a VRC01 or placebo recipient. In case of VRC01-related death or life-threatening SAE, knowledge of whether a participant received VRC01 or placebo can be critical for the interpretation of the significance of clinical findings and thus impact decisions regarding continuation of study participation. In such cases, the assignment of a participant will be unblinded.

Episodes of unblinding, whether accidental or intentional, will be reported by the site investigator with an explanation to the Protocol Chair who will inform participating IRBs, Sponsor and other necessary regulatory bodies. Follow-up of such participants will continue through the duration of the trial.

8.0 STATISTICAL CONSIDERATIONS

8.1 POWER AND SAMPLE SIZE FOR SAFETY OBJECTIVE

The goal of the safety evaluation for this study is to identify safety concerns associated with VRC01 administration. Sample size calculations for safety are expressed in terms of the ability to detect SAEs.

Table 5 shows possible two-sided exact 95% confidence intervals for various proportions of VRC01 subjects experiencing an adverse event. If no subjects experience an SAE in the VRC01 arm, then the upper limit of the two-sided exact 95% confidence interval will be 18.5%.

Table 5. Exact Two-Sided 95% Confidence Intervals for Various Proportions of VRC01 Subjects Experiencing a Serious Adverse Event

Enrollment (N)				
Total	Placebo	VRC01	Observed SAEs in VRC01 Arm	SAE Rate (95% Confidence Interval)
24	6	18	0	0 (0-18.5)
24	6	18	1	5.6 (0.1-27.3)
24	6	18	2	11.1 (1.4-34.7)
24	6	18	4	22.2 (6.4-47.6)
24	6	18	6	33.3 (13.3-59.0)
24	6	18	9	50.0 (26.0-74.0)

8.2 POWER AND SAMPLE SIZE FOR EFFICACY OBJECTIVE

The primary efficacy endpoint for success is sustained virologic control, as defined above, at 24 weeks following ATI. Assuming a placebo success rate of 15% and using a type I error of 5% as the threshold for statistical significance, this study design has 84% power for a two-sided exact unconditional test to detect an 80% success rate in the VRC01 arm. Exact unconditional tests have been shown to have more power than Fisher's Exact test and have been recommended for use in 2 x 2 tables [74]. Other assumptions and power predictions are summarized in Table 6.

Table 6. Power to Detect Differences in Success Rates Between VRC01 and Placebo with 3:1 Randomization and Two-Sided Type I Error of 5%

Enrollment (N)			Success Rate Assumptions (%)		
Total	Placebo	VRC01	Placebo	VRC01	Power
24	6	18	5	50	46%
24	6	18	5	65	82%
24	6	18	5	70	89%
24	6	18	15	50	27%
24	6	18	15	70	68%
24	6	18	15	80	84%

8.3 ANALYSIS

The primary analysis will consist of all subjects receiving at least one dose of the study product. A secondary per-protocol analysis will consist of subjects compliant with study treatment. Analysis will be performed for the entire study population and also stratified by Fiebig stage in order to explore the impact of Fiebig stage on study endpoints, recognizing that the study is not powered to detect outcomes across participants at any single Fiebig stage.

Baseline characteristics including demographics and laboratory measurements will be summarized using descriptive statistics.

The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Summary statistics will be calculated, along with point and interval estimates of solicited and unsolicited adverse event and immune response rates. This study is exploratory, and any statistical inferences will be hypothesis generating, and not confirming.

8.3.1 Primary Endpoints

The primary efficacy endpoint is sustained virologic control (HIV RNA <50 copies/mL) at 24 weeks after ATI. The rate of virologic control will be compared between treatment groups using a two-sided exact unconditional test with a significance level of 0.05.

To assess safety, summaries of the number and percentage of subjects experiencing any SAE, AE, or reactogenicity will be tallied by treatment group and presented along with two-sided exact 95% confidence intervals for the proportion.

For solicited AEs/reactogenicity, number and percentage of subjects experiencing each type of solicited sign or symptom will be tabulated by severity. For a given sign or symptom, each subject's solicited AEs will be counted once under the maximum severity for all assessments.

For unsolicited AEs, number and percentages of participants experiencing each specific adverse event will be tabulated by severity and relationship to treatment. For the calculations in these tables, each participant's adverse experience will be counted once under the maximum severity or strongest recorded causal relationship to treatment.

Further, frequency of solicited and unsolicited adverse events will be reported (together and seperately) by system organ class, preferred term, and treatment group overall and at various timepoints throughout the study.

A complete listing of adverse experiences for each participant will provide details including severity, relationship to treatment type, onset, duration and outcome.

8.3.2 Secondary Endpoints

1. Time to viral rebound and level of rebound viremia after cessation of ART.

Time to viral load rebound will be described using a Kaplan-Meier estimator to account for

possible censoring and compared between treatment groups using an exact log-rank test. Number of HIV RNA copies at the time of rebound viremia will be described using medians and interquartile ranges and compared between treatment groups using a Wilcoxon-Rank Sum test.

2. Time to ART resumption for any reason after cessation of ART

Time to ART resumption will be described using a Kaplan-Meier estimator to account for possible censoring and compared between treatment groups using an exact log-rank test.

3. Detectable HIV RNA via single copy assay at various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.

Number of HIV RNA copies will be described using medians and interquartile ranges at baseline, week 24, and week 48 for subjects with HIV RNA <50 copies/mL by standard PCR. Change from baseline at week 24 and week 48 will be compared between treatment groups using a Wilcoxon-Rank Sum test.

4. CD4+ T cell count various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.

CD4+ T cell counts will be described using medians and interquartile ranges at baseline, week 24, and week 48. Change from baseline at week 24 and week 48 will be compared between treatment groups using a Wilcoxon-Rank Sum test.

5. Cell-associated HIV RNA and DNA in the peripheral compartment various timepoints, such as weeks 24 and 48, as compared to baseline at week 0.

Cell-associated HIV RNA and DNA in the peripheral compartment will be described using medians and interquartile ranges at baseline, week 24, and week 48. Change from baseline at week 24 and week 48 will be compared between treatment groups using a Wilcoxon-Rank Sum test.

6. Neuropsychological battery performance at weeks 24 and 48, as compared to baseline at week 0.

Neropsychological data will be summarized using z-scores based on age-matched normative data when such data is available or as raw scores when not available. With either approach, individual performance can be compared longitudinally to determine the impact of the intervention on cognitive performance, the primary interest of the neuropsychological testing portion of this study.

7. Frequency of hospitalization and incidence of non-AIDS related conditions.

Frequency of hospitalizations will be summarized and described by treatment group, Number of hospitalizations can be compared between groups using a Wilcoxon-Rank Sum test and proportion of subjects experiencing a hospitalization will be compared using an

exact unconditional test. Incidence of non-AIDS related conditions will be compared in a similar fashion.

Exploratory objectives will be analyzed in a similar fashion to primary and secondary objectives although if the rate of consent for invasive procedures is low then analyses may be primarily descriptive. Continuous variables will bedescribed at each timepoint using medians and interquartile ranges. Change from baseline will be compared between treatment groups at weeks 24 and 48 using Wilcoxon-Rank Sum tests. If possible repeated measures models will be fit to account for within subject correlation and assess a treatment group effect. Binary endpoints will be compared between treatment groups using exact unconditional tests. Clinical characteristics will be summarized and described by treatment groups. Significance will be assessed using two-sided testing at the 0.05 level. Given the size and exploratory nature of the trial, adjustments for multiple comparisons will not be made.

9.0 DATA COLLECTION

Data collection will be conducted using paper records or tablets or microcomputers with eventual secure transfer to a central database. Paper records will include CRFs without personally identifiable information. These files will be maintained in secured cabinets with access restricted to study personnel via key. Access to any software used for data collection is limited by individual username and password. Data is stored in encrypted fashion on the local computer. After the data is uploaded to the central database it is automatically deleted from the local tablet or microcomputer.

Data obtained in the conduct of this study are housed in a secure database maintained by the DCAC, MHRP. All research data are entered in a secure database with standardized quality assurance review procedures in accordance with Good Clinical Practices (GCP).

The DCAC serves as the central data management facility for MHRP research protocols. Data managed by DCAC are entered into and maintained in a password-protected database. Data are accessible only to participating sites, DCAC, and Information Technology staff authorized to work on the protocol. The database is located at the Bethesda campus of MHRP and is protected by a firewall. Data from this protocol will be retained indefinitely.

This data does not contain participant names or Social Security or other national identification number, but is referenced only by the study specific identification code.

Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. However, ethical considerations or other events may result in the failure to obtain and record certain data, or to record data at the times specified. If this occurs, the events and, the reasons for the event must be clearly documented on the case report form for deviations and reported as described above.

Analysis files are created on a periodic basis and made available to the Protocol Chair, Principal Investigator (PI) and Associate Investigators (AI) at the direction of the PI and/or Protocol Chair. Other collaborators may be given access to these analysis files, or data gathered from them, at the direction of the PI. Data may be made available as a listing, external file, or through a query program.

10.0 ETHICAL CONSIDERATIONS

10.1 PARTICIPATION OF CHILDREN

Children are not eligible to participate in this clinical trial because it does not meet the guidelines for inclusion of children in research. These guidelines (45 CFR 46, Subpart D, 401-409) state the Department of Health and Human Services protections for children who participate in research. Generally, healthy children can be studied when the research is considered as "not greater than minimal risk." Children can be involved in research with greater than minimal risk only when it presents the prospect of direct benefit to the individual child or is likely to yield generalizable knowledge about the child's disorder or condition.

10.2 RISKS

10.2.1 Risks Related to IV infusions

General risks of IV infusion include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site.

10.2.2 Risks Related to VRC01

Limited human experience with administration of VRC01 has thus far demonstrated IV infusion to be safe and well tolerated (described in Section 2.7 Phase 1 Clinical Trials of VRC01). In a preclinical study performed in rats, there was a small dose-dependent, but transient, increase in aspartate aminotransferase (AST) and alkaline phosphatase (ALP), but not in alanine aminotransferase (ALT) following IV administration. In rats, there were no histopathology findings following IV administration.

Administration of any mAb may carry a risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies against the mAb; however, these reactions are rare and more often associated with mAb targeted to human proteins or with the use of 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 (IgG1), 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. Clinical use of monoclonal antibodies that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections and cytokine release syndrome (CRS) [75, 76]. 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 murine mAb, is used. The VRC01 mAb is a human mAb that is directed to a viral target rather than a host cell target. Severe CRS has not been reported in such pathogen-directed human mAbs, and CRS has not been observed in the human experience with VRC01. With licensed therapeutic

mAbs, CRS is managed by temporarily stopping the infusion, administration of histamine blockers and restarting the infusion at a slower rate [77]. 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 are noted to be more common with chimeric types of mAbs [75].

There are several FDA-licensed mAbs for which reactions related to the rate of infusion have been described. Some symptoms may be treated by slowing or stopping the infusion. Supportive treatment may also be indicated for some signs and symptoms.

A theoretical risk is that receiving VRC01 might affect the subject's drug sensitivity profile for ARV medications that work through entry or fusion inhibition, or may limit eligibility for some future monoclonal antibody treatments. There is also the risk that not all viruses within a swarm may be neutralized by VRC01, which could lead to selection of viruses with resistance against this agent. The frequent monitoring and strict ART resumption criteria in this study are designed to catch breakthrough viremia early and investigators will evaluate for VRC01 resistance in volunteers experiencing breathrough during this therapy.

10.2.3 Risks Related to Blood Drawing

Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken.

10.2.4 Risks Related to Treatment Interruption

Treatment interruption is not a therapeutic intervention and the possible effects of treatment interruption in the setting of volunteers who began ART during early acute HIV infection have not been characterized. This protocol includes multiple measures to minimize risk for study participants during the period of treatment interruption, including frequent monitoring for viral rebound and procedures to initiate ART before HIV viremia reaches levels that may cause symptoms or expansion of HIV reservoirs. It is possible, however, that volunteers experiencing viral rebound could experience symptoms of acute retroviral syndrome, which can include fever, rash, pharyngitis, fatigue, myalgias, arthralgias and lymphadenopathy. It is also possible that volunteers may establish or expand reservoirs of HIV infection or develop resistance to certain antiretroviral medications, including those used prior to ATI (Appendix I). Volunteers may experience an increase in immune activation during ATI.

If subjects develop viremia, there is a risk of transmitting HIV to sexual partners. All subjects will be notified of this risk and advised to use condoms for any sexual contact during participation in the study.

There is a risk that subjects could develop HIV resistant virus after ATI. Changing all subjects to a PI-based ART regimen is designed to minimize this risk. If HIV resistance develops it could potentially lead to a higher risk of treatment failure or death during future ART. To detect and address any possible HIV resistance, an HIV genotype test will be done on all patients with rebound viremia before restarting ART.

10.2.5 Risks Related to Pregnancy

The possible effects of VRC01 on a fetus or nursing infant are unknown. Since VRC01 is a human monoclonal antibody and not a chemotherapeutic agent, traditional toxicology and animal reproduction studies are not possible. However, the antibody is directed against a viral protein and showed no cross-reactivity with fetal or adult human tissue in preliminary safety studies. Furthermore, anti-HIV antibodies are routinely transferred from the mother to the fetus during pregnancy without any known adverse affect on the mother or infant [78]. As with the majority of IgG antibodies, transfer of anti-HIV antibodies occurs from the mother to the fetus predominantly during the third trimester; since VRC01 ($T_{1/2}$=13.6 days; range 6.76-21.3 days) infusions will be stopped if pregnancy is diagnosed, they are unlikely to be present at the time of IgG transfer to the fetus [78].

This evidence suggests that adverse affects to the infant of a mother exposed to VRC01 are unlikely, but pregnant women are still conservatively excluded from participation in this phase II study of an investigational new agent. Women of reproductive potential must agree to not get pregnant during study participation and must use at least one method of effective birth control during study participation. Effective birth control includes not having sex; male or female condoms; diaphragm or cervical cap with spermicide; intrauterine device; birth control pills, patch or injections; and other prescription methods; or a male partner who has previously undergone a vasectomy.

Women must have a negative pregnancy test before each infusion of study drug and before collection of cervicovaginal secretion samples. Women becoming pregnant during the study will be referred for obstetric care, reported to the antiviral pregnancy registry and offered enrollment in RV 412. Via that protocol, a pregnant woman will be prescribed ART and monitored for sustained viral suppression. The outcome of the pregnancy will be documented.

10.2.6 Risks Related to Possible Breach of Confidentiality

Loss of confidentiality about HIV status could result in discrimination by family, employers, and in the community. It is also acknwledged that involuntary disclosure of HIV status may result in depression and rarely suicide. Breaching of confidentiality is greatest during enrollment and the interviewing stages of the study, and steps have been taken to mitigate that risk. All interviews and data collection procedures will take place in private rooms where subjects can neither be seen nor heard from the outside. Source documents such as medical records and laboratory reports will be coded with only subject ID numbers and will be stored in locked cabinets in the clinic, The clinic itself is not accessible to anyone other than study staff and is locked on nights and weekends. The electronic database will contain only coded data and is stored and maintained on a password-protected computer system.

In addition to procedures put in place to assure participant confidentiality, participants will not be identified in any reports on this study. Mitigating steps also include that, by design, no subject identifying information will be extracted from clinical records. Any copies of case report forms and data forms bearing any identifiers will be kept in locked, secured areas. Finally, data management security measures are in place at the local site to assure data safety and confidentiality.

10.2.7 Risks Related to Questionnaires and Neuropsychological Testing

Subjects will be asked to provide information about their sexual behavior, mood, cognitive functioning, and overall mental health. Some of the questions may make subjects feel uncomfortable or cause anxiety. In order to mitigate risks, subjects reserve the right not to answer certain questions. In addition, study staff are trained to administer questionnaires about sensitive topics, recognize signs of adverse psychological impact, and can provide referrals for counseling or mental health services if necessary.

10.3 RISKS RELATED TO OPTIONAL PROCEDURES

Mucosal Secretion Collection

Mucosal secretion samples collected in the clinic (rectal sponges, semen, and cervicovaginal cups) will be obtained non-invasively. Semen will be self-collected and for the collection of cervical-vaginal secretions, women may elect to insert and remove cervical cups themselves, as well. Inserting an instrument or collection device into the anus or the vagina may cause discomfort and slight irritation. There is no evidence of rectal sponge or cervical cup sampling contributing to risk of HIV or other sexually transmitted infection. For these non-invasive mucosal collections, men and women will be asked to refrain from receptive anal or vaginal, intercourse, douching, or inserting any product into the rectum or vagina for 3 days prior to the mucosal collection. Men will be asked not to masturbate nor ejaculate 3 days prior to semen collection.

Use of the for vaginal secretion collection carries the theoretic risk for toxic shock syndrome (TSS). Female subjects who agree to genital secretion collection will be warned of this risk and will be advised to use the soft up for no more than 12 hours to decrease the risk. In addition, they will be advised of the symptoms of TSS and to contact the study team immediately if any symptoms develop while using the soft cup.

Colon Biopsy (via Sigmoidoscopy)

Rectosigmoid biopsies will be performed through a flexible sigmoidoscopy. Brief cramping and gas pains may be flet as air iis inserted or as the scope advances. The passing of gas is necessary and should be expected after the procedures are terminated. Volunteers may choose to receive sedation during the procedure in order to ameliorate the discomfort and anxienty they may feel. There may be slight bleeding from the biopsy site, which generally stops spontaneously. There is a remote possibility that a biopsy may result in significant bleeding or even perforation requiring emergency medical care. A gastroenterologist will perform this procedure in order to minimize these risks. All volunteers will be counseled to avoid sexual rectal intercourse for 3 days prior to and 7 days following biopsy.

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Lymph Node Biopsy

Excisional inguinal lymph node biopsy will be performed under local anesthesia by a qualified surgeon. As with all surgical procedures, there is a risk of scarring, bruising or bleeding at the

surgical site; these risks are minimized by the small nature of the incision (approximately 1-2 centimeters) and by prior clinical and laboratory evaluation to determine any bleeding risks. Subjects may experience some discomfort following the procedure despite use of local anesthesia; for subjects who complain of any subsequent discomfort, additional analgesia will be made available.

There is a possibility of seroma formation at the biopsy site, which may require subsequent drainage or further management, or sensory nerve injury during the procedure which could result in temporary or permanent local reduction in feeling. Surgical site infection is a possible complication of any procedure involving an incision, however the risk is low. There is a possibility of seroma formation at the biopsy site, which may require subsequent drainage or further management, or sensory nerve injury during the procedure which could result in temporary or permanent local reduction in feeling. There is a possibility of developing lymphedema, particularly with multiple lymph node biopsies. To minimize the risk of lymphedema, volunteers will be limited to a maximum of 4 inguinal lymph node biopsies over their lifetime in all studies, consistent with the report from Skarda et al in which a similar population of HIV-infected subjects underwent a mean of 3.1 biopsies each.[79] Surgical site infection is a possible complication of any procedure involving an incision; Skarda et al reported a single infection out of 137 sterile asymptomatic inguinal lymph node biopsies, occurring in an individual whose wound dehisced following strenuous activity several days after biopsy and resulting in an overall infection rate of 0.7%. They report an overall complication rate of 5%, The non-infectious complications were universally local and resolved completely with minimal medical management; they included two postoperative hematomas, a dorsal vein thrombosis with associated epididymitis (which may not have been related to the procedure) and a lymphocoele.

Finally, there is the unlikely possibility that the procedure will be unsuccessful and no lymph node will be recovered.

Leukapheresis

Adverse reactions to leukapheresis procedure are rare and include vaso-vagal episodes related to needle insertions and transient volume shifts, peri-oral paresthesias, chills, nausea, and heartburn cause by the citrate anticoagulant used during the procedure. Vaso-vagal reactions are handled by postural manipulation and fluid administration. Volunteers will be observed closely by an experienced technician during the procedure. Citrate reations are usually relieved by slowing the rate of the anticoagulant infusion and by administering oral calcium carbonate tablets. Seizures and allergic reactions are very rare possible reactions.

Lumbar Puncture

The risks of lumbar puncture include local soreness at the site of needle entry. There is a risk of headache or decreased blood pressure from removing the small amount of fluid or leaking of cerebral spinal fluid after the procedure. About 1 in 10 people will experience a headache following lumbar puncture. There is a small risk of infection. There is also a very small risk of damage to nerves in the lumbar spinal roots after the procedure, which could cause pain, numbness, or loss of sensation to the legs. In order to reduce side effects of the lumbar puncture, the volunteers will be asked to remain lying flat for about an hour after the procedure and be given fluid to drink after the procedure. A band-aid will be placed on the skin where the needle went in and the volunteer will be asked to remove it the next day and tell the study doctor right away if any redness

or tenderness is present. The investigators will ask the volunteers about history of any allergies to anesthetics and will not perform lumbar puncture is any volunteer with such history.

MRI/MRS/DTI

Because MRI/MRS/DTI is a medical device which uses a magnet, any metal object placed in the strong magnetic field of the MRI/MRS/DTI scanner will be pulled to it and may cause injury. In order to avoid this, the volunteers will be asked to leave as many metal objects as possible at home, and they will be asked to remove all metallic objects including jewelry, dentures, glasses, watches, and artificial limbs before the MRI/MRS/DTI. Gadolinium will not be used for research purposes. The volunteers may feel claustrophobic (fear of being in a small, closed space) or anxious. If this is likely to happen, the investigators can give the volunteers a sedative such as lorazepam to take by mouth.

10.4 BENEFITS

Volunteers should expect no direct benefit from participation in this study and VRC01 may not ultimately be developed for the treatment of HIV. This study explores the safety, pharmacokinetics, and antiviral effects of VRC01 given during ATI in patients who were treated with ART during early acute HIV infection. It is a proof of concept study that may help guide the development of VRC01 or other antibody-based therapies. This represents a novel paradigm for the treatment of HIV, the exploration of which has the potential to benefit society and shift research agendas related to achieving a functional cure of HIV.

10.5 INFORMED CONSENT

The study informed consent describes the investigational product and placebo to be used and all aspects involved in protocol participation. A properly executed written site specific informed consent based on the template provided here, in compliance with the Declaration of Helsinki, guidelines of the Council of International Organization of Medical Sciences (CIOMS), the Belmont Report, the U.S. Code of Federal Regulations 21 CFR 50, must be obtained from each subject prior to entering the subject into trial or prior to performing any unusual or non routine procedure that involves risk to the subject. The signed informed consent form will be maintained in the subject's record file, and a copy of the signed consent form will be given to the subject to keep. Before a subject's participation in the study, it is the investigator's responsibility to obtain this written informed consent from the subject, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or study medications are administered.

For illiterate subjects, a thumbprint will be substituted for signature, and their informed consent will be witnessed by an adult who is not a member of the research study staff. Volunteers may take as much time as needed to decide if he/she wants to participate and may share the consent form with family members or friends prior to agreeing to participate.

10.5.1 Test of Understanding

The procedures for informed consent include a test of understanding. The test of understanding will be a "one-on-one" review with the volunteer by a member of the study team. To pass, the volunteer must answer 90% or 9 out of 10 of the questions correctly. If the volunteer is unable to do so, he or she will be given 3 opportunities to repeat the test of understanding. If after 3 attempts to pass the test of understanding, the volunteer is unable to do so, the volunteer will become ineligible for study participation.

Volunteers who pass the test of understanding and have given written informed consent will be enrolled in the study.

10.6 LANGUAGE

The ICF and other study documents given to participants will be translated into Thai.

10.7 COMPENSATION

Participants will be compensated for time and inconvenience in accordance with the standards and legal obligations for compensation. Any applicable guidelines by IRBs/ECs for compensation of research subjects will be sought and followed.

There may be compensation for lost time, travel expenses and inconvenience, for each scheduled visit. Any applicable guidelines by IRBs/ECs for compensation will be sought and followed.

10.8 DOD RESEARCH MONITOR

The DoD Research Monitor is required to review all unanticipated problems involving risks to participants or others, serious adverse event (SAE) reports, and all deaths. The DoD Research Monitor will provide an unbiased written report of all unanticipated problems involving risks to participants or others, and related SAEs and deaths, promptly within 10 working days to the WRAIR IRB by phone (301) 319-9940, or by email (usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil), by facsimile (301) 319-9961 or at the following address: Walter Reed Army Institute of Research, ATTN: Human Subjects Protection Branch, 503 Robert Grant Ave., Silver Spring, MD 20910. All DoD Research Monitor's reports for unrelated SAEs and deaths should be kept with the corresponding SAE reports at the study site.

The WRAIR HSPB will submit copies of these reports to the USAMRMC ORP HRPO as per SOP UWZ-C-636. The DoD Research Monitor at a minimum must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The DoD Research Monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator.

The DoD Research Monitor or their approved alternate should review all initial, follow up and final reports for SAEs, unanticipated problems involving risks to participants or others, and all participant deaths in a timely manner, and provide their own independent report.

The DoD research monitor will also:

1. Discuss research progress with the PI, interview participants, consult on individual cases, or evaluate suspected adverse reaction reports on behalf of the IRB.

2. Perform at the direction of the IRB, oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection and analysis)

3. Promptly report discrepancies or problems to the IRB.

4. Have the authority to stop a research study in progress, remove individual participants from a study, and take whatever steps are necessary to protect the safety and well-being of research participants until the IRB can assess the research monitor's report.

10.9 PARTICIPANT CONFIDENTIALITY

The PI will maintain research records of participant's participation at the site for this study. All participants will receive study numbers that are known only to the investigators and clinic staff. Clinical tests will be identified by study number and the specimen bag will be identified by study number and bar code only. Clinical and research records may be reviewed by the representative of the DAIDS, USAMRMC, WRAIR, representatives of the USAMRMC ORP HRPO, representatives of the FDA, OHRP, the product and device providers, and other regulatory agencies as part of their responsibilities for insuring the protection of research participants.

Every effort will be made to keep the records as confidential as possible within the limits of the law. All data and medical information obtained about participants, as individuals will be considered privileged and held in confidence. Research and clinical information relating to participants will be shared with other investigators and the scientific community through presentation or publication; however, participants will NOT be identified by name or social security number. Electronic data will be stored at least as long as the IND remains open.

10.10 INSTITUTIONAL REVIEW BOARD

A copy of the protocol, proposed informed consent form, other written participant information, and any proposed advertising material will be submitted to the appropriate ethical and scientific review committees in each country for review and approval. In addition, the protocol will undergo review and approval by both the WRAIR IRB and the USAMRMC ORP at Medical Research and Materiel Command, U.S. Army (MRMC).

10.11 FUTURE USE AND STORAGE OF BLOOD SAMPLES

Each study participant will be asked to separately, and voluntarily consent to storage of their blood samples for other research studies that may be done after this study is completed. As stated above, the sample will be labeled with the bar code of the subject ID that can be linked to their study information. In case the volunteer is unwilling to have their blood samples stored for future use,

they can consent to participate in this study only, without having their blood samples stored for future testing. In this case, their blood samples will be destroyed after all the tests specified for this study have been concluded.

Biological samples will be stored at the Thai Red Cross AIDS Research Centre in Bangkok, Thailand; the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand; and/or the U.S. Military HIV Research Program in Bethesda, MD, USA.

All samples for which consent has been obtained and for which additional material is available after study specified testing is complete will be stored for future testing at the site. However, WRAIR IRB and Chulalongkorn University IRB approval will be sought before any such samples are used for analysis not specified in the protocol or a protocol amendment approved by the IRB. All samples belong to the site from which they were obtained and MHRP.

10.12 STUDY DOCUMENTATION AND STORAGE

Source documents are original documents, data, and records from which the subject's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and staff are responsible for ensuring maintenance of a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the WRAIR, MRMC, DAIDS, FDA, and/or applicable regulatory authorities.

11.0 ADMINISTRATIVE AND LEGAL PROCEDURES

11.1 PROTOCOL DEVIATION REPORTING

All major protocol deviations that adversely affect the safety or rights of a subject or scientific integrity of the study, will be reported to the WRAIR IRB within 48 hours and written reports should be submitted within 10 working days. The contact information for the WRAIR IRB is as follows:

Director, Human Subjects Protection Branch
503 Robert Grant Avenue
Silver Spring, MD 20910
Telephone: 301-319-9940
Fax: 301-319-9961
Email: usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil

All protocol deviations occurring within the reporting period should be summarized in the continuing review reports that are submitted to the WRAIR IRB. Protocol deviations will be reported to the USAMRMC ORP HRPO by the HSPB as per UWZ-C-636.

11.2 PROTOCOL MODIFICATIONS

Amendments to the protocol will be made only after consultation and agreement between DAIDS, the protocol chair, and the principal investigators. All protocol modifications (including but not limited to changes in the principal investigator, inclusion/exclusion criteria, number of participants to be enrolled study sites, or procedures) must be submitted as a written amendment to DAIDS, Chulalongkorn University IRB, and the WRAIR IRB for approval before implementation of the amendment. The WRAIR HSPB will submit protocol amendments and modifications to the USAMRMC ORP HRPO as per UWZ-C-636.

Modifications or updates to the investigational brochures (IBs) will also be submitted as protocol amendments to the ERCs/IRBs for review and approval.

The Informed Consent Form must be revised to concur with any significant amendment that directly affects volunteers, and must also be reviewed and approved with the amendment. New volunteers enrolled in the study will be consented with the most recent approved consent form. Volunteers already enrolled in the study will be informed about the revision and, depending on the impact of the amendment, may be asked to re consent. This may be accomplished by repeating the consent process with the revised consent form with attention given to the changes, or it may be done using an addendum consent that states the revision or new information. The new document must be signed, placed in the study record, and a copy given to the volunteer.

Prior to implementation of this protocol, and any subsequent full version amendments, the protocol and the protocol consent form(s) must be approved, as appropriate, by the Chulalongkorn

University institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, the site will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and the site will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, the study site should implement the amendment immediately. The site is required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and the site will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

A list of proposed modifications or amendments to the protocol and an explanation of the need for these modifications will be submitted, along with a revised protocol incorporating the modifications. The only exception occurs when the investigator considers that a study participants's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform DAIDS and the IRB within five working days after the emergency occurred. As previously mentioned, all study amendments will be submitted as a written amendment to DAIDS for possible CSRC review and regulatory submission to the Chulalongkorn University IRB, and WRAIR. In accordance with 21 CFR 312.30 (b) any change in a Phase 1 protocol that significantly affects the safety of subjects will be submitted to the FDA.

11.3 CONTINUING REVIEWS/CLOSEOUT REPORT

A continuing review report (CRR) will be submitted in the proper format to all ERCs/IRBs prior to the date determined by the IRBs. This report will also be submitted to the Thai FDA. If the continuing review is not approved by the Chulalongkorn University ERC/IRB and WRAIR IRB by the anniversary date, all protocol activities must stop at that site until such time as the approval is obtained. A copy of the approved CRR and Chulalongkorn University IRB approval notifications will be submitted to the WRAIR HSPB as soon as these documents become available. After all study related activities, including data analysis, are completed a closeout report will be submitted as required to the IRBs and Thai FDA. A copy of the approved closeout report and Chulalongkorn University IRB approval notifications will be submitted to the WRAIR HSPB as soon as these documents become available.

11.4 VOLUNTEER REGISTRY DATABASE

It is the policy of the USAMRMC that Volunteer Registry Data Sheets are completed on all volunteers participating in greater than minimal risk research for entry into the Command's Volunteer Registry Database. Ordinarily this information would include the individual's unique identifier (e.g. SSN in the U.S.A.), study name and dates. But because many countries do not have a national identification system that would uniquely identify each person in the country, the Volunteer Registry Data Sheets will collect the following data on the volunteers:

names (first and last name)
date of birth, home district
study name and study dates

The intent of the database is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at AFRIMS for a minimum of 75 years. In countries other than the U.S., social security numbers do not exist and cannot be collected; all other data can. If available, country-specific identity numbers may be used. This database will not be used for research.

11.5 POLICY REGARDING RESEARCH-RELATED INJURIES

The US DoD and DAIDS/NIAID/NIH are funding this protocol. As stated in the consent form, participants who experience illness or injury arising from participation in the study will receive medical care for such illness or injury with costs for such care provided by a limited set-aside fund that is used for HJF/MHRP studies in Thailand and a clinical trials medical insurance policy that will be obtained by HJF/MHRP. While we anticipate the combination of the set-aside fund and the insurance policy is more than enough to pay for the research related injury medical care cost associated with this study, there is a limit to the amount of coverage available. Other than medical care, and other payments as stated in the consent form, there is no other compensation available from this research study.

11.6 USE OF INFORMATION AND PUBLICATION

It is understood by the investigator that the information generated in this study may be used in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the investigator is obliged to provide DAIDS with complete test results, all study data, and access to all study records.

WRAIR recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Any results of medical investigations and or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the investigator, and the USAMRMC 60 days prior to submission for publication or presentation.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. WRAIR will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference). All publications written by WRAIR investigators must be reviewed and approved by the WRAIR Office of Research Technology and Applications (ORTA).

12.0 CONDUCT OF THE RESEARCH STUDY

This research study will be conducted in accordance with GCP, ICH guidelines, DOD Directive 3216.2, the Declaration of Helsinki, the Belmont Report, the U.S. Code of Federal Regulations 21 CFR 312, 812, 50 and 56, 32 CFR 219, 45 CFR 46, and all applicable local laws and regulations.

12.1 REGULATORY AUDITS

The knowledge of any pending compliance inspection/visit by the US FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to DAIDS and the WRAIR HSPB. The WRAIR HSPB will report knowledge of any pending inspections/audits by regulatory agencies to the USAMRMC ORP HRPO as per UWZ-C-636.

12.2 DAIDS STUDY MONITORING

Site visits by study monitors will be made in accordance with DAIDS policy to monitor the following: study operations, the quality of data collected in the research records, the accuracy and timeliness of data entered in the database, and to determine that all process and regulatory requirements are met.

Site investigators will allow the study monitors, DAIDS, the IRB/Ethical Review Committee (ERCs), MRMC, and the FDA to inspect study documents (e.g., consent forms, drug distribution forms, case report forms), and pertinent hospital or clinic records for confirmation of the study data.

Study data will be closed and final after data cleaning activities are completed and resolutions have been documented.

13.0 RELEVANCE

13.1 MILITARY RELEVANCE

The HIV pandemic currently stands as one of the greatest threats to global public health. An estimated 35 million people are living with HIV/AIDS and 5700 new HIV infections are occurring in the world each day, the majority of which require life-saving ART. Recent advances in efforts to prevent and treat HIV disease are encouraging, but AIDS is still among the leading causes of death in the developing world; areas that are already burdened with lowered life expectancy and reduced economic growth. HIV/AIDS, therefore, exacerbates the disintegration of social and political cohesion in these affected areas. These conditions, in turn, affect the stability of nations and thus pose a risk to global security.

The military relevance of HIV has, therefore, been recognized from the very beginning of the pandemic. In 1985, the U.S. military recognized the emerging HIV-1 epidemic as a new threat to U.S. and allied forces worldwide. Soon after, at the height of the HIV global pandemic, the United States Congress mandated the establishment of the U.S. Military HIV Research Program (MHRP) to develop effective prevention measures to combat the rise of HIV. Then, in 2001, the DoD Report on Biological Warfare Defense Vaccine Research and Development identified HIV as the 4th greatest infectious disease threat to DoD forces. Even as the global incidence of HIV has fallen in the past decade, the 2002, 2006 and 2010 President's National Security Strategy plans have continued to highlight HIV as a persistent threat to national security as it continues to contribute to regional instability and, thus, affect military force readiness and deployment[80]. The US Department of Army Headquarters designated HIV vaccine development as an Army Technology Objective (ATO), a status reserved for the highest priority science and technology efforts.

HIV also poses a direct health risk to military personnel through multiple modes of transmission. Bloodborne transmission is of particular concern given the potential contamination of the combat theater blood supply. The "walking blood bank," which draws upon donated blood supplies from local populations, was used more than 21,000 times in the recent operations in Iraq and Afghanistan. In order to provide life-saving blood and plasma products in an expedient way for the battlefield, HIV screening cannot always be screened according to standard U.S. medical practice.

In 2013, there were over 340 incident HIV infections in the U.S. military [81]. Currently, the cost to the US government for the treatment and care of its 1500 HIV-infected active service members ranges from 21 to 54 million dollars per year with an estimated lifetime accrued cost of $418 million [82, 83] . The total lifetime cost to the US government of the approximately 5000 active and non-active infected service members identified since active force-wide screening was initiated is $8-$10 billion. Thus, in addition to identifying and implementing effective methods for HIV prevention, strategies to cure the disease will greatly benefit HIV-infected personnel, eliminate a potential source for HIV transmission and relieve an enormous health care burden necessitated by lifetime ART.

13.2 THAI RELEVANCE

Thailand has the highest adult HIV prevalence in Asia, reported as 1.2% of the adult population living with HIV in 2012 [84]. In the early 1990s, Thailand was facing a generalized HIV epidemic

with HIV prevalence peaking at 4.0% among male military recruits and 2.6% among women attending antenatal clinics. In 1991 alone, over 160,000 new HIV infections were estimated to have occurred [85] . In the past few years, it is estimated that the rate of new infections has fallen dramatically to approximately 8,000 per year [85]. Despite the great success in HIV prevention, Thailand faces an ongoing challenge in providing ART to the large number of Thai people living with HIV infection (PLHIV). Almost uniquely among developing countries, Thailand provides ART with entirely domestic funding and does not rely on international donors.

In 2014 Thailand revised its national HIV treatment guidelines to recommend ART for all PLHIV [86]. Immediate ART along with increasing coverage of HIV testing among key populations are key strategies currently used by the country aiming to end its AIDS epidemic by 2030. This change will increase the number of Thai citizens eligible for ART from 246,000 to 407,000 in 2015, an increase of 65% [87]. An increase in ART provision of this magnitude will challenge the Thai health system to provide the clinics and health care workers to manage the increased case load of ART patients as well as finding the financial resources to pay for the additional medications required.

This study will contribute to the national HIV treatment program in Thailand by potentially demonstrating the therapeutic efficacy of VRC01 monoclonal antibody infusions in lieu of ART in selected patients who started ART during acute infection. If a subset of patients remains clinically and immunologically stable off ART and after completing a course of VRC01 infusions, this could result in substantial financial savings to public health systems. In addition, all of the patients who could be recruited for the study are Thai citizens who acquired HIV infection in Thailand, which provides direct relevance to the HIV epidemic in the country.

14.0 PRINCIPAL INVESTIGATOR AGREEMENT:

1. I agree to follow this protocol version as approved by the IRBs/ERCs.
2. I will conduct the study in accordance with applicable IRB/ERC requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I will not modify the protocol without first obtaining an IRB/ERC approved amendment and new protocol version unless it is necessary to protect the health and welfare of study participants.
5. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
6. In accordance with Command Policy 2008-35, I will ensure that the Commanding General receives a pre-brief (or Executive Summary) and approves the study prior to execution.
7. I will ensure that the data (and/or specimens) are maintained in accordance with the data (and/or specimen) disposition outlined in the protocol. Any modifications to this plan should first be reviewed and approved by the applicable IRBs/ERCs.
8. I will promptly report changes to the research or unanticipated problems to the WRAIR IRB immediately via the WRAIR Human Subjects Protection Branch at (301) 319-9940 (during duty hours) or to the usarmy.detrick.medcom-wrair.mbx.hspb@mail.mil and submit a written report within 10 working days of knowledge of the event.
9. I will prepare continuing review reports at an interval established by the IRB/ERC, and a study closure report when all research activities are completed.
10. I will immediately report to the WRAIR Human Subjects Protection Branch knowledge of any pending compliance inspection by any outside governmental agency.

11. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

_____	_____
RV 397 Protocol Chair	Date (DD/MM/YYYY)
_____	_____
RV 397 PI	Date (DD/MM/YYYY)

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APPENDIX I: CASE DEFINITION FOR ACUTE RETROVIRAL SYNDROME (ARS)

Case definition must include all of the following:

- Occurs within 30 days after documented rise in plasma HIV-1 RNA of ≥ 1 log10 or to ≥ 1,000 copies/mL
- Occurs within 60 days after discontinuation of ART
- Documented fever (temperature >38.5°C)
- At least two major criteria
- At least two minor criteria
- No other cause for signs and symptoms identified

Major criteria (must be present for >7 days):

- Pharyngitis
- Fatigue
- Morbilliform rash
- Myalgia/arthralgia
- Lymphadenopathy
- Subjective fever as reported by subject (may be intermittent)

Minor criteria (must be present for >7 days):

- Headache
- Nausea/vomiting
- Diarrhea
- Mucocutaneous ulceration (oral, genital, and/or anorectal)
- Meningismus/aseptic meningitis
- Night sweats
- Thrombocytopenia (platelets <150,000)
- Leukopenia (WBC <4,000)
- Malaise
- Abdominal pain
- Weight loss (loss of >5% of body weight)

APPENDIX II: SCHEDULE OF EVALUATIONS

Procedure/Study Week[1]	**-6**	**-4**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Screening	X																					
Enrollment	X																					
Consent	X																					
Collection of Contact Information	X			X			X			X			X			X			X			X
PI Substition[3]		X																				
VRC01/Placebo Infusion				X			X			X			X			X			X			X
Interruption of ART				X																		
History				X			X			X			X			X			X			X
Physical Exam				X			X			X			X			X			X			X
Neuropsychological exam				X																		
Control and attention testing	X			X	X			X								X						
Plasma NNRTI level[4]		4	4	4																		
Qualitative HIV RNA				X	X						X	X		X	X		X	X		X	X	
Twice Weekly HIV RNA[5]				*	*	X	X	X	X	*	*	*	*	*	*	*	*	*	*	*	*	*
HIV RNA PCR	6			6		3	6			6			3			6			3			6
CD4/CD8 Count	NB			NB			NB			NB						NB						NB
Complete Blood Count	NB			NB			NB			NB						NB						NB
Liver Enzymes				6			4			4						4						4
Creatinine				NB																		
Lipids				NB																		
Syphilis, HBV, HCV screen	4																					
Urine HCG[6]	X			X			X			X			X			X			X			X
Urinalysis	X			X			X			X			X			X			X			X
Integrated HIV DNA, Total HIV DNA, 2LTR Circles	8.5[13]			8.5		8.5	8.5			8.5			8.5			8.5			8.5			8.5
Single Copy HIV RNA[7]				8.5			8.5			8.5			8.5			8.5			8.5			8.5
QVOA[7]				NB																		
TILDA[7]				8.5			8.5			8.5			8.5			8.5			8.5			8.5
TULDA[8]				8.5			8.5			8.5			8.5			8.5			8.5			8.5
PBMC/Plasma Collection				51	17	17	25.5			25.5			25.5			25.5			25.5			25.5
Plasma collection (EDTA)				3	3	3	3			3			3			3			3			3
Serum collection				4	4	4	4			4			4			4			4			4
HIV Genotype[9]																						
Chest X-ray				X																		
EKG				X																		
Optional Leukapheresis[10]*				X																		
Optional Mucosal Secretion Collection[11]*				X																		
Optional Colon Biopsy*				X																		
Optional Inguinal Lymph Node Biopsy*				X																		
Optional Lumbar Puncture[12]*				X																		
Optional Brain MRI/MRS/DTI*				X																		
Daily Volume	18.5	4	4	108	24	35.5	76.5	0	0	76.5	0	0	69.5	0	0	76.5	0	0	69.5	0	0	76.5
Cumulative Volume	18.5	22.5	26.5	134.5	158.5	194	270.5	270.5	270.5	347	347	347	416.5	416.5	416.5	493	493	493	562.5	562.5	562.5	639
12week cumulative volume																358.5	334.5	299	292	292	292	292

															390							

Procedure/Study Week[1]	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**[2]
Visit Number	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Screening																						
Enrollment																						
Consent																						
Collection of Contact Information			X			X				X		X		X		X		X		X		X
PI Substition[3]																						
VRC01/Placebo Infusion			X			X																
Interruption of ART																						
History			X			X		X		X		X		X		X		X		X		X
Physical Exam			X			X		X		X		X		X		X		X		X		X
Neuropsychological exam						X																X
Control and attention testing						X																X
Plasma NNRTI level[4]																						
Qualitative HIV RNA[5]	X	X		X	X		X						X		X		X		X		X	
Twice Weekly HIV RNA[5]	*	*	*	*	*	*	*	X	X	X	X	*	*	*	*	*	*	*	*	*	*	
HIV RNA PCR			3			6		3		6		3		6		6		6		6		6
CD4/CD8 Count						NB				NB				NB		NB		NB		NB		NB
Complete Blood Count						NB										NB						NB
Liver Enzymes						X										4						6
Creatinine																						NB
Lipids																						NB
Syphilis, HBV, HCV screen																						NB
Urine HCG[6]			X			X				X				X				X		X		X
Urinalysis			X			X																X
Integrated HIV DNA, Total HIV DNA, 2LTR Circles			8.5			8.5								8.5				8.5				8.5
Single Copy HIV RNA[7]			8.5			8.5				8.5				8.5		8.5		8.5		8.5		8.5
QVOA[7]						NB																NB
TILDA[7]			8.5			8.5												8.5				8.5
TULDA[8]			8.5			8.5												8.5				8.5
PBMC/Plasma Collection			25.5			51		25.5		25.5		25.5		25.5		25.5		25.5		25.5		51
HIV Genotype[9]																						8.5
Chest X-ray																						
Plasma collection (EDTA)			3**			3**																
Serum collection			4**			4**				4		4		4		4		4		4		4
EKG																						
Optional Leukapheresis[10]*						X																X
Optional Mucosal Secretion Collection[11]*						X																X
Optional Colon Biopsy*						X																X
Optional Inguinal Lymph Node Biopsy*						X																X
Optional Lumbar Puncture[12]*						X																X
Optional Brain MRI/MRS/DTI*						X																X

Daily Volume	0	0	69.5	0	0	98	0	28.5	0	44	0	32.5	0	52.5	0	48	0	69.5	0	44	0	109.5
Cumulative Volume	639	639	708.5	708.5	708.5	806.5	806.5	835	835	879	879	911.5	911.5	964	964	1012	1012	1081.5	1081.5	1125.5	1125.5	1235
12 week cumulative volume	292	292	292	292	292	313.5	313.5	342	272.5	316.5	316.5	272.5	272.5	325	255.5	205.5	177	202.5	170	161.5	161.5	223

This Schedule of Evaluations summarizes the required and optional evaluations to be performed at each scheduled study visit. Blood volumes (mL) associated with each evaluation are presented. Evaluations that require no blood collection are marked with an "X" at the study visits at which they are performed. Evaluations that will be performed using blood already drawn for other tests on the SOE for that visit are marked "NB" (no additional blood required). Daily, cumulative, and 12-week cumulative volumes of blood collection are shown. Blood collection volumes may be reduced for volunteers weighing <50 kg.

[1] Study procedures for each visit may be performed on different days depending on scheduling for mandatory and optional procedures, within pre-specified allowable time windows (± 3 days for mandatory procedures during study weeks 0-36 and ± 1 week for all other visits; ± 12 weeks for optional procedures).

[2] The duration of follow-up may vary among subjects depending on time to rebound viremia or other criteria for the resumption of ART. There is no minimum time in this study. For subjects whose study duration is less than 48 weeks, procedures listed for end of study under "Study Week 48" will be performed at the last study visit.

[3] PI substitution will be performed only for participants prescribed an NNRTI at the time of enrollment.

[4] Plasma NNRTI level will be scheduled only for participants prescribed an NNRTI at the time of enrollment and will occur at the time of NNRTI discontinuation, and 2 and 4 weeks following discontinuation. ART blood levels (NNRTI or other drugs) will be checked on all subjects who are virologically suppressed at week 24 in order to monitor for possible ART use. NNRTI and other ART levels may be checked at additional time points at the discretion of investigators.

[5] HIV-1 RNA VL will be performed twice per week from weeks 2 until week 6 and from week 26 until week 30 either quantitatively using a venous blood sample (3mL) or qualitatively using a small blood volume collection (0.6mL). Positive qualitative samples will be rechecked using the quantitative method. Participants with detectable viremia (>50 copies/mL) will be checked every 3 days. Once ART is resumed, HIV-1 RNA VL will be checked every 4 weeks until the result is undetectable (<50 copies/mL). Willing participants may optionally present for twice weekly HIV RNA testing at any time throughout the study. Small blood volume collection for this assay, performed via finger stick or venous sampling, contributes negligible additional volume to the reported daily total volumes.

[6] Urine HCG (pregnancy test) will be done only on females of childbearing age.

[7] Single copy HIV RNA, QVOA (quantitative viral outgrowth assay), and TILDA (tat/rev induced limiting dilution assay) will be performed only if plasma HIV RNA <50 copies/mL and adequate blood sample is available.

[8] TULDA (tat/rev uninduced limiting dilution assay) will be performed only if plasma HIV RNA >1000 copies/mL.

[9] HIV genotype will only be performed at time of reinitiating ART, either on plasma or pro-viral DNA, if levels are sufficient to allow amplification.

[10] Leukapheresis will be performed at select visits to collect PBMC and plasma in non-pregnant subjects who provide separate informed consent. Subjects who wish not to have leukapheresis performed will undergo phlebotomy for PBMC/plasma collection. The amount of blood drawn will be the same for either procedure.

[11] Mucosal secretion collection includes semen (male), cervico-vaginal secretion collection by Softcup (female), anal rectal sponge (men who have sex with men).

[12] Blood glucose, protein and HIV RNA will be performed at time of cerebrospinal fluid collection via lumbar puncture. The optional lumbar puncture scheduled for week 48/EOS may be performed earlier if impending viral rebound is suspected.

[13] Integrated HIV DNA, Total HIV DNA, and 2LTR Circles will be performed at week -6 only if volunteer does not have an available result within the preceding 12 weeks.

***** Optional studies

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ATTACHMENT II: ROLES AND RESPONSIBILITIES

ATTACHMENT III: DAIDS AE GRADING TABLE

ATTACHMENT IV: TEST OF UNDERSTANDING