IMPAACT 2008

Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

Study Product Provided by:
National Institute of Allergy and Infectious Diseases Vaccine Research Center

DAIDS Study ID #20735
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Version 2.0
PROTOCOL SIGNATURE PAGE

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record	Date
Name of Investigator of Record (printed)	

ABBREVIATIONS AND ACRONYMS

ACTG A5342	A Phase I Study to Evaluate the Safety, tolerability, and Effect of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01) on Markers of HIV Persistence in ART-treated, HIV-infected Adults
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATI	Analytic treatment interruption
bNAb	Broadly neutralizing monoclonal antibodies
cART	Combination antiretroviral therapy
CBC	Complete blood count
CDR	Complementarity-determining regions
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
CNS	Central nervous system
CRF	Case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS	Clinical research site
CSF	Cerebral spinal fluid
CTLVI	Cytotoxic T lymphocyte-mediated viral inhibition
D/C	Discontinuation
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DAIDS PRO	Division of AIDS Protocol Registration Office
ddPCR	Digital droplet polymerase chain reaction
DMC	Data Management Center
DNA	Deoxyribonucleic acid
EAE	Expedited Adverse Event
EC	Ethics committee
eCRF	Electronic case report form
EMLA	Eutectic Mixture of Local Anesthetics
FDA	Food and Drug Administration

FDAAA	United States Food and Drug Administration Amendments Act of 2007
FSTRF	Frontier Science & Technology Research Foundation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HVTN	HIV Vaccine Trials Network
HVTN 104	A Phase I Clinical Trial to Evaluate the Safety and Drug Levels of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered in Multiple Doses Intravenously and Subcutaneously in Different Dosing Schedules to Healthy, HIV-Uninfected Adults
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICF	Informed consent form
IgG1	Immunoglobulin G1
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IMPAACT P1030	A Phase I/II Study of Lopinavir/Ritonavir in HIV-1 Infected Infants <6 Months of Age
IMPAACT P1112	Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous VRC01, a Potent Anti-HIV Neutralizing Monoclonal Antibody, in HIV-1 Exposed Infants
IMPAACT P1115	Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
IND	Investigational New Drug
IQA	DAIDS Immunology Quality Assurance program
IRB	Institutional Review Board
IUPM	Infectious units per million cells
IV	Intravenous
KA	Absorption rate constant
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
LPV/r	Lopinavir/ritonavir
mAb	Monoclonal antibody
MOP	Manual of Procedures
NAT	Nucleic acid testing
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NVITAL	NIAID Vaccine Immune T-Cell and Antibody Laboratory
NVP	Nevirapine
OHRP	Office for Human Research Protections
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PID	Participant Identification Number
PK	Pharmacokinetics
qPCR	Real-time polymerase chain reaction
QVOA	Quantitative viral outgrowth assay

RNA	Ribonucleic acid
RSC	Regulatory Support Center
RV 398	Safety and Virologic Effect of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), With Broad HIV-1 Neutralizing Activity, Administered Intravenously to Adults During Early Acute HIV Infection
SAE	Serious adverse event
SC	Subcutaneous
SCA	Single copy assay
SD	Standard deviation
SDMC	Statistical and Data Management Center
SES	Subject Enrollment System
SHIV	Simian/human immunodeficiency virus
SID	Study Identification Number
SMC	Study Monitoring Committee
SoE	Schedule of Evaluations
SOP	Standard operating procedures
SUSAR	Suspected, unexpected, serious adverse reaction
TB	Tuberculosis
TILDA	Tat/rev induced limiting dilution assay
US	United States
VQA	DAIDS Virology Quality Assurance program
VRC	Vaccine Research Center
VRC01	VRC-HIVMAB060-00-AB, a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody
VRC 601	A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults
VRC 602	A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults
WHO	World Health Organization

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IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

SCHEMA

Purpose:	To evaluate the safety and antiviral activity of VRC01 administered in addition to combination antiretroviral therapy (cART) to HIV-1-infected infants to promote clearance of HIV-1-infected cells.
Design:	Phase I/II, multisite, two-arm, randomized, controlled, open-label study.
Study Population:	HIV-1-infected infants initiating cART within 12 weeks of birth. Infants' mothers may optionally be enrolled in the study for one-time specimen collection for exploratory evaluations.
Sample Size:	68 infants
Study Product:	Infants will be randomly assigned in a 1:1 ratio to either receive VRC01 (Arm 1) or not receive VRC01 (Arm 2). Infants assigned to Arm 1 will be administered subcutaneous injections of VRC01 (40 mg/kg) at study Entry (Week 0) and at study Weeks 2, 6, and 10. Infants assigned to Arm 2 will receive no study product.
Study Duration:	Approximately two years. Accrual is expected to require approximately one year, and each infant will complete 48 weeks of follow-up.

Primary Objectives:

To assess the following among HIV-1-infected infants:

- Safety of VRC01 administered with cART (cumulatively through Week 14)
- Effect of VRC01 on HIV-1 DNA concentrations in peripheral blood mononuclear cells (change from Week 0 to Week 14)

Secondary Objective:

To assess the following among HIV-1-infected infants:

- Pharmacokinetics of VRC01 (through Week 16)

Other Objectives:

To assess the following among HIV-1-infected infants:

- Longer-term safety of VRC01 administered with cART (cumulatively through Week 48)
- Development of anti-VRC01 antibodies (at Weeks 14, 24, and 48)
- Effect of VRC01 on time to achieve plasma HIV-1 RNA below 40 copies/mL (through Week 48)
- Effect of VRC01 on biomarkers of HIV persistence in peripheral blood mononuclear cells:
  - HIV-1 DNA concentration (at Weeks 24 and 48)
  - HIV-1 RNA concentration (multiply-spliced and unspliced; at Weeks 14, 24, and 48)
  - Total inducible HIV-1 RNA concentration (at Weeks 24 and 48)
- Effect of VRC01 on HIV-1-specific antibody-dependent cellular cytotoxicity and virus neutralization against infant viral isolates (at Weeks 14, 24, and 48)

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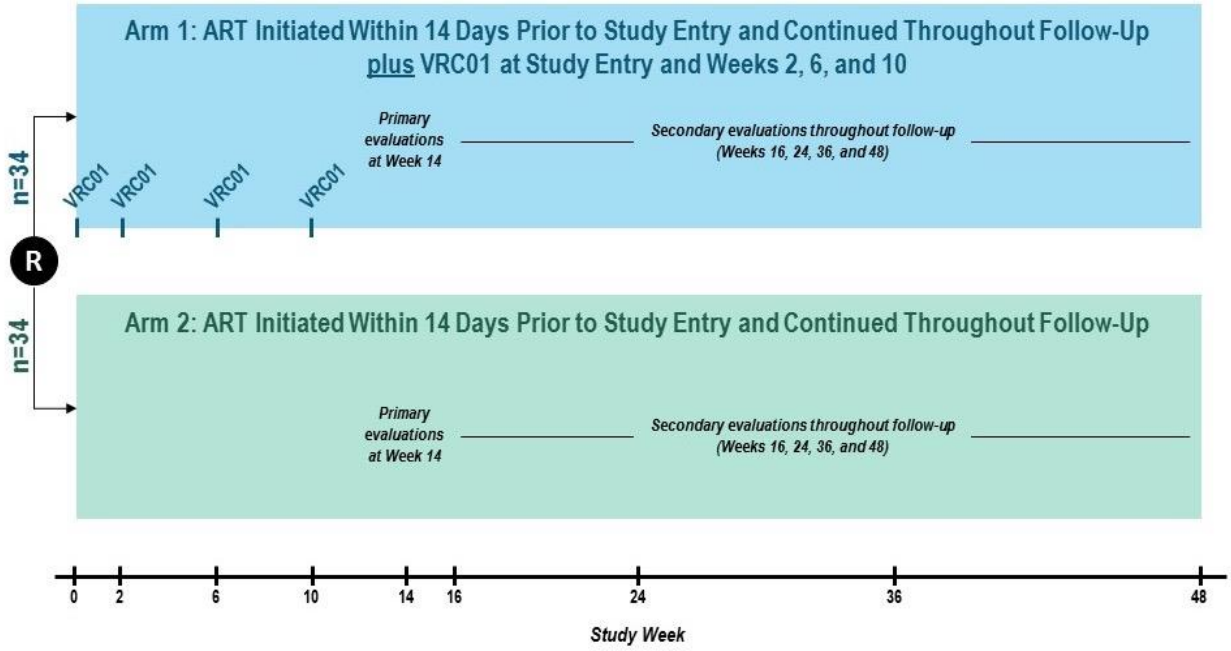
Figure 1
Overview of Study Design



1 INTRODUCTION

1.1 Background

1.1.1 Global Impact of Pediatric HIV and Need for Interventions to Induce ARV-Free Remission

There are an estimated 1.8 million children living with HIV-1 worldwide. In 2015, an estimated 150,000 new perinatal cases occurred [1]. This is despite progress over the past two decades in identifying strategies to dramatically reduce *in utero*, peripartum, and breastfeeding HIV-1 transmission. With this pattern of ongoing HIV-1 transmission to infants, it is critical to continue to direct efforts towards identifying novel strategies for the treatment of HIV-1 infection in infants, who face a lifetime of antiretroviral therapy (ART) due to almost immediate establishment of HIV-1 reservoirs that re-establish viremia when treatment is stopped [2-4].

Achieving low concentrations of HIV-1 infected cells on combination antiretroviral therapy (cART) is emerging as a biomarker that is predictive of time to rebound when cART is stopped [5]. Very early therapy, within 48 hours of life, may result in early restriction of the HIV-1 reservoir [6], and this approach to HIV-1 treatment is currently under study in another IMPAACT protocol (P1115). However, for many infants, HIV-1 infection is not identified until one to three months of age, even in settings with access to early infant diagnosis [7, 8]. In IMPAACT P1030, infants received cART initiated at two to three months of age, but this was not sufficient to block HIV-1 reservoir formation [9]. In addition, the time to achieving undetectable plasma viremia among early treated infants is prolonged, with many infants continuing to have detectable plasma virus beyond the first 24 weeks of therapy [10]. Early infant HIV-1 treatment is challenged by erratic drugs levels related to adherence lapses, somatic growth, or concurrent illnesses that affect drug intake, all common problems among young infants taking cART. Therefore, novel treatments for infants that restrict HIV-1 reservoir establishment and have long acting antiviral activity are needed.

Broadly neutralizing monoclonal antibodies (bNAbs) are an emerging class of HIV-1 therapeutics with direct antiviral properties, largely mediated through virus neutralization [11-13]. However, bNAbs may also facilitate viral clearance through antibody dependent cellular cytotoxicity (ADCC) [14], which promotes killing of HIV-1 infected cells [15]. Combining ART with bNAbs offers a novel approach to HIV-1 therapeutics for infected infants that will perhaps result in faster clearance of plasma viremia and HIV-1-infected cells, thereby lowering viral reservoir size. This will be the focus of the clinical trial. It is hypothesized that concurrent administration of bNAbs with cART will hasten clearance of viremia and HIV-1 producing cells and lead to lower reservoir size.

1.1.2 Characteristics of Viral Reservoirs in Early Treated Infants

Dynamics of HIV-1 DNA decay in early treated infants

The dynamics of decay of HIV-1-infected cells was recently studied during the first two years of cART in perinatally-infected infants initiating cART at a median of two months of age in the IMPAACT P1030 study [9]. The IMPAACT P1030 study was a multicenter, Phase I/II, open-label trial of lopinavir/ritonavir (LPV/r) for treatment of HIV-1-infected infants between 4 weeks and 6 months of age in which the pharmacokinetic properties of LPV/r were established [10, 16]. Lopinavir/ritonavir (LPV/r)-based cART remains the mainstay of treatment for HIV-1-infected infants, for whom ARV drugs are extremely limited. Prior to cART, the median concentration of

HIV-1-infected cells (measured by the concentration of cellular HIV-1 DNA, also known as proviral DNA) in peripheral blood mononuclear cells (PBMC) was 3.16 log_{10} [IQR:1.7, 3.0] HIV-1 DNA copies/million PBMC. By 24 weeks of cART, the concentration of cellular HIV-1 DNA decreased by approximately one log. After two years of plasma virus suppression, proviral HIV-1 DNA remained detectable in 100% of 12 infants at a median concentration of approximately 1.99 log_{10} copies/million PBMCs. Concentrations of 2-LTR circles (episomal HIV-1 DNA that is usually cited as a measure of ongoing virus replication) were also high at baseline (median 2.0 log_{10} copies/ million PBMCs) and persisted at a median concentration of 1.0 log_{10} copies/million PBMC even after 96 weeks of cART. The primary correlate of infected cell concentration at 96 weeks of cART was pre-cART infected cell concentrations. Pre-cART infected cell concentrations were associated with time to suppression of plasma viremia, in support of the notion that infected cells generated before cART are the dominant virus producing cells during treatment.

HIV-1 multiply-spliced (a marker of productively infected cells) and unspliced (a marker of transcriptionally active genomes) transcripts were detected in 100% and 93%, respectively, of the 15 infants studied [9]. After two years of treatment, HIV-1 RNA transcripts (unspliced) were detectable in six of eight infants, although most were unspliced [9].

Measures of the latent reservoir in early treated infants

Persistent infection with replication competent HIV-1 latent in resting memory $CD4^+$ T cells, the source of rebound viremia following cART cessation and precluding cure, was detected in 86% of the 14 infants in the P1030 trial who were tested at 24 weeks of treatment (approximately eight months of age). Thus, latent HIV-1 reservoir cells at concentrations readily detectable by the standard quantitative viral outgrowth assay (QVOA) are established even with cART started at a median age of two months [17]. As would be expected, HIV-1 DNA concentrations in PBMC (which measures both replication competent and defective virus) exceeded the frequency of resting $CD4^+$ T cells bearing replication-competent virus (infectious units per million cells or IUPM) at all time points tested. HIV-1 DNA concentrations and the IUPM in resting $CD4^+$ T cells were correlated (but present at 66-fold excess) at 24 weeks of cART (ρ=0.66, p=0.028) but not at 48 and 96 weeks of cART, supporting depletion of replication-intact genomes over the time course of cART [9]. Therefore, at least through 24 weeks of cART, HIV-1 DNA concentrations provide a reasonable measure of persistence of the clinically relevant, replication-competent reservoir cells, although an overestimate by a median of 66-fold [9].

Another more sensitive assay to detect inducible transcriptionally active HIV-1 genomes is the tat/rev inducible limiting dilution assay (TILDA). TILDA detects inducible HIV-1 genomes following T-cell stimulation *in vitro*. TILDA measures cells containing HIV-1 genomes that can be induced to produce multiply-spliced (msRNA). The unit of measurement is ms-RNA cells per million. TILDA estimates of the frequencies of infected cells persisting in HIV-infected adults on ART are 48-fold greater than the QVOA and 6-27 times lower than HIV-1 DNA, which also measures non-inducible proviral genomes. TILDA has not been studied in pediatric populations but will be used as a reservoir measure in this study. Preliminary studies show detection of inducible ms-transcripts in CD4+ T cells of ART-suppressed HIV-1- infected children (preliminary data; Persaud Laboratory).

Antiviral effects of bNAbs

Non-human primate studies

Several HIV-1-specific bNAbs, including VRC01 mAb — the antibody to be evaluated in this study — have been studied in mice [18], non-human primates (NHP) with recombinant simian immunodeficiency virus expressing HIV-1 envelope (SHIV) [15, 19, 20], and in HIV-1-infected humans [12, 13]. The NHP studies in chronically infected ART-naïve macaques demonstrated the antiviral effects of bNAbs with a rapid and steep decline in plasma SHIV RNA concentrations to undetectable viral load levels within four to seven days of treatment that was sustained for a median of 56 days after antibody infusion [15, 19]. In one study in NHP, bNAbs led to improved immune status as measured by increased cell-mediated viral inhibition (CTLVI), Gag-specific responses, cellular proliferation, and less end-stage T cell differentiation [15]. The bNAbs eliminate free virus through antibody-antigen complex-mediated clearance mechanisms, but those with an appropriate Fc, such as IgG1, will also engage particular Fc receptors that induce ADCC to eliminate infected cells [14]. The NHP studies found a decrease in SHIV DNA in PBMC and in lymph node and gut mucosa [15], supporting antiviral activity in tissues. Recent studies in acute SHIV infection found that bNAbs combined with ART, when compared to ART only, delayed rebound after treatment interruption [21]. A study in acute SIV infection with a single infusion at 10 days after viral inoculation of VRC01 or a combination of two bNAbs (VRC07-523 and PGT121) demonstrated plasma virus suppression and reduction of cell-associated virus in peripheral blood and lymph nodes, with preferential protection of naïve CD4+ T cells [20].

A recent study demonstrated prevention of long term reservoir formation and viral eradication with a combination of bNAbs given very early to infant macaques with acute SHIV-infection [22]. Newborn macaques were inoculated orally with an infectious dose of $SHIV_{SF162P3}$ which resulted in virus disseminated to multiple tissue sites as determined by necropsy of a subset of animals at 24 hours. However, the infant macaques that received a combination of two bNAbs (VRC07-523 and PGT121) started at 24 hours after inoculation were free of detectable virus in the blood as well as integrated virus in lymph nodes at week 12 and in tissues at 24 weeks. VRC07-523 is an engineered clonal relative of VRC01 with increased neutralization and improved potency against $SHIV_{SF162P3.}$ The bNAb PGT121 interacts with variable regions and glycans of HIV-1 gp120. This study suggests that very early passive immunotherapy, but given after dissemination beyond the directly draining lymph nodes, restricted the establishment of viral reservoirs. The same study found that VRC01 given in advance of oral SHIV inoculation was effective in preventing infection.

Human trials

Two bNAb, VRC01 and 3BNC117, were found to be safe and to reduce plasma viremia in HIV-1-infected adults not receiving ART [12, 13]. In both studies, viremic adults receiving a single IV infusion of bNAb had significant decreases (1-2 log_{10}) in plasma HIV RNA levels. As plasma levels of the bNAb declined, or after selection of virus resistant to neutralization by the respective bNAb, the plasma virus increased. However, the bNAb were given as a single dose and without other antiviral agents so ongoing suppression would not be expected. The study of VRC01 also administered the bNAb to virally suppressed, HIV-1-infected adults on cART [12]. Although no changes in markers of HIV-1 persistence were found, the participants received only two doses of bNAb, were already on long term suppressive cART, and had chronic latent viral reservoirs; therefore, the frequency of cells expressing HIV-1 antigens that would be targeted by bNAb is expected to be very low such that detectable changes in HIV-1 biomarkers of persistence might require prolonged treatment to be apparent. The viral dynamics during early treatment of early infection (i.e., the setting for this study), are different from the viral dynamics in the setting of chronic HIV-1 infection treated with cART [23].

The effect of VRC01 administration during analytic treatment interruption (ATI) has been investigated in two studies among adults with viral suppression achieved with cART started during chronic HIV-1 infection [24]. In one study (A5340), among 13 evaluable participants who underwent ATI, 38% remained suppressed at the week 4 visit, compared to 13% of historic controls ($p = 0.04$). By week 8, only one of 13 (8%) maintained viral suppression compared to 3% of historic controls ($p = 0.44$). Similarly in the other study (I5-I-0140), the time to plasma viral rebound was longer than in historical controls. Eighty percent of participants versus 13% of controls had viral suppression at week 4 ($p < 0.001$) and 10% and 3%, respectively, had viral suppression at week 8 ($p = 0.37$). In these studies using VRC01 as monotherapy during ATI, there was emergence of VRC01-resistant virus, further evidence that the bNab had viral activity. These studies indicate that VRC01 given alone during ATI is not sufficient to maintain viral suppression. In contrast to these studies, IMPAACT 2008 does not include ATI and is focused on the effects of VRC01 given in combination with cART on makers of HIV-1 persistence. In addition, VRC01 will be administered during early cART, a period of active viremia, rather than during established treatment.

Potential of monoclonal antibodies to reduce plasma viremia and viral reservoirs

There are several potential mechanisms by which bNAbs may enhance cART to promote faster clearance of HIV-1-infected cells in perinatal infection [25]. At the time of initiation of cART, there is active viremia and viral replication. The neutralizing activity of bNAb may augment cART to clear free infectious virus, thereby more rapidly controlling viremia. A second mechanism may be elimination of infected cells through ADCC or through enhancement of other humoral immune responses stimulated by virus antibody complexes [20, 26]. Longer-lived cells contribute to plasma viremia during second-phase decay including tissue macrophages, partially activated $CD4^+$ T cells, and recently re-activated, latently infected $CD4^+$ T cells [23]. These virus-expressing cells serve as continued sources of virus production and can contribute to ongoing cycles of virus replication, if at any time point during treatment drug concentrations are compromised due to non-adherence, somatic growth, or concurrent illnesses that affect drug intake, all common problems among young infants taking cART. Since bNAbs bind to free virus [27], administration of VRC01 during the second phase decay after initiation of cART may reduce ongoing virus replication and reservoir seeding [28]. Although viral escape to bNAbs, including VRC01, has been observed in trials using bNAbs as monotherapy for HIV-1 infected adults [12], this study uses VRC01 in combination with cART and thus resistance is much less likely.

Importantly, among HIV-1-infected infants, founder viruses are generally neutralized by VRC01 [29, 30], likely due to VRC01 binding to a highly conserved epitope (the CD4 binding site) [31]. In addition, a study of untreated HIV-1-infected Kenyan infants demonstrated that higher titers of transplacental maternal antibodies that mediate ADCC activity are associated with improved infant survival [32]. This study provides support that HIV-1-infected infant immune cells can use passively acquired antibodies to mediate ADCC, providing promise for potential benefit from VRC01, which may enhance ADCC.

Infants with untreated perinatal HIV-1 are capable of generating neutralizing antibody later in infancy [33]. However, effective cART treatment begun during early infancy blunts the infant HIV-1 antibody response, and 50% or more of children effectively treated from infancy will lack long-lasting HIV-1-specific antibodies [34]. Therefore, it is expected that many early treated infants will have neither neutralizing antibody nor ADCC once maternal antibody wanes. The lack of production of autologous anti-HIV-1 antibodies with early treatment of perinatal infection provides additional rationale for testing whether adding bNAb as an adjunct to cART will hasten

clearance of plasma virus and virus-producing cells and ultimately reduce residual HIV-1-infected cells compared with cART alone.

1.2 VRC-HIVMAB060-00-AB (VRC01)

VRC01 is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line that binds to the CD4 binding site of gp120. The VRC01 mAb was originally isolated from an adult infected with HIV-1 for more than 15 years who maintained viral control without cART [31]. Using novel methods to isolate and screen memory B lymphocytes from the peripheral blood mononuclear cells (PBMC) of HIV-1-infected donors, investigators at the Vaccine Research Center (VRC) were able identify this antibody clone. At a concentration of 50 mcg/mL, VRC01 was found to neutralize more than 90% of genetically diverse heterologous strains of HIV-1, and at a concentration of 1 μg/mL, more than 70% are neutralized [31]. Since the initial isolation and characterization of the VRC01 mAb, subsequent investigations on longitudinal serum samples show that VRC01-like epitopes are induced in a subset of HIV-1-infected individuals but take years to develop [35].

The structure of VRC01 complexed with the HIV-1 core glycoprotein (gp) 120 has been determined. It is highly affinity-matured, has a disulfide link between complementarity-determining regions (CDR) hypervariable loop 1 (H1) and hypervariable loop 3 (H3) and has a glycan in the variable (V) region of the light chain [36]. However, none of these features appears to affect its binding affinity or neutralization activity [36]. VRC01 does not have an unusually long CDR-H3 region like some other HIV-1 neutralizing antibodies. It is not self- or poly-reactive, lacks anti-phospholipid antibody activity (see Investigator's Brochure (IB)), and it does not bind to human adult or fetal tissue. These features suggest that mAb administration will not precipitate adverse immune phenomena.

The VRC01 mAb has many characteristics that make it an outstanding bNAb for this study. It has high potency with *in vitro* neutralizing activity at concentrations that are readily achievable in plasma [31]. The anti-viral breadth of VRC01 is greater than many other bNAb thus far discovered [31]. VRC01 is an IgG1, thereby allowing it to mediate ADCC, an activity which may be an important mechanism to eliminate infected cells [14, 37]. This bNAb is advancing rapidly in clinical development for prevention and treatment of HIV-1 infection, including in HIV-1-exposed infants (see Clinical Studies below). Information from Preclinical and Clinical studies of VRC01 are summarized below; additional details are provided in the IB.

1.2.1 Preclinical Studies

1.2.2 Preclinical GLP Toxicology Study

A repeat dose intravenous (IV) and subcutaneous (SC) toxicity study (SRI Study No. M896-11) was performed by SRI International (Menlo Park, CA) with VRC-HIVMAB060-00-AB (VRC01) in male and female Sprague-Dawley rats in accordance with US FDA "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies." This study was conducted with a pre-GMP pilot lot of VRC01 using a purification process similar to that of the GMP clinical-grade drug product.

For the safety assessment, vehicle or 4 mg/kg, 40 mg/kg, or 400 mg/kg VRC01 was administered by tail vein injection on days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via SC administration to the dorsal scapular region on days 1 and 8.

Results obtained showed that both IV and SC routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, injection site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate aminotransferase (AST) and alkaline phosphatase (ALP) on day 9, one day after the second dose. The increase in AST was up to 1.5-fold when compared with prestudy levels; the increase in ALP was up to 2.3-fold. By day 30, AST values had returned to normal, and ALP values were returning to normal. The small and transient elevations in AST and ALP are of minimal toxicological significance because of the following: (1) the animals had recovered or were recovering by Day 30; (2) there were no corresponding histopathology findings in the organs typically associated with AST and/or ALP increases (liver, kidney, muscle, bone, or intestines); and (3) other biomarkers of liver or kidney damage such as alanine aminotransferase, creatinine, blood urea nitrogen, and electrolytes were not meaningfully affected after administration of VRC01.

Other than erythema/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 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.

This GLP repeat dose toxicology study, which included an IV dose 10 times higher than the intended dose in humans, supports both the IV and SC administration of VRC01 in human studies.

1.2.3 Tissue Cross-Reactivity GLP Study of VRC01 with Human Tissues *in vitro*

A tissue cross-reactivity study of 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 US FDA "Good Laboratory Practice for Nonclinical Laboratory Studies" (GLP). 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, Characterization and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use on December 18, 2008" and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997)." In addition, the tissue cross-reactivity study used additional neonate/infant tissues suggested by the FDA to support trials in infants.

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 IgG secondary antibody, and binding was 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, and it supports the future use of VRC01 in humans.

1.2.4 Nonhuman Primate Studies of VRC01

Several non-GLP studies of VR01 have been completed in non-human primates (NHP) to assess for preclinical evidence of antiviral activity and potential efficacy in human HIV-1 infection. A summary of these studies is provided in Table 1 below. Additional details are provided in the IB.

Table 1
Preclinical Proof-of-Concept Studies Performed with VRC01 in NHP

Study Purpose	Study Outcome
Pharmacokinetics	
Demonstration of plasma and secretion concentrations of VRC01 given by IV or SC routes in rhesus macaques	Kinetics of decay of 40 mg/kg of VRC01 given IV or SC in plasma, rectal, vaginal and nasal secretions established
Effect on protection from viral challenge	
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 challenge-protection against oral inoculation of SHIV-SF162P3 in newborn rhesus macaques	100% protection (2/2) from challenge at 20 mg/kg subcutaneously and partial protection (4/5) at 5mg/kg.
Effects on viremia after infection	
Demonstration of effect of VRC01 during the acute and chronic phases of SHIV SF162P3 infection in rhesus macaques	The administration of VRC01 (40 mg/kg dose administered IV) during the acute phase of infection led to a reduction of peak viremia and control of viremia during the chronic phase of infection.

1.2.5 Clinical Studies

Clinical evaluation of VRC01 in humans began in September 2013. Since that time, clinical studies have been planned, initiated, and/or completed in the US and internationally to evaluate the product for preventive and therapeutic indications, in adult and pediatric populations (see Table 2). As of 10 January 2017, VRC01 had been administered in doses ranging from 1 mg/kg to 40 mg/kg to more than 840 HIV-uninfected and HIV-infected adults and to 40 HIV-uninfected infants. Further information pertaining to each study is provided below; across all studies, there have been no serious adverse events related to VRC01 that required expedited reporting to drug regulatory authorities and no study safety pauses for adverse events.

Table 2
Completed and Planned Studies of VRC01

Study	Study Design	Participant Population	Dosage (mg/kg) route x numbers of administrations	Target Accrual VRC01/placebo
VRC 601 (Completed, [12])	Phase I, open label, dose escalation of VRC01	HIV-infected adults	1 mg/kg IV x 2 doses 5 mg/kg IV x 2 doses 5 mg/kg SC x 2 doses 20 mg/kg IV x 2 doses 40 mg/kg IV x 2 doses	23 (up to 5 per dose group; 11 in 40 mg/kg)
VRC 602 (Completed [38])	Phase I, open label, dose escalation of VRC01	Healthy adults	5 mg/kg IV x 2 doses 5 mg/kg SC x 2 doses Placebo SC x 2 doses 20 mg/kg IV x 2 doses 40 mg/kg IV x 2 doses	23/5 (5 per dose group)
VRC 606 (Enrolling)	Phase I, open label, dose escalation of VRC01 and VRC01LS	Healthy adults aged 18-50 years	Four dose escalation groups (Groups 1-4) to assess VRC01LS administered IV and SC once per participant Two groups (Groups 5 and 6) to assess VRC01LS at 5 mg/kg SC or at 20 mg/kg IV administered every 12 weeks for a total of three administrations per participant Two groups (Groups 7 and 8) to assess VRC01 at 5 mg/kg SC or at 20 mg/kg IV administered every 4 weeks for a total of two administrations per participant	49/0
IMPAACT P1112 (Ongoing)	Phase I, open label, dose escalation of VRC01	Newborn infants of HIV-infected mothers	Dose Group 1: 20 mg/kg SC x 1 dose Dose Group 2: 40 mg/kg SC x 1 dose Dose Group 3: 40 mg/kg SC at ≤ 5 days of life then, 20 mg/kg SC q 4 weeks for minimum of 24 weeks and no more than 72 weeks while breastfeeding (in addition to standard perinatal ARV prophylaxis for all arms)	52/0 (13 per dose group)

Table 2
Completed and Planned Studies of VRC01

Study	Study Design	Participant Population	Dosage (mg/kg) route x numbers of administrations	Target Accrual VRC01/placebo
HVTN 104 (Completed)	Phase 1, multicenter randomized trial, Groups 1, 2, 4, and 5 are open-label VRC01 and Group 3 is double-blind, placebo controlled	HIV-uninfected adults aged 18-50 years	Group 1 (open-label): 40 mg/kg, IV at Month 0 then 20 mg/kg IV at Month 1, 2, 3, 4, 5 Group 2 (open-label): 40 mg/kg IV at month 0 then 40 mg/kg IV at month 2, 4 Group 3 (double-blind): 40 mg/kg IV at month 0 then 5 mg/kg SC at month 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 Group 3 (placebo controlled) IV placebo at month 0 then SC placebo at month 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 Group 4 (open-label): 10 mg/kg IV at Month 0, 2, and 4 Group 5 (open-label): 30 mg/kg IV at Month 0, 2, and 4	Group 1: 20/0 Group 2: 20/0 Group 3 (double blind): 20/0 Group 3 (placebo controlled): 0/4 Group 4: 12/0 Group 5: 12/0
HVTN 116 (Open to accrual)	Phase I, multicenter, randomized, open-label VRC01 and VRC01LS	HIV-uninfected adults aged 18-50 years	Group 1: VRC01 10 mg/kg IV at Month 0, Month 2, Month 4, and Month 6 Group 2: VRC01 30 mg/kg IV at Month 0, Month 2, Month 4, and Month 6 Group 3: VRC01LS 30 mg/kg IV Month 0, Month 3, and Month 6 Group 4: VRC01 30 mg/kg IV at Month 0 Group 5: VRC01LS 30 mg/kg IV at Month 0	101/0
HVTN 703/ HPTN 081 (Ongoing)	Phase 2b, multicenter randomized trial, double-blind, placebo controlled VRC01	HIV-uninfected sub-Saharan African women aged 18-40 years	Group 1: 10 mg/kg IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72 Group 2: 30 mg/kg IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72 Group 3: IV placebo at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72	1000/500
HVTN 704/ HPTN 085 (Ongoing)	Phase 2b, multicenter randomized trial, double-blind, placebo controlled VRC01	HIV-uninfected men and transgender persons who have sex with men aged 18-50 years	Group 1: 10 mg/kg IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72 Group 2: 30 mg/kg IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72 Group 3: IV placebo at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72	1800/900

Table 2
Completed and Planned Studies of VRC01

Study	Study Design	Participant Population	Dosage (mg/kg) route x numbers of administrations	Target Accrual VRC01/placebo
A5342 (Participants off study and primary analysis completed)	Phase 1, multicenter randomized trial, double-blind, placebo controlled VRC01	HIV-infected adults	Arm A: Two infusions of VRC01 (40 mg/kg) IV at weeks 0 and 3 and two infusions of placebo IV at weeks 6 and 9 Arm B: Two infusions of placebo IV at weeks 0 and 3 and two infusions of VRC01 (40 mg/kg) IV at weeks 6 and 9	20/20
A5340 (Participants off study and primary analysis completed [24])	Phase 1, open label VRC01	HIV-infected adults	40 mg/kg IV x 3 doses; One each on days 0, 21, and 42. ATI during VRC01 treatment.	15/0
15-I-01040 (Closed to accrual, [24])	Phase I/II, open label VRC01	HIV-infected adults	40 mg/kg IV x 3-8 doses, given on days -3, 14, 28, and monthly up to 6 months. ATI during VRC01 treatment.	10/0
RV397 (Closed to accrual)	Phase II single center randomized placebo controlled trial of VRC01	HIV-infected adults, acutely treated	Arm 1: 40 mg/kg/dose VRC01 IV at Weeks 0, 3, 6, 9, 12, 15, 18, 21 and 24 Arm 2: Placebo IV at the same time points ART interruption will occur at week 0	Arm 1: 18 Arm 2: 6
RV398 (Ongoing)	Phase I multicenter randomized placebo controlled trial of VRC01	HIV-infected adults with acute HIV infection	Arm 1: Immediate ART and placebo infusion at Week 0 Arm 2: Immediate ART and single infusion of 40 mg/kg VRC01 IV at Week 0 Arm 3: Single infusion of 40 mg/kg VRC01 IV at Week 0 and ART at Week 1	24 (8 per arm)
IMPAACT 2008 (Pending)	Phase I/II, multicenter randomized trial, open label VRC01	HIV-infected infants aged up to 84 days	Arm 1: 40 mg/kg/dose SC at Weeks 0, 2, 6, 10 with cART (provided outside the study) Arm 2: cART (provided outside the study)	34/34

Completed studies include first-in-humans dose escalation studies for safety, tolerability, and PK of IV and SC routes in HIV-1-infected (VRC 601) [12] and HIV-1-uninfected (VRC 602) [38] adults as well as a study (HVTN 104) that evaluated serial dosing using several different IV or SC doses with different dosing schedules among HIV-uninfected adults [39]. Two Phase 2b studies are ongoing to evaluate the safety and efficacy of VRC01 in preventing HIV infection among adults (HVTN 703/HPTN 081 and HVTN 704/HPTN 085). Also ongoing is a Phase I study (IMPAACT P1112) evaluating single and repeated doses of VRC01 to HIV-exposed infants for a prevention indication (i.e., for prevention of perinatal transmission) [40].

Studies of VRC01 for therapeutic indications are also ongoing. These include studies of the safety and virologic effects of VRC01 in acute HIV infection (RV398), in chronic infection (A5342) [41], and during ATU (RV397, A5340, 15-I-0140) [24]. Two of the studies (A5342, 15-I-0140) include evaluation of the effects of VRC01 on markers of HIV persistence.

1.2.6 VRC 601

VRC 601 (NCT01950325) is titled, "*A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults*."

VRC 601 was the first study of the VRC01 mAb in HIV-1-infected participants [12]. It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti-antibody immune responses. VRC 601 opened in September 2013 as a single-site study at the NIH Clinical Center, Bethesda, Maryland. Twenty-three evaluable HIV-1-infected participants, including 15 aviremic ARV-treated participants and eight viremic non-ARV treated participants received one or two doses of VRC01 IV or SC at doses ranging from 1 mg/kg to up to 40 mg/kg. The eight viremic patients received a single dose of study product IV and at 40 mg/kg. The first infusion at 1 mg/kg IV was administered in the VRC 601 study on September 30, 2013. Beginning on March 28, 2014, the dose escalation proceeded according to the schema. The first 40 mg/kg IV administration in this study occurred May 12, 2014, and the last infusion in VRC 601 occurred on April 6, 2015. There were a total of 36 infusions in 23 participants. All IV and/or SC infusions were well tolerated with no serious adverse events (SAEs) or dose-limiting toxicity. There were no moderate or severe local or systemic reactions. One participant had mild tenderness at the injection site. Systemic events reported in the three days post-infusion included headache (7), myalgia (6), malaise (4), nausea (4), joint pain (3), and fever (1); all were mild [12].

VRC 601 demonstrated antiviral effect. A single 40 mg/kg IV dose led to a 1.1 to 1.8-$\log_{10}$ drop in plasma viral load in 6 of the 8 viremic participants not on ART [12]. Two viremic participants had only a marginal drop in plasma viral loads of 0.26 and 0.18 $\log_{10}$ copies/mL, respectively; however, these two individuals were found to have baseline virus that was relatively neutralization resistant. Two adults, who had baseline plasma viremia <1000 copies/mL, had sustained suppression of viremia for over 20 days, until the plasma level of VRC01 decreased. The adults with higher baseline plasma viremia had evidence of outgrowth of escape variants in rebound viremia. These data indicate that a single dose of VRC01 at 40 mg/kg IV given as monotherapy resulted in an average virus load significantly decreased between days 3 and 21 after infusion compared to baseline, with the nadir at day 9. A 0.5 $\log_{10}$ copies/mL or greater decrease in plasma viral load is considered a positive antiviral response to a single ARV drug. Among the ART-treated, virally suppressed adults, no change in proviral DNA load was observed after receiving two infusions of VRC01. However, the study demonstrated a VRC01-mediated anti-viral effect, with preferential suppression of neutralization-sensitive strains.

1.2.7 VRC 602

VRC 602 (NCT01993706) is titled, "*A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults*."

VRC 602 was the first study of the VRC01 mAb in HIV-1-uninfected adults [38]. It was a dose-escalation study to examine safety, tolerability, dose, and PK of VRC01. VRC 602 opened in December 2013 as a single-site study at the NIH Clinical Center, Bethesda, Maryland, and the final infusion was administered in August 2014. There were three open-label, dose-escalation groups receiving intravenous doses at Week 0 and Week 4 (5 mg/kg, 20 mg/kg, 40 mg/kg) and one double-blinded, placebo-controlled group for SC administration (5 mg/kg). Cumulatively, 28 participants received 43 doses of VRC01, including five participants who each received two SC 5mg/kg doses. As observed in VRC 601, the IV and/or SC infusions were well tolerated with no SAEs or dose-limiting toxicity [38]. There were only mild local reactions (5/23 participants) limited to redness and tenderness which were more common for the SC dose recipients. Similarly, only mild systemic reactions (nausea, headache, myalgia, malaise) were observed in a minority of participants. Anti-VRC01 antibody responses were not detected, and the mAb retained its expected neutralizing activity in serum.

1.2.8 HVTN 104

HVTN 104 (NCT0216526) is titled, "*A Phase I Clinical Trial to Evaluate the Safety and Drug Levels of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered in Multiple Doses Intravenously and Subcutaneously in Different Dosing Schedules to Healthy, HIV-Uninfected Adults*."

HVTN 104 examined safety profiles and serum levels of five different regimens for IV and SC administration of VRC01 to 88 healthy, HIV-1-uninfected adults. The study had five arms: Group 1 evaluated IV administration of a 40 mg/kg loading dose, with two subsequent 20 mg/kg doses given at eight-week intervals. Groups 2, 4, and 5 evaluated three infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg respectively given eight weeks apart. Group 3 evaluated 5 mg/kg given SC every two weeks for 24 weeks. The first participant was enrolled in September 2014 and follow-up was completed in March 2016.

A total of 249 IV infusions and 208 SC injections were administered during study, and were very well tolerated. Most participants had either no local reaction or only mild (Grade 1) local reactogenicity from a particular infusion or injection. For 76% of infusions or injections, participants reported no systemic reactogenicity symptoms. When present, most systemic symptoms were mild, with malaise/fatigue, myalgias, and headaches being most common. Of three participants who reported severe (Grade 3) systemic reactogenicity symptoms, two had concurrent viral infections, and one had malaise lasting one day.

Adverse events attributed to study product administration on the basis of temporal relationship and other considerations have included AST, ALT and creatinine elevation, decreased neutrophil count, diarrhea, chest discomfort, herpes zoster, generalized rash, and pruritus at the administration site. These laboratory changes and clinical events resolved and did not require discontinuation of study product administration. Adverse events attributed to study product administration (VRC01 or placebo) on the basis of temporal relationship for which the schedule of study product administration was discontinued included chest discomfort (in one placebo

recipient) and generalized rash in one participant (slightly raised and very itchy). Symptoms developed three days after the second dose of study product and had resolved by the next day.

1.2.9 HVTN 703/HPTN 081 and HVTN 704/085

HVTN 703/HPTN 081 and HVTN 704/085 (NCT02568215 and NCT02716675) are *Evaluating the Safety and Efficacy of the VRC01 Antibody in Reducing Acquisition of HIV-1 Infection* among women, and men and transgender persons who have sex with men. In these Phase IIb studies, HIV-uninfected participants are randomly assigned to receive ten intravenous infusions of either 10 mg/kg of VRC01, 30 mg/kg of VRC01, or placebo over a period of 72 weeks. As of 2 January 2017, 941 participants had been enrolled in these studies and approximately 2500 infusions had been administered.

Infusions have generally been well tolerated to date. As of 2 January 2017, no related SAEs have been reported and most study participants had no local or systemic reactogenicity symptoms from a particular infusion. When present, local and systemic reactogenicity symptoms were of mild or moderate severity. Infusion site pain and/or tenderness developed in 26% of participants. Infusion site erythema and/or induration developed in 9% of participants. The most common systemic reactogenicity events were malaise (21%), headache (19%), headache followed by nausea (8%), and myalgia (7%).

Six participants have experienced urticaria deemed related to the blinded study product (severe in one participant, mild to moderate in the other five participants). Urticaria developed at the first infusion in five participants and at the fourth infusion in one participant. Urticaria developed during the infusion in four of six participants (within approximately 10 to 40 minutes into the infusion) resulting in an incomplete administration of study product. Urticaria developed after completion of the infusion in the other two participants (from 10 minutes up to two days after the infusion). In all six participants, urticaria resolved the same day spontaneously or with antihistaminics. One dose of IV steroids was administered to one participant with severe urticaria. Study product administration (IV infusion of VRC01 or placebo) was discontinued in all six participants with urticaria.

1.2.10 IMPAACT P1112

IMPAACT P1112 (NCT02256631) is titled, "*Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, a Potent Anti-HIV Neutralizing Monoclonal Antibody, in HIV-1-Exposed Infants.*"

P1112 is a Phase I trial enrolling at birth HIV-1-exposed infants at higher risk of transmission to determine the PK and safety of VRC01, given with standard-of-care ARV perinatal prophylaxis, as a potential modality to further reduce peripartum and postpartum breast milk HIV-1 transmission. There are three dose groups. Dose Group 1 (n=13) received a single dose of VRC01 at 20 mg/kg SC. Dose Group 2 (n=14) received a single dose of 40 mg/kg SC. In Dose Group 3 (n=13), breastfed infants receive a first dose of 40 mg/kg SC followed by monthly doses of 20 mg/kg for at least 24 weeks and until cessation of breastfeeding (up until 72 weeks). VRC01 has been well tolerated at 20 mg/kg and 40 mg/kg SC [40]. As of 12 January 2017, there have been no related SAEs, no systemic reactions, and no urticarial reactions. Local reactions (erythema, induration, or edema) have been common, occurring in six and 11 infants in the 20 and 40 mg/kg dose groups, respectively, and in six infants in Dose Group 3 as of 17 January

2017. All local reactions were grade mild or moderate and all but one resolved within four hours of injection.

1.2.11 Therapeutic Studies (ACTG 5340, I5-I-0140, RV 398, RV 397, ACTG 5342)

There are five studies being conducted in HIV-1-infected adults, each designed to evaluate safety and anti-viral activity of VRC01 in different stages of HIV-1 infection (see Table 2). As of 23 March 2017, about 89 HIV-1-infected participants have received VRC01 in these studies. Cumulatively across all studies, there have been no SAEs related to VRC01 that required expedited reporting to the FDA or other regulatory authorities and no study safety pauses for adverse events. The unsolicited adverse events in all studies have been mild or moderate in severity except for an unrelated, grade 3 neutropenia in 15-I-0140. One participant in RV 397 received an incomplete administration of study drug and permanent discontinuation of study drug secondary to an infusion reaction consisting of grade 2 urticaria and grade 1 pruritus and nausea. The nausea resolved without intervention, and the urticaria and pruritus resolved with IV chlorpheniramine and dexamethasone.

1.2.12 Summary of Safety in Clinical Trials

In summary, as of January 2017, over 800 HIV-1-uninfected and infected adults and 40 HIV-1-exposed infants have received one or more VRC01 administrations, with the number of infusions exceeding 2500. There have been no SAEs related to VRC01 that required expedited reporting to the FDA or other regulatory authorities and no study safety pauses for adverse events. A non-serious occurrence of severe (grade 3) urticaria was submitted to regulatory authorities as a safety report because urticaria, at grade 3 severity, was not reported in the prior IB (Version 6.0, dated 5 October 2016). There have been mild to moderate injection site reactions with subcutaneous infusion that have been transient and self-limited. There have been rare episodes of urticaria associated with infusions. When present, most systemic reactions (only in adults to date) after administration of VRC01 SC or IV have been mild and have included malaise, myalgia, headache, chills, nausea, and joint pain.

1.2.13 Pharmacokinetics

The PK results in HIV-infected and uninfected adults for VRC 601 and 602 have been published [12, 38] and are detailed in the IB. These results indicate that PK parameters are comparable in these two adult populations.

At 28 days after second administration of 20 mg/kg and 40 mg/kg IV, mean VRC01 serum levels were 55.9±16.8 and 88.9±40.4 mcg/mL in uninfected adults, and were 46.0±26.7 and 64.9±56.7 mcg/mL in HIV-infected adults, respectively. The time to maximum concentration (Tmax) is about one to three hours after IV administration and about one to three days after SC administration. For uninfected and infected participants, the terminal half-life was 15±3.9 and 12±4.5 days for IV dosing and 17±2.9 and 11±5 days for SC dosing, respectively.

Preliminary PK parameters determined in IMPAACT P1112 are available for HIV-exposed infants receiving single SC doses of VRC01 at 20 mg/kg/dose and 40 mg/kg/dose. Mean (SD) day 28 levels were 39.3 (14.9) mcg/mL and 75.2 (21.4) mcg/mL for the 20 and 40 mg/kg doses, respectively. For the 20 mg/kg dose group, the estimated serum half-life was 19.7 (5) days. Peak levels occurred at a median of two days and one day for the 20 and 40 mg/kg doses [40]. These

PK data for newborns in IMPAACT P1112 are consistent with the PK parameters observed in adults.

1.3 Rationale

Perinatal HIV-1 infection offers a unique population to determine whether early combination therapy plus bNAbs can limit HIV-1 reservoirs. It is hypothesized that, for HIV-1-infected infants, combining the bNAb VRC01, as a long-acting antiviral and potential immune effector agent, with cART will decrease HIV-1 reservoirs and significantly reduce levels of HIV-1-infected cells in peripheral blood. This is a patient population for which the timing f HIV acquisition is known and can be targeted. These early treated infants will have blunted production of endogenous HIV-1-specific antibody [34]; therefore, passive immunotherapy may have great benefit. Initiation of cART in early infancy reduces the frequency of HIV-1 latently infected cells with long-term virologic suppression [3]; adjunctive treatment with bNAbs, which may reduce plasma viremia and eliminate infected cells, may further impact on the size of the reservoir. The time to suppression of plasma viremia after cART during infancy is prolonged for many infants, up to one year [10], and viral decay may be accelerated with the addition of bNAbs [20]. The bNAbs, with their long half-life and lack of requirement for daily adherence, may provide enhanced antiretroviral activity during periods of suboptimal cART levels, which are common among young infants. Although viral resistance has been observed to arise rapidly when bNAbs are administered as partially suppressive mono-therapy during active viral replication [12, 13], this study uses bNAb in combination with cART, likely avoiding induction of resistance. Moreover, administering bNAb with cART during early infection and during initial cART has potential to both neutralize the virus, thereby reducing the potential for ongoing low-level replication, and also potentially eliminate HIV-1-expressing cells through ADCC.

1.3.1 Rationale for Study Design and Population

This is a Phase I/II, multisite, two-arm, randomized, controlled, open-label study to evaluate the safety and antiviral activity of VRC01 among 68 HIV-1-infected infants initiating cART within 12 weeks of birth. Enrolled infants will be randomly assigned in a 1:1 ratio to either receive VRC01 (Arm 1) or to not receive VRC01 (Arm 2). Infants in both arms will continue to receive cART throughout their participation in the study. The open-label study design was selected to avoid exposure to the discomfort and risk of a placebo injection for infants randomized to Arm 2. However, the study is designed such that evaluations are the same between arms, with the exception of assessment of for local reactions at site of VRC01 administration, which will occur only in Arm 1.

Infants aged up to 12 weeks will be eligible for this study. This young population is chosen as previous work has documented that effective, long-term treatment at this age is associated with lower levels of HIV-1 reservoirs compared to infants and children initiating treatment at older ages [3]. In addition, this is the age at which early cART may preclude the development of anti-HIV-1 antibodies, making this a unique population for this study [34].

Infants must receive their first dose of VRC01 no more than 14 days after starting their first cART regimen. The study goal is to evaluate the safety and effect of VRC01 on HIV-1 DNA concentrations at 14 weeks; other objectives also include effects on kinetics of viral decay during first and subsequent phases of plasma viral load decay. Initiation of cART is recommended for infants as soon as possible after diagnosis of HIV-1 infection for its lifesaving effect [7]. Depending on where the infant's HIV-1 initial care is located, it may not be possible to orchestrate study entry and VRC01 dosing to coincide with the day of cART initiation. Therefore, the study will allow infants to receive the first dose of VRC01 within two weeks after cART initiation, since delaying cART could result in a potentially unsafe deviation from standard of care or present a significant barrier to study accrual. Nevertheless, it is expected that infants receiving their first dose of VRC01 within two weeks of starting cART will still have high levels of plasma virus, given the high levels of plasma viremia that occur in perinatal infection.

1.3.2 Rationale for Dose Regimen

The dosing regimen selected for this study is based on pharmacokinetic (PK) modeling using data from the VRC 601 and 602 studies in HIV-1-infected and uninfected adults and the IMPAACT P1112 study in HIV-exposed infants (Figures 2 and 3 in Section 10). Subcutaneous dosing is planned, because this route will be feasible in larger trials and will avoid the potential for participants to miss doses due to inability to obtain intravenous access in the participating infants. Subcutaneous dosing also allows this study to build on the safety and PK data obtained from IMPAACT P1112, which is using a subcutaneous route.

The regimen of 40 mg/kg dose at 0, 2, 6, and 10 weeks was selected for this study based on PK modeling using data from the VRC 601, VRC 602, and P1112 studies and the dose used in adult studies of VRC01 for antiviral activity. The optimal plasma level of VRC01 required for anti-viral activity is yet to be defined in human trials, although viremic adults with low baseline plasma virus concentration have sustained suppression until VRC01 plasma levels dropped to 10 mcg/ml [12]. Likewise, the *in vivo* level of VRC01 to mediate ADCC activity is unknown. Therefore, targeted plasma levels for this study are selected based on the preclinical studies of VRC01 demonstrating that over 91% of viral isolates tested across clades are neutralized at an ID_{50} of 50 mcg/ml with more than 70% neutralized at 1 mcg/ml [31]. Notably, the geometric mean IC_{50} for HIV-1 strains from all clades tested is 0.33 mcg/mL. The PK modeling based on adult studies of VRC01 indicates that using a subcutaneous dose of 40 mg/kg will achieve an initial mean peak of approximately 450 mcg/mL, greatly exceeding the 50 mcg/mL associated with broad neutralization for VRC01 *in vitro*. In order to maintain levels above 50 mcg/ml during the initial weeks of treatment, a second dose will be given two weeks after the first dose. The third and fourth doses will be given at four-week intervals with the final dose at Week 10. This regimen is projected to maintain mean VRC01 levels above 50 mcg/ml through the first 16 weeks after starting cART, covering the median time to undetectable plasma viremia for infants treated in P1030 [10, 16]. The 40 mg/kg dose has been administered to HIV-1-exposed newborns in IMPAACT P1112 and has been well tolerated to date; preliminary PK data suggest that the PK is similar to that observed in the adult studies [40].

1.3.3 Rationale for Study Endpoints—Virologic

Several biomarkers have been identified for quantifying HIV-1 persistence in infected persons; details of these measures, their advantages and limitations are summarized in Table 3.

For this study, total HIV-1 cell-associated DNA will be used as the primary outcome measure to assess effects of VRC01 in combination with cART. As shown in Table 3, each biomarker provides different information on the state of HIV-1 persistence and each has different limitations, with HIV-1 DNA being the most feasible and reliable biomarker to estimate the total burden of circulating HIV-1 infected cells using the small blood volumes in this study. Detailed analyses have recently been performed on the various biomarkers using samples collected during standard lopinavir-based early cART in IMPAACT P1030 [9], and these data were used to calculate the sample size for this study. In addition, HIV-1 DNA quantification has been performed on approximately 600 pediatric samples to date for studies of HIV-1 DNA dynamics during long-term cART in children, and wide differences have been observed in the concentrations of HIV-1-infected cells persisting in children on effective cART [3]. While this biomarker overestimates the number of clinically-relevant infected cells due to detection of both defective and replication-intact genomes, it is correlated with the number $CD4^+$ resting T cells infected with latent replication competent HIV-1 [9] and should provide an overall estimate of clearance of infected cells during the first few months of cART.

Planned analyses of cell-associated HIV-1 RNA and inducible HIV-1 RNA (TILDA) [44] will provide additional information on the transcriptional activity of the cells and the size of the inducible reservoir along with their potential for clearance by bNAbs [9]. While the TILDA provides a more sensitive marker of the clinically-relevant inducible reservoir compared with HIV-1 DNA load, larger blood volumes are required to obtain purified total CD4+ T cells for the assay. Given that most study participants will be from sub-Saharan Africa, wide variation in the yield of viable cells following specimen storage and shipment is anticipated. In some cases, insufficient cells will preclude measurement of the inducible reservoir. The TILDA will therefore be used as an additional measure in this first proof-of-concept study.

The study of two doses of VRC01 administered to six adults with chronic HIV-1 infection on established cART did not find significant decline in any of the biomarkers of HIV-1 persistence examined, including most of those listed in Table 3 [12]. However, this study will be evaluating the effect of VRC01 in a very different scenario—during early treatment of acute infection of infants who lack early autologous antibody production—and results from either acutely or chronically infected adults cannot be assumed to predict the effects of VRC01 for this infant population.

Table 3
Biomarkers to Quantify HIV-1 Persistence in Peripheral Blood

Biomarker (Units)	Assay Measure	Origin	Assay	Advantages	Limitations
DNA (copies/million cells)	Total HIV-1 DNA	Cell-associated	ddPCR or qPCR	Relatively Inexpensive and simple High throughput	Not a strict measure of HIV-1 "reservoir" as most of the DNA species fail to integrate or harbor defective genomes
	Episomal DNA (2LTR)	Cell-associated	ddPCR; qPCR	Conflicting data on the labile nature of 2LTR	Conflicting data on the labile nature of 2LTR
RNA (copies/ml)	Residual viremia	Plasma	Single Copy Assay (SCA)	Measure of ongoing virus producing cells	Variability increases at low limit of detection; infectious nature unknown; requires 3-4 mL plasma
(copies/1000 ng cellular RNA)	Unspliced mHIV-1 RNA	Cell-associated	ddPCR; qPCR	Measure transcriptionally active genomes	May represent read-through transcripts
	Multiply spliced HIV-1 RNA	Cell-associated	qPCR	Measure transcriptionally active genomes; ongoing replication, virus-specific transcripts	Undetectable with effective cART
Quantitative Viral Outgrowth Assay (Infectious Units per Million Cells-IUPM)	Replication-competent HIV-1-genomes	Resting or total $CD4^+$ T cells	Co-culture	Measure of clinical relevant, replication-competent genomes	Limited by blood volume Expensive and time-consuming
Total inducible HIV-1 RNA concentration (TILDA; cells expressing multiply spliced RNA per million CD4+ T cells)	Inducible HIV-1 genomes	Total CD4+ T cells	T cell stimulation	Measure of inducible genomes	No outgrowth for genetic characterization of the reservoir

1.3.4 Rationale for Study Endpoints—Immunologic

The study will evaluate the effect of VRC01 on anti-HIV-1 neutralization and ADCC activity in infant blood. The responses will be evaluated against autologous virus isolated from the baseline sample and a panel of infant founder viruses. Assessment of these responses will be a key to understanding the mechanism of anti-viral effects of VRC01 and is therefore included as another study objective. Plasma neutralization responses and ADCC activity against a multiclade panel of viruses will be measured and correlated to the viral kinetics. Assessment of autologous neutralizing activity after VRC01 is no longer circulating will be also be of interest since administration of passive anti-SHIV antibody to SHIV-infected infant macaques resulted in improved production of endogenous neutralizing antibody [45].

In VRC 601, two of eight (25%) of individuals harbored HIV-1 that is relatively resistant to VRC01 [12]. Although this proportion is higher than expected based on the activity of VRC01 against panels of tier 2 virus, this study plans for an analysis that will exclude infants determined to have baseline virus with VRC01 neutralization resistance. Infants will not be screened for VRC01 neutralization in advance of entry, which would delay initiation of treatment, but the sensitivity of the infant's baseline virus to VRC01 will be determined after trial completion. Antibodies against VRC01 have not been detected to date in the studies of VRC01 in adults and are not expected, since the antibody is fully humanized. However, the study will test to determine if anti-VRC01 Ab arise.

1.3.5 Rationale for Cerebral Spinal Fluid Collection

The central nervous system (CNS) is likely an important anatomic HIV-1 reservoir [46]; thus, it would be desirable to assess the concentration of bNAbs in cerebral spinal fluid (CSF) in infants, as well as evaluating the effect on viral persistence in the CNS. There are no human data at present on the levels of VRC01 in CSF, but the levels in adults would be expected to be low based on studies of other IgG1 antibodies used for immunotherapeutics [47]. In young infants, the blood brain barrier may be more permeable [48], which may present an opportunity for higher concentrations of mAbs to be present in CSF. This study includes provisions to store any residual CSF left over after clinical testing is complete from participants who have a lumbar puncture for clinical care. These "opportunistic samples" will be analyzed for the concentration of VRC01, as well as HIV-1 nucleic acid and inflammatory biomarkers. If this study demonstrates an effect on viral reservoir in the peripheral circulation, subsequent clinical trials may be justified to include research-specific procedures to evaluate CNS and tissue reservoirs such as gut or lymphoid tissue.

1.3.6 Rationale for Other Specimen Collection for Exploratory Evaluations — Infant

It will be important to understand the mechanism and covariates for the effect of VRC01 on viremia and latent virus. This will require additional assays to be conducted. Since there will be limited specimens and since the precise effects of VRC01 on viral persistence are yet unknown, the specific exploratory objectives to be tested will be determined after the study is complete. However, specimens will be obtained and stored pending the completion of the study for these tests. Examples of the objectives may include additional assessments of the viral reservoir, inflammation, and immune activation. Assays to determine the frequency of replication competent virus may be performed if sufficient cells are available. This measure of infectious virus persistence is obtained by the quantitative viral outgrowth assay which detects only persistent replication-competent genomes. Knowing the frequency at which HIV-1 replication-competent reservoirs persists in perinatal infection following standard cART versus

when combined with VRC01 will provide important information on the long-term effects of this novel treatment strategy. Markers of immune activation and inflammation may serve as markers of viral persistence so these may be examined. HIV-1-specific immune responses may be evaluated to assess for enhancement of responses to VRC01 as observed in NHP models [15]. The impact of VRC01 on HIV-1 envelope sequence evolution in participants with persistent viremia may be evaluated to determine if there is viral escape from the passively administered antibody [12]. The effect of endogenous VRC01-like antibodies at baseline (as a result of transplacental transfer) on the impact of VRC01 on markers of HIV-1 persistence might be evaluated since this may impact the pharmacokinetics and therefore clinical effect. In addition to the above, exploratory evaluations may include genetic testing (e.g., for different alleles for Fc function, IgG1 alleles, or HLA). A correlation of polymorphisms in CCR5 (or other markers of HIV disease outcomes) and Fc receptors (or other markers of immune function) with VRC01 activity may be of interest since these genetic variables could have a strong impact on the antibody-mediated viral clearance.

1.3.7 Rationale for Specimen Collection for Exploratory Evaluations — Maternal

There are no published data on interactions between autologous maternal HIV-1-specific antibodies and the clinical or virologic impact of bNAbs. It is therefore valuable to archive maternal samples to assess these interactions, and for detailed characterization of maternal and infant transmission events and virus evolution in the context of bNAbs, with respect to selection of transmitted variants or *de novo* escape under monoclonal antibody pressure, if this outcome is observed in the study.

1.3.8 Summary

This study will evaluate whether the bNAb VRC01 given as an adjunct to cART, with the first dose administered within two weeks of the start of cART, to HIV-1-infected infants aged up to 12 weeks, will lead to lower infected cell concentrations at four weeks after receipt of four doses of VRC01. The study will also examine the effects at 24 and 48 weeks. As another study objective, the extent to which plasma viremia and transcriptionally active cells are diminished compared to cART-only treated infants will be examined. A study of bNAb in early therapy of an infant population is distinct from studies of acute HIV infection in adults because this infant population is expected to have limited autologous production of HIV-1-specific antibodies.

1.4 Hypotheses

- A regimen of four doses of VRC01 (40 mg/kg per dose) will be safe among HIV-1-infected infants initiating cART.

- HIV-1-infected infants who receive a regimen of four doses of VRC01 (40 mg/kg per dose) in addition to cART will experience a greater decrease in the concentration of HIV-1 DNA in PBMCs at four weeks after the final dose compared to infants who do not receive VRC01.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to assess the following among HIV-1-infected infants:

2.1.1 Safety of VRC01 administered with cART (cumulatively through Week 14)

2.1.2 Effect of VRC01 on HIV-1 DNA concentrations in PBMCs (change from Week 0 to Week 14)

2.2 Secondary Objective

A secondary objective of this study, which will be evaluated approximately concurrently with the primary objectives, is to assess the following among HIV-1-infected infants:

2.2.1 Pharmacokinetics of VRC01 (through Week 16)

2.3 Other Objectives

Other objectives of this study are to assess the following among HIV-1-infected infants:

2.3.1 Longer-term safety of VRC01 administered with cART (cumulatively through Week 48)

2.3.2 Development of anti-VRC01 antibodies (at Weeks 14, 24, and 48)

2.3.3 Effect of VRC01 on time to achieve plasma HIV-1 RNA below 40 copies/mL (through Week 48)

2.3.4 Effect of VRC01 on biomarkers of HIV persistence in PBMCs:

- HIV-1 DNA concentration (at Weeks 24 and 48)
- HIV-1 RNA concentrations (multiply-spliced and unspliced; at Weeks 14, 24, and 48)
- Total inducible HIV-1 RNA concentration (at Weeks 24 and 48)

2.3.5 Effect of VRC01 on HIV-1-specific ADCC and virus neutralization against infant viral isolates (at Weeks 14, 24, and 48).

2.4 Exploratory Objectives

Biological specimens will be collected over the course of this study for exploratory investigations related to the virologic and immunologic mechanisms of action of VRC01. The specific investigations undertaken will be guided by the primary, secondary, and other outcomes of the study and may include additional assessments of the viral reservoir, inflammation, and immune activation; ARV concentrations may also be explored if considered important for the interpretation of primary, secondary, and other outcomes. HIV-1-specific immune responses may be evaluated to assess for enhancement of responses to VRC01 as observed in NHP models. VRC01 concentrations and markers of viral persistence may be evaluated in CSF if samples are available following lumbar puncture for clinical care. Human genotyping for alleles associated with HIV disease outcomes or immune function may be performed to explore associations with differences in the effect of VRC01.

For illustrative purposes, a listing of potential exploratory objectives is provided in Table 4. This listing will be further refined and prioritized by the Protocol Team after the primary, secondary, and other outcomes are assessed and before any exploratory evaluations are undertaken.

Table 4
Potential Exploratory Objectives for IMPAACT 2008

To explore the following among HIV-1-infected infants:

- Impact of VRC01 on the following biomarkers:
  - Titer of replication competent virus in PBMCs
  - Soluble markers of inflammation and monocyte activation
  - Activation and differentiation of peripheral CD4 and CD8 T lymphocytes (e.g., memory phenotype, CD38, HLA-DR, PD-1)
  - Change from baseline and persistence of episomal HIV-1 DNA as measured by 2-LTR circles
- Impact of VRC01 on cell-mediated viral inhibition, CD4 T-cell proliferation, cell-mediated cytotoxicity
- Impact of VRC01 on HIV-1 envelope sequence evolution in participants with persistent viremia
- Effect of endogenous VRC01-like antibodies at baseline (maternal) on the impact of VRC01 on markers of HIV-1 persistence
- Concentrations of VRC01 and markers of HIV-1 persistence in CSF
- Correlation of polymorphisms in CCR5 (or other markers of HIV disease outcomes) and Fc receptors (or other markers of immune function) with VRC01 activity

3 STUDY DESIGN

This is a Phase I/II, multisite, two-arm, randomized, controlled, open-label study to evaluate the safety and antiviral activity of VRC01 among HIV-1-infected infants initiating cART within 12 weeks of birth. Refer to Figure 1 for an overview of the study design and Section 4 for details regarding the study population. A total of 68 infants are expected to be enrolled at study sites located in Botswana, Brazil, Haiti, Malawi, South Africa, Zimbabwe, and the US.

Infants enrolled in this study may have acquired HIV-1 infection *in utero* or peripartum or postpartum; they may be breastfed or formula fed prior to and after enrolling in the study. They may have received ARVs for prophylaxis or treatment prior to study entry, consistent with the eligibility criteria in Sections 4.1 and 4.2.

Enrolled infants will be randomly assigned in a 1:1 ratio to either receive VRC01 (Arm 1) or to not receive VRC01 (Arm 2). Infants in both arms will continue to receive cART throughout their participation in the study. Each infant's cART regimen will be selected by his or her primary care provider and supplied through non-study sources (i.e., cART will not be provided through the study). Infants assigned to receive VRC01 will be administered 40 mg/kg at study Entry (Week 0) and at study Weeks 2, 6, and 10 by subcutaneous injection. To maximize the potential activity of VRC01 within the first phase of viral decay following cART initiation, the first dose of VRC01 will ideally be administered on the day of cART initiation; however, cART may be initiated up to 14 days prior to study entry and first dose of VRC01. To minimize discomfort and potential risks, infants assigned to Arm 2 will not receive placebo injections; therefore, random assignments will not be blinded.

Enrolled infants will be followed for 48 weeks, with safety, pharmacokinetic, and antiviral activity evaluations performed throughout the duration of follow-up as specified in Appendix I.

An interim analysis of safety will be conducted when the first five infants in Arm 1 have completed their Week 3 visits; refer to Section 9.5.1 for a description of this analysis. The primary safety outcome will be assessed among all infants through Week 14, i.e., four weeks after the last dose of VRC01 for infants in Arm 1, through collection of medical history information, physical examinations, reactogenicity assessments, and laboratory testing. This outcome will also be assessed throughout the duration of follow-up, i.e., through Week 48.

The primary antiviral activity outcome — change in concentration of HIV-1 DNA in PBMCs — will be assessed at Week 14. The sample size of 34 infants per arm was selected to provide at least 20 infants per arm who are considered evaluable for analysis of this outcome. To be considered evaluable, infants in both arms must not interrupt cART for more than three consecutive days prior to the Week 14 visit; infants in Arm 1 also must receive at least the first scheduled dose of VRC01. This analysis is expected to be performed once all enrolled infants have reached Week 14 of follow-up.

Change in concentration of HIV-1 DNA in PBMCs will also be assessed at Weeks 24 and 48; other analyses will also include infants who are not considered evaluable per the strict criteria described above. Other outcomes, including additional markers of viral persistence, will likewise be assessed at Weeks 14, 24, and 48. Specimens required for these evaluations will be collected and stored for batched testing. Plasma HIV-1 RNA levels will also be assessed as a study outcome; these assays will be performed in real-time to inform participant management as well as the interim analysis of antiviral activity described below. Refer to Section 9.6 for a description of the statistical analyses planned to evaluate primary, secondary, and other outcomes.

As described in Section 1.3.2, the regimen of VRC01 administered in this study is expected to maintain targeted concentrations of VRC01. To confirm that targeted concentrations are being achieved, an interim PK analysis will be undertaken when six infants randomized to Arm 1 have received two doses of VRC01 and have specimens available for analysis through Week 6. At this time, all available samples collected for evaluation of VRC01 concentrations will be analyzed. Currently available data suggest that dose adjustment will not be necessary to achieve targeted concentrations; therefore, the study will not be paused pending the results of the interim analysis. Nonetheless, a dose adjustment may be considered if indicated based on the findings of the interim PK analysis.

An interim analysis of antiviral activity will also be performed. As described in greater detail in Section 9.5.2, when approximately half of the targeted number of infants have reached Week 14, the Study Monitoring Committee (SMC) will review HIV-1 RNA levels and other relevant data and provide recommendations on any action to be taken with respect to ongoing study conduct.

In addition to the evaluations and analyses described above, biological specimens will be collected and stored for exploratory investigations of the virologic and immunologic mechanisms of action of VRC01. Infant blood will be collected for this purpose, as will blood from consenting mothers. For any infant who undergoes lumbar puncture for clinical care during follow-up, residual samples of CSF will be obtained and stored for this purpose, if possible. The specific evaluations to be performed with these specimens, and whether to test all specimens versus those of relevant subsets of participants, will be determined based on the primary, secondary, and other outcomes of the study and on state-of-the art assays available at the time.

Note: Mothers who consent to specimen collection for study purposes will be enrolled in the study but then discontinued from follow-up immediately upon completion of specimen collection.

4 STUDY POPULATION

This study will be conducted among 68 HIV-1-infected infants initiating cART within 12 weeks of birth. Infants will be selected for study participation according to the criteria in Sections 4.1 and 4.2; infants' mothers will be selected for specimen collection and storage according to the criteria in Section 4.3. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.5. Considerations related to participant retention and withdrawal/ termination from the study are provided in Sections 4.6 and 4.7, respectively.

4.1 Infant Inclusion Criteria

All of the criteria listed below must be met in order for infants to be included in this study.

4.1.1 Parent or legal guardian is willing and able to provide written informed consent for infant participation in the study, including collection and storage of biological specimens for exploratory virology and immunology investigations.

4.1.2 Infant is within 12 weeks (84 days) of birth at study entry.

4.1.3 Infant weighs at least 2500 g at study entry.

4.1.4 Infant has confirmed HIV-1 infection based on positive results from two samples (whole blood or plasma) collected at different time points using the following methods:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

At least one of the two samples must be tested in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. For tests performed in other (non-certified) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

4.1.5 Infant has the following laboratory values at screening (with samples collected for testing within 30 days prior to entry):

- CD4 lymphocyte percentage greater than 15
- Severity grade 1 or lower hemoglobin, platelet count, and absolute neutrophil count
- Severity grade 1 or lower ALT, AST, and alkaline phosphatase

See Section 7.3 for guidance on severity grading.

4.1.6 Infant's initial cART regimen has been selected and documented at study entry, prior to randomization, with the first dose taken on the day of randomization or within 14 days prior to the day of randomization.

4.1.7 Infant is expected to be available for 48 weeks of follow-up at study entry.

4.1.8 Parent or legal guardian is willing and able to complete reactogenicity memory aids for study purposes, based on parent/guardian report.

4.2 Infant Exclusion Criteria

Infants must be excluded from the study if any of the following are identified at any time prior to randomization:

4.2.1 Infant or infant's mother received exclusionary active or passive HIV-specific immunotherapy, as follows:

- Infant received any active or passive HIV-specific immunotherapy prior to study entry.
- Infant's mother received any active HIV-specific immunotherapy prior to infant study entry.
- Infant's mother received any passive HIV-specific immunotherapy within two years prior to infant study entry.
- If infant's mother is breastfeeding: mother is planned to receive any active or passive HIV-specific immunotherapy at any time during infant study participation.

4.2.2 Infant initiated a combination of three or more ARVs, all at or above recommended treatment doses, within 48 hours of birth. Recommended treatment doses are as follows:

NRTIs	As per WHO or US Department of Health and Human Services pediatric treatment guidelines
NVP	At least 8 mg for infants weighing up to 2 kg, at least 12 mg for infants weighing more than 2 kg
LPV/r	300 mg/75 mg per m^2 of body surface area twice daily
All other ARVs	Consult with IMPAACT 2008 Clinical Management Committee (CMC)

Note: Regimens comprised of fewer than three ARVs, or of three ARVs with at least one ARV below the recommended treatment dose, are permitted, even if initiated within 48 hours of birth.

4.2.3 Infant received within 30 days prior to study entry, or is identified as requiring, any of the following:

- Chronic (more than 14 days) systemic steroid treatment
- Immunoglobulin treatment
- Immunomodulators (interleukins, interferons, cyclosporin)
- Cytotoxic chemotherapy
- Treatment for active tuberculosis (TB) disease
- Any investigational agent

Note: Treatment for latent TB infection is permitted.

4.2.4 Infant has any documented or suspected clinically significant medical illness, clinically significant congenital anomaly, or immediately life-threatening condition that, in the opinion of the site investigator or designee, would interfere with the infant's ability to comply with study requirements.

4.2.5 Infant has any other condition that, in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.3 Maternal Inclusion Criteria

The mothers of enrolled infants will be asked to consent to blood collection and storage for this study. The following criteria must be met in order for mothers to undergo blood collection for this purpose:

4.3.1 Mother is willing and able to provide independent written informed consent for blood collection and storage for virology and immunology investigations.

4.3.2 Mother has no documented or suspected condition that, in the opinion of the site investigator or designee, would make blood collection unsafe.

Note: Maternal study participation is not required for infant study participation.

4.4 Co-Enrollment Considerations

Co-enrollment in other studies is not precluded, although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies. Requests for such approval should be emailed to the CMC.

4.5 Recruitment, Screening, and Enrollment Process

Recruitment methods for this study may vary across sites but are expected to rely on active identification and referral of infants newly diagnosed with HIV infection in each study site community. In some communities, infants of known HIV-infected mothers may be tested for HIV infection within hours to days after birth. In other communities, routine testing occurs at 4-6 weeks of age. Testing may also be performed at later time points in response to signs and symptoms of infection. Because infected infants are expected per current standards of care to initiate cART immediately upon diagnosis of infection, active referral from HIV testing providers will be necessary to permit enrollment in the study as soon as possible after initiation of cART.

Upon identification of a potentially eligible infant, study staff will provide information about the study to the infant's parent or legal guardian. Each parent or guardian who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process will include detailed review of the study informed consent forms, time to address any questions or concerns the parent or guardian may have, and an assessment of the parent's or guardian's understanding before proceeding to the informed consent decision. The process will be fully documented, and only parents or guardians who are able to demonstrate understanding will be asked to provide written informed consent for study participation.

Eligibility screening will be initiated after written informed consent is provided. Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment (randomization). Screening evaluations must be performed within 30 days prior to randomization, and randomization must occur within 84 days of birth and within 14 days after initiation of cART; initial cART regimens must be selected and documented prior to randomization.

Infants who are found to meet the study eligibility criteria will be randomized to one of the two study arms, and infants randomized to Arm 1 will be administered their first dose of VRC01 on the day of randomization. If the first dose cannot be administered on the day of randomization for any reason, the CMC should be contacted immediately. On a case-by-case basis, the CMC may permit administration of VRC01 after the day of randomization, within 14 days after initiation of cART.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, a participant identification number (PID) will be assigned to the infant, and a study-specific screening number will be obtained through the SES. For infants found to be eligible, randomization will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and, for infants randomized to Arm 1, prescribing information for the study product (VRC01) regimen. In the event that twins (or other multiplets) are found to be eligible for the study, both (all) infants will be randomized to the same arm. For infants who are found to be ineligible for the study, or who do not enroll in the study for any reason, an electronic case report form (eCRF) will be entered to record the screening outcome. Refer to Section 9.5 for more information on monitoring participant accrual in this study.

As part of the study informed consent process, infants' mothers will be asked to consent to collection and storage of their own blood for exploratory virology and immunology investigations. This consent is optional. For mothers who choose to provide consent and are assessed as eligible, a PID will be assigned and registered in the SES for purposes of sample collection and storage only. Maternal blood will be collected at the time of infant entry into the study or within seven days thereafter; immediately following blood collection, mothers will be discontinued from follow-up.

4.6 Participant Retention

Once an infant is enrolled in this study, study staff will make every effort to retain him or her for the protocol-specified duration of follow-up, i.e., through Week 48, thereby minimizing potential biases and loss of statistical power associated with loss-to-follow-up. Infants in Arm 1 will be retained in follow-up regardless of the number of doses of VRC01 received. Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.7 Participant Withdrawal or Termination from the Study

Regardless of the participant retention efforts referenced above, infants may be withdrawn from the study by their parents or legal guardians. Infants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Infant re-locates away from the study site and cannot be transferred to another site or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the infant
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs

For any infant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations of the infant as described in Section 6.13. In the event that the circumstances that led to an infant's withdrawal or termination change (e.g., the family returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

5 STUDY PRODUCT CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

Study product is defined for this study as VRC-HIVMAB060-00-AB (VRC01).

Refer to Figure 1 for an overview of the study design and study product dosing scheme and to the VRC-HIVMAB060-00-AB (VRC01) IB for further information about the study product. In the event that the IB is revised to specify updated study product storage or thawing procedures, the IB will take precedence over the specifications of this section of the protocol.

5.1 Study Product Regimen

Arm 1: 40 mg/kg of VRC01 by subcutaneous injection at study Entry (Week 0) and study Weeks 2, 6, and 10 in addition to (non-study) cART. Tables listing the volume of study product needed to provide the specified dose by infant weight band will be provided in the study-specific Manual of Procedures (MOP).

Arm 2: No VRC01 in addition to (non-study) cART.

Each infant's cART regimen will be selected by his or her primary care provider and supplied through non-study sources (i.e., ARVs will not be provided through the study). Refer to Section 5.7.1 for more information on concomitant ARVs.

5.2 Study Product Formulation and Storage

VRC01 will be supplied in 3 mL glass vials. The vials are filled to 2.25 ± 0.1 mL at a concentration of 100 (±10) mg/mL. 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. The vials are intended for single use only and thus contain no preservative.

The VRC01 product label designates long-term storage at -35°C to -15°C (-31°F to 5°F). At clinical research sites, storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions from -45°C to -10°C (-49°F to 14°F) is acceptable.

Following thawing, vials of VRC01 may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. If stored at 2°C to 8°C, vials should be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation. The product may not be stored in direct sunlight.

For subcutaneous administration, the required volume of VRC01 will be loaded into a 5 or 10 mL sterile syringe. Preparation must be performed using aseptic technique in a laminar flow biosafety cabinet. Prepared syringes containing VRC01 may be stored at 2°C to 8°C for up to 24 hours or at controlled room temperature (maximum 30°C) for up to 4 hours (unless institutional policies specify shorter expiry timeframes, in which case institutional policies should be followed). The product may not be stored in direct sunlight.

Refer to the study-specific MOP for further information on product storage, thawing, preparation, and stability.

5.3 Study Product Administration

Topical anesthetic preparations (e.g., EMLA) should not be applied prior to VRC01 administration.

VRC01 will be administered subcutaneously by slow push in the thigh using an RMS High-Flo Subcutaneous Safety Needle Set with a 26-gauge needle. Dose volumes are expected to range from 0.8 to 4.0 mL, corresponding to infant weights ranging from 2 to 10 kg. Refer to the study-specific MOP for weight-based dosing tables and detailed instructions for use of RMS needle sets. All dose volumes are expected to be administered as a single infusion over approximately 5-10 minutes; up to 15 minutes may be required for the largest dose volumes. However, if appropriate for an infant's size, a divided dose may be infused at two sites.

When administering VRC01, the thigh in which concomitant immunizations may have been administered within the preceding two weeks should be avoided, if possible, as should any site where the skin or tissue is irritated. The location of each injection site (left or right thigh) must be documented.

If an immediate hypersensitivity reaction occurs during administration, administration should be stopped consistent with instructions provided in the study-specific MOP.

Refer to Section 6.16 for more information on monitoring for reactogenicity following each administration of VRC01.

5.4 Study Product Supply

VRC01 will be provided by the VRC and made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). RMS High-Flo Subcutaneous Safety Needle Sets with 26-gauge needles will be purchased centrally and made available to sites through the CRPMC. Upon successful completion of protocol registration procedures, VRC01 and infusion sets may be obtained by the site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.5 Study Product Accountability

Site pharmacists must maintain complete records of all study product supplies and needle sets received from the CRPMC. The product lot number associated with each dose of VRC01 administered will be recorded in participant study records and entered into eCRFs.

5.6 Final Disposition of Study Product

Partially used vials are not permitted to be administered to other study participants or used for *in vitro* experimental studies. Any unused portion of entered vials, any used syringes, and any unused filled syringes should be disposed of in a biohazard container and incinerated or autoclaved per approved local site policy.

Any unopened vials that remain at US sites after the study is completed or terminated will be returned to the CRPMC. At non-US sites, any unopened vials that remain after the study is completed or terminated will be destroyed. Site pharmacists will follow the relevant instructions for return or destruction of unused study product provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.7 Concomitant Medications

All concomitant medications received by enrolled infants — including prescription and non-prescription (over-the-counter) medications; immunizations and other preventive medications; therapeutic foods and nutritional supplements; and alternative, complementary, and traditional medications and preparations — must be source documented as part of the medical and medications histories obtained at each study visit. As described in greater detail in the remainder of this section, the following concomitant medications must also be entered into eCRFs:

- ARVs
- Immunizations
- Immunosuppressive medications
- Active or passive immunotherapy agents
- Medications or other treatments administered by injection in the thigh
- All other medications received through Week 16 of follow-up

5.7.1 Concomitant ARVs

All ARVs received by enrolled infants must be source documented and entered into eCRFs as part of the ARV exposure history obtained at each study visit. Likewise, ARVs taken by each infant's mother, to which the infant may have been exposed *in utero* or through breast milk, will be source documented and entered into eCRFs.

Each infant's initial cART regimen will be selected by his or her primary care provider and supplied through non-study sources. Regimen changes are permitted during follow-up in response to intolerance, toxicity, incidence of concomitant illnesses (e.g., tuberculosis) and/or virologic or immunologic failure, consistent with local standards of care and the clinical judgement of the treating clinician. Site clinicians may order ARV resistance testing at their discretion to inform regimen management and ARV selection; if such testing is performed, results will be entered into eCRFs. The details of each regimen change will be source documented and entered into eCRFs, including the specific reason for the change.

5.7.2 Concomitant Immunizations

All immunizations received by enrolled infants must be source documented and entered into eCRFs as part of the immunization history obtained at each study visit.

Enrolled infants are expected to receive immunizations in accordance with country-specific standard immunization schedules. Study staff should facilitate these immunizations in order to minimize visit burden, ensure compliance with both the study product administration schedule and the standard immunization schedule, and optimize documentation of all immunizations received.

For infants in Arm 1, immunizations may be administered on the same day as VRC01. In this case, for immunizations that are administered by injection in the thigh, the immunizations should preferably be administered in the thigh opposite of the VRC01 injection; if that is not possible, the immunization should be administered at least 2.4 cm away from the site of VRC01 injection, and each injection site should be marked so that each can be clearly identified for purposes of assessment of injection site reactions.

5.7.3 Other Concomitant Medications

In addition to the concomitant ARVs and immunizations described in Sections 5.7.1 and 5.7.2, all other concomitant medications received by enrolled infants must be source documented as part of the medical and medications history obtained at each visit. Through Week 16, all concomitant medications must also be entered into eCRFs. After Week 16, only ARVs, immunizations, immunosuppressive medications, and medications or other treatments administered by injection in the leg(s) where VRC01 has been administered are required to be entered into eCRFs.

5.8 Prohibited and Precautionary Medications

Enrolled infants should not receive any of the following:

- Investigational products (other than VRC01)
- Immunoglobulin-based treatments
- Immunosuppressive medications for a duration of greater than 14 days
- Topical anesthetic preparations (e.g., EMLA) applied to the VRC01 injection site

In the event that a need for one or more such medications is identified, the site investigator or designee should consult the CMC.

Antipyretic and pain relief medications should not be used for prophylaxis in anticipation of possible reactions to VRC01 administration but may be provided to treat elevated temperatures and pain/tenderness that may occur after administration.

6 STUDY VISITS AND PROCEDURES

An overview of the study visit and evaluation schedule is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures. As indicated in Appendix I, optional maternal evaluations are performed for consenting mothers only at study Entry. Thereafter, only infant evaluations are performed.

All visits and procedures must be performed at the approved clinical research site or approved associated facilities and must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 11 for more information on documentation and data management requirements. Refer to Section 7.3 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up. All procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the allowable visit window.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform mothers (or other authorized guardians if applicable) of clinically meaningful physical exam findings and laboratory test results when available.

6.1 Screening Visits

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process.

Screening may be initiated after written informed consent is obtained. Screening procedures may be performed on multiple days, including on the date of enrollment (randomization); all screening procedures must be performed within 30 days prior to randomization.

For potential participants who do not meet eligibility criteria, screening may be discontinued once ineligibility is determined (enter the relevant eCRF to record the screening outcome).

Screening Visit Procedures (within 30 days prior to Entry)		
Administrative and Regulatory		• Obtain written informed consent • Assign PID to infant; also assign PID to mother if she consents to maternal specimen collection • Obtain infant screening number from SES
Clinical		• Obtain available medical records and infant history information (since birth) – HIV-related testing – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Perform physical examination
Laboratory	**Infant blood**	Collect blood for: • Confirmatory HIV NAT (if needed per Section 4.1.4) • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine • CD4 and CD8 cell count and percentage

6.2 Entry Visit

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process.

All Entry Visit procedures are expected to be performed on the day of enrollment, which is defined as the day of randomization. Procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical examination), should be performed first, prior to final eligibility determination. Eligibility must be confirmed and the infant's initial cART regimen must be documented prior to randomization. In the event that an infant is found to be ineligible on the scheduled day of enrollment, randomization should not occur (enter the relevant eCRF to record the screening outcome).

For infants randomized to Arm 1, the first dose of VRC01 will be administered on the day of randomization. If the first dose cannot be administered on the day of randomization for any reason, the CMC should be contacted immediately. On a case-by-case basis, the CMC may permit administration of the first dose after the day of randomization, within 14 days after initiation of cART. If such permission is granted, the infant's eligibility for the study must be re-confirmed and documented on the day of administration of the first dose, prior to administering the dose.

Additional requirements for sequencing of procedures at the Entry Visit for infants randomized to Arm 1 are as follows:

- Physical examination should occur prior to randomization (as described above) and must precede prescribing and administering of VRC01
  - Weight measurement is required for prescribing
  - Assessment of vital signs and visual inspection of the injection site must precede administration
- Randomization must precede prescribing of VRC01
- Prescribing must precede dispensing and administering of VRC01
- Blood collection must precede administering of VRC01
- Monitoring for injection site reactions must be performed for two hours after administering VRC01 as described in Section 6.16

On the day of this visit and on the following six days, reactogenicity assessments will be performed and documented as described in Section 6.16.

Entry Visit Procedures (Day 0)		
Administrative and Regulatory		• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll/randomize the infant, print and file a copy of the confirmation file • *For consenting mothers:* Complete paper-based eligibility checklist, enter checklist data into SES to enroll the mother, print and file a copy of the confirmation file
Clinical		• Obtain infant history information (since last visit)* – HIV-related testing – Medical/medications including ARVs (all exposures) *document initial cART regimen prior to randomization* – Immunizations – Feeding • Perform physical examination* • Assess adherence to cART *if infant initiated cART prior to study entry* • ***For infants in Arm 1:*** Monitor for reactogenicity for two hours after administering VRC01 per Section 6.16 • Provide instructions for completing reactogenicity memory aid
Study Product		***For infants in Arm 1:*** • Prescribe VRC01 • Prepare and dispense VRC01 • Administer VRC01
Laboratory	**Infant blood**	Collect infant blood for: • HIV-1 RNA • Stored plasma and PBMCs for primary, secondary, and other evaluations • Stored serum for neutralizing assay • Stored plasma and PBMCs for exploratory evaluations *if infant weighs ≥ 3 kg at the visit*
	Infant urine	Collect urine for: • Dipstick urinalysis; if 1+ for protein, blood, or leukocytes, perform microscopic evaluation
	Maternal blood	*If mother has consented,* collect blood and store plasma, PBMCs, and serum for exploratory evaluations

*Perform prior to randomization.

Note: For consenting mothers, blood should ideally be collected at the Entry Visit; however, these specimens may be collected within seven days after the Entry Visit. No further maternal evaluations are performed following specimen collection; therefore, mothers will be discontinued from follow-up immediately upon completion of specimen collection.

6.3 Week 1 Visit

The Week 1 Visit is targeted to take place on Day 7, counted from the date of randomization as Day 0, with an allowable window of ± 3 days. There is no required sequencing of procedures at this visit.

Week 1 Visit Procedures (Day 7 ± 3 days)		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications – Reactogenicity • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product		• None
Laboratory	**Blood**	Collect blood for: • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine • HIV-1 RNA (with storage of residual PBMCs if possible)
	Urine	Collect urine for: • Dipstick urinalysis; if 1+ for protein, blood, or leukocytes, perform microscopic evaluation

6.4 Week 2, Week 6, and Week 10 Visits

The Week 2, Week 6, and Week 10 visits are targeted to take place on Days 14, 42, and 70, respectively, counted from the date of randomization as Day 0. The allowable visit window for the Week 2 visit is ± 3 days. The allowable visit window for the Week 6 and Week 10 visits is ± 7 days.

For infants randomized to Arm 2, there is no required sequencing of procedures at these visits. For infants randomized to Arm 1, because VRC01 is scheduled to be administered at these visits, the following sequencing of procedures is required at these visits:

- Physical examination must precede prescribing and administering of VRC01
  - Weight measurement is required for prescribing
  - Assessment of vital signs and visual inspection of the injection site must precede administration
- Confirmation of eligibility to receive VRC01 must precede administering of VRC01
- Prescribing must precede dispensing and administering of VRC01
- Blood collection must precede administering of VRC01
- Monitoring for injection site reactions must be performed for one hour after administering VRC01 as described in Section 6.16

On the day of each of these visits and the following six days, reactogenicity assessments will be performed and documented as described in Section 6.16.

Week 2 (Day 14 ± 3 days), Week 6 (Day 42 ± 7 days), and Week 10 (Day 70 ± 7 days) Visit Procedures		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination *including inspection of prior injection sites and pre-injection inspection of planned injection site for this visit for infants in Arm 1* • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated) • ***For infants in Arm 1****:* Confirm eligibility to receive VRC01 • ***For infants in Arm 1:*** Monitor for reactogenicity for one hour after administering VRC01 per Section 6.16 • Review instructions for completing reactogenicity memory aid as needed
Study Product		***For infants in Arm 1:*** • Prescribe VRC01 • Prepare and dispense VRC01 • Administer VRC01
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA (with storage of residual PBMCs if possible) *(Weeks 6 and 10)* • Stored plasma and PBMCs for primary, secondary, and other evaluations

6.5 Week 3, Week 7, and Week 11 Visits

The Week 3, Week 7, and Week 11 visits are targeted to take place on Days 21, 49, and 77, respectively, counted from the date of randomization as Day 0. The allowable visit window for these visits is ± 3 days. There is no required sequencing of procedures at these visits.

Week 3 (Day 21 ± 3 days), Week 7 (Day 49 ± 3 days), and Week 11 (Day 77 ± 3 days) Visit Procedures		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications – Reactogenicity • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product		• None
Laboratory	**Blood**	Collect blood for: • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine

6.6 Week 14 Visit

The Week 14 Visit is targeted to take place on Day 98, counted from the date of randomization as Day 0, with an allowable window of ± 7 days. In addition to other routine study procedures, blood is collected and stored at this visit for primary antiviral activity evaluations. There is no required sequencing of procedures at this visit.

Week 14 Visit Procedures (Day 98 ± 7 days)		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product		• None
Laboratory	**Blood**	Collect blood for: • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine • CD4 and CD8 cell count and percentage • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for primary, secondary, and other evaluations • Stored serum for neutralization assay • Stored plasma and PBMCs for exploratory evaluations *if infant weighs ≥ 3 kg at the visit*
	Urine	Collect urine for: • Dipstick urinalysis; if 1+ for protein, blood, or leukocytes, perform microscopic evaluation

6.7 Week 16 Visit

The Week 16 Visit is targeted to take place on Day 112, counted from the date of randomization as Day 0, with an allowable window of ± 7 days. There is no required sequencing of procedures at this visit.

Week 16 Visit Procedures (Day 112 ± 7 days)	
Administrative and Regulatory	• None
Clinical	• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product	• None
Laboratory	Collect blood for: • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for primary, secondary, and other evaluations

6.8 Week 20 Visit

The Week 20 Visit is targeted to take place on Day 140, counted from the date of randomization as Day 0, with an allowable window of ± 14 days. There is no required sequencing of procedures at this visit.

Week 20 Visit Procedures (Day 140 ± 14 days)	
Administrative and Regulatory	• None
Clinical	• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product	• None
Laboratory	Collect blood for: • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine

6.9 Week 24 Visit

The Week 24 Visit is targeted to take place on Day 168, counted from the date of randomization as Day 0, with an allowable window of ± 14 days. There is no required sequencing of procedures at this visit.

Week 24 Visit Procedures (Day 168 ± 14 days)		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product		• None
Laboratory	**Blood**	Collect blood for: • Complete blood count with differential and platelets • ALT, AST, ALP, creatinine • CD4 and CD8 cell count • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for primary, secondary, and other evaluations • Stored serum for neutralization assay • Stored plasma and PBMCs for exploratory evaluations
	Urine	Collect urine for: • Dipstick urinalysis; if 1+ for protein, blood, or leukocytes, perform microscopic evaluation

6.10 Week 36 Visit

The Week 36 Visit is targeted to take place on Day 252, counted from the date of randomization as Day 0, with an allowable window of ± 14 days. There is no required sequencing of procedures at this visit.

Week 36 Visit Procedures (Day 252 ± 14 days)	
Administrative and Regulatory	• None
Clinical	• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product	• None
Laboratory	Collect blood for: • CD4 and CD8 cell count and percentage *and complete blood count if needed for calculation of absolute cell counts* • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for exploratory evaluations

At this visit, information and counseling will be provided to the infant's parent or guardian to begin to prepare for study exit at the Week 48 visit. Referrals to non-study care and treatment will be discussed if applicable, and the importance of retention in care and adherence to cART will be emphasized.

6.11 Week 48 Visit

The Week 48 Visit is the last scheduled follow-up visit. It is targeted to take place on Day 336, counted from the date of randomization as Day 0, with an allowable window of ± 14 days. There is no required sequencing of procedures at this visit.

Week 48 Visit Procedures (Day 336 ± 14 days)	
Administrative and Regulatory	• None
Clinical	• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product	• None
Laboratory	Collect blood for: • CD4 and CD8 cell count and percentage *and complete blood count if needed for calculation of absolute cell counts* • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for primary, secondary, and other evaluations • Stored serum for neutralization assay • Stored plasma and PBMCs for exploratory evaluations

At this visit, prior discussion of continuation in non-study care and treatment will be reviewed, with information, counseling, and/or referrals provided if needed. Arrangements will be made to provide the infant's parent or guardian with the infant's final CD4/CD8 cell count and HIV-1 RNA level (viral load). The parent or guardian will also be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

6.12 Residual Cerebral Spinal Fluid (CSF) Collection Visit

Lumbar punctures will not be performed for this study. However, for any infant who undergoes lumbar puncture for clinical care during follow-up, residual CSF should ideally be stored for exploratory evaluations. Infants' mothers (or legal guardians) will be asked to provide optional informed consent for this; consent may be declined with no impact on other aspects of infant study participation. For infants for whom informed consent is provided, and who have a lumbar puncture for clinical care during follow-up, within seven days (inclusive) after the lumbar puncture, residual CSF should be retrieved and stored when available, and the evaluations indicated in the "CSF Collection" column of the Schedule of Evaluations in Appendix I (and described below) should be performed. If these evaluations cannot be performed within seven days, the site investigator should contact the CMC for further guidance. If the residual CSF cannot be retrieved and stored for any reason, the evaluations indicated in the "CSF Collection" column of the Schedule of Evaluations in Appendix I (and described below) should not be performed.

CSF Collection Visit Procedures (within 7 days after lumbar puncture)		
Administrative and Regulatory		• None
Clinical		• Obtain available medical records and medical/medications history since the last visit to document the clinical indication for the lumbar puncture and the results of clinical care evaluations of the CSF including cell count and differential, protein, glucose, and microbiologic testing results • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product Laboratory		• None
Laboratory	**Blood**	Collect blood for: • Stored plasma and PBMCs for exploratory evaluations
	CSF	Retrieve and store residual CSF for exploratory evaluations

6.13 Early Discontinuation Visit

Refer to Section 4.7 for criteria for infant withdrawal or termination from the study. For any infant who is withdrawn or terminated from the study prior to the scheduled completion of follow-up at Week 48, every effort should be made to perform a final series of study evaluations, if possible, according to the "Early D/C" column of the Schedule of Evaluations in Appendix I. However, any laboratory evaluations performed within the two weeks prior to the Early Discontinuation Visit need not be repeated at the Early Discontinuation Visit.

Early Discontinuation Visit Procedures		
Administrative and Regulatory		• None
Clinical		• Obtain history information (since last visit) – Medical/medications including ARVs (all exposures) – Immunizations – Feeding • Assess adherence to cART • Perform physical examination • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8.1 and/or if clinically indicated (consult CMC if indicated)
Study Product		• None
Laboratory	**Blood**	If not done within the prior two weeks, collect blood for: • Complete blood count with differential and platelets • CD4 and CD8 cell count and percentage • HIV-1 RNA (with storage of residual PBMCs if possible) • Stored plasma and PBMCs for primary, secondary, and other evaluations • Stored serum for neutralization assay • Stored plasma and PBMCs for exploratory evaluations
	Urine	*If the Early Discontinuation Visit occurs prior to the Week 24 Visit*, collect urine for: • Dipstick urinalysis; if 1+ for protein, blood, or leukocytes, perform microscopic evaluation

Arrangements should be made to provide the infant's parent or guardian with clinically meaningful test results from the Early Discontinuation visit. The parent or guardian should be provided information on how to remain in contact with study staff (if desired) and learn about the results of the study when available. The parent or guardian should also be provided information and referrals, as applicable, to non-study sources of care and treatment for the infant.

6.14 Infant Histories

HIV-Related Testing

Infant HIV-related testing history information is collected at the Screening Visit and updated as needed at the Entry Visit. Available source documentation should be obtained and data entered into eCRFs for all of the following: all documented HIV diagnostic tests since birth, all documented quantitative HIV-1 RNA tests since birth, all documented CD4 cell counts and percentages since birth, and all documented ARV resistance testing since birth. As indicated in Section 5.7.1, the results of any ARV resistance testing performed during follow-up will also be entered into eCRFs.

Medical and Medications History

Infant medical and medications history information is collected at the Screening Visit and updated at each scheduled visit. A baseline history is established at the Screening and Entry Visits, and interval (since the last visit) histories are documented at follow-up visits. History information should be collected from the infant's parent or guardian and all available medical records should be obtained to source document infant medical and medications histories, to the extent possible, since birth. During follow-up, the following should be source documented based on parental/guardian report and all available medical records: current status of conditions that were ongoing at the previous visit; current status of medications that were ongoing at the previous visit; occurrence of any new conditions since the last visit; use of any new medications since the last visit. Refer to Section 7.2 for requirements for entering signs, symptoms, and diagnoses into eCRFs and to Section 5.7 for requirements for entering concomitant medications into eCRFs.

ARV History

Infant ARV history is collected at the Screening Visit and updated as needed at each scheduled visit. All of the following should be source documented and entered into eCRFs: all exposures to ARVs *in utero*, all exposures to ARVs through breast milk, and all exposures to ARVs through direct ingestion, prior to study entry and throughout follow-up. See also Section 5.7.1. As indicated above for other medical history information, parental/guardian report of ARV history should be supplemented with available medical records whenever possible.

Immunization History

Infant immunization history is collected at the Screening Visit and updated as needed at each scheduled visit. All immunizations should be source documented and entered into eCRFs. See also Section 5.7.2. As indicated above for other medical history information, parental/guardian report of immunization history should be supplemented with available medical records whenever possible.

Feeding History

Infant feeding history is collected at the Screening Visit and updated as needed at each scheduled visit. All of the following should be sourced documented and entered into eCRFs: feeding method, including whether the infant has been breastfed or formula fed; date of last exposure to breast milk (if applicable); and other types of foods received. Any therapeutic foods received should be documented as concomitant medications; see also Section 5.7.

6.15 Infant Physical Examinations

A physical examination is required at each scheduled study visit. Each examination should include the following:

- Head circumference measurement
- Weight measurement
- Length measurement
- Vital signs including temperature, heart rate, respiratory rate; blood pressure (if possible) should also be measured at Entry and Weeks 2, 6, and 10
- Auscultation of chest
- Examination of skin, eyes, mouth, neck, abdomen, extremities (including the study product injection site)
- Examination of other body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician. All exam findings will be source documented and entered into eCRFs if applicable per the instructions in Section 7.2 below.

6.16 Monitoring for Reactogenicity

Reactogenicity outcomes will be source documented and entered into eCRFs as specified in Section 7.2 below. Refer to Section 8 for further information on management of reactogenicity events.

Monitoring by Site Clinicians

Site clinicians will monitor infants randomized to Arm 1 for reactogenicity on each day of administration of VRC01, i.e., at Entry and at Weeks 2, 6, and 10:

- Prior to each injection, as part of the physical exam required at the visit, the infant's skin, temperature, heart rate, respiration rate, and blood pressure (if possible) will be assessed, and the site of injection will be visually inspected.

- At 15 and 30 minutes (±5 minutes) after each injection, the infant's skin, heart rate, and respiration rate will be assessed, and the site of injection will be visually inspected. If these assessments suggest a possible local or systemic reaction, the infant's temperature and blood pressure should be assessed, and a physical examination of relevant body systems and any other clinically indicated procedures should be performed.

- One hour (±15 minutes) after each injection, the infant's skin, temperature, heart rate, respiration rate, and blood pressure (if possible) will be assessed. The site of injection will be visually inspected and gently palpated to assess for induration and tenderness. On Day 0, these assessments will also be performed two hours (±15 minutes) after injection. If these assessments suggest a possible local or systemic reaction, a physical examination of relevant body systems and any other clinically indicated procedures should be performed.

- If any grade 3 or higher local or systemic reaction is identified following any injection, the infant should be observed at the study site for at least two hours after administration of VRC01 (see Section 8).

Note: If any scheduled dose of VRC01 is missed for any reason, the above-listed monitoring is not required on the date of the scheduled dose.

At all time points, additional assessments may be performed at the discretion of the examining clinician. The findings of all reactogenicity assessments will be source documented and entered into eCRFs. Site clinicians may choose to photograph observed reactions and to share photographs with the CMC for awareness and to assist with evaluation of the reaction; all grade 3 or higher reactions should ideally be photographed. Standard precautions will be followed to ensure that participant privacy and confidentiality are protected when photographs are shared.

Monitoring by Mothers (or Caregivers) including +3-Day Contacts

The mothers (or caregivers) of infants in both arms will be instructed to complete memory aid documents to record infant signs and symptoms for seven days following the Entry and Week 2, 6, and 10 visits (VRC01 administration visits), beginning on the day of each visit. The memory aids will capture mothers' assessments of local injection site reactions (redness, warmth, swelling, tenderness) for infants in Arm 1) and systemic signs and symptoms (temperature, rash, swelling of joints, vomiting, diarrhea, alertness, feeding, sleeping, irritability) for infants in both arms. For infants in Arm 1, if any scheduled dose of VRC01 is missed, monitoring for local injections site reactions is not required, but monitoring for systemic signs and symptoms should still be performed.

Three days after visits at which VRC01 is administered, mothers (or caregivers) will be contacted by study staff to report their reactogenicity assessments by telephone. In-person or home visits may also be substituted for telephone contacts if preferred by study staff or mothers. Seven days after each visit (i.e., at Weeks 1, 3, 7, and 11), an in-person visit will be conducted. The allowable window for the three-day contacts is -1 to +3 days; the allowable window for the seven-day visits is ±3 days. During the three-day contacts and seven-day visits, study staff will ask mothers questions that follow the format of the memory aid document, probing as needed to clarify relevant details, and will record reported signs and symptoms on study-specific source documents. Mothers will also be instructed to proactively contact study staff at any time between contacts and visits if any grade 1 or higher signs or symptoms are identified. If grade 1 or higher reactogenicity signs or symptoms are reported, mothers will be instructed to return to the study clinic with their infants as soon as possible (within 48 hours) for further evaluation.

As specified in Section 7.2, all reactogenicity findings will be entered into eCRFs.

6.17 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:
www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

6.17.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations in Appendix I and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the IMPAACT web site: www.impaactnetwork.org.

In accordance with US National Institutes of Health (NIH) recommendations, infant blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period. In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) hematology, (2) chemistry, (3) HIV RNA, (4) CD4 and CD8 cell count and percentage, (5) stored PBMCs and plasma for primary evaluations, (6) stored serum for neutralizing assays, (7) stored plasma and PBMCs for exploratory evaluations. Exceptions to the above apply at Entry and at Weeks 14, 24, and 48 when highest priority should be given to storage of plasma and PBMCs for primary, secondary, and other evaluations, which includes HIV-1 DNA concentration assays for primary antiviral activity evaluations.

6.17.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored, and/or shipped in accordance with the DAIDS policy referenced in Section 6.17, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC.

Quantitative plasma HIV-1 RNA assays performed to assess viral load at time points specified in the SoE must be performed in laboratory that is CLIA-certified (US sites) or VQA-certified (non-US sites) for the assay performed. At least one of the diagnostic tests used to confirm infant HIV infection per Section 4.1.4 must be performed in a CLIA-certified (US sites) or VQA-certified (non-US sites). Blood collected for HIV-1 RNA assays should be processed for storage of PMBCs in addition to plasma for the RNA assay, when possible. PBMCs must be processed and cryopreserved in a laboratory that is IQA-certified using methods consistent with the HIV/AIDS Network Coordination Cross-Network PBMC Processing SOP which is available at: www.hanc.info/labs/labresources/procedures/Pages/pbmcSop.aspx

Specimens stored at site laboratories for the interim PK analysis of VRC01 concentrations are expected to be requested for shipment when the required specimens (through Week 6) have been collected from a minimum of six infants in Arm 1 who received the first two scheduled doses of VRC01; all additional specimens stored for PK analysis of VRC01 concentrations are expected to be requested once all participants have reached Week 16 of follow-up. Specimens stored at site laboratories for the primary antiviral activity outcome — concentration of HIV-1 DNA in PBMCs at Week 14 — are expected to be requested for shipment once all enrolled infants have reached Week 14 of follow-up; specimens for ARV drug concentration assays and VRC01 resistance assays are also expected to be requested at this time. Other specimens stored for secondary, other, and exploratory evaluations are expected to be tested after follow-up has been completed. However, if specimens for ARV drug concentration assays, VRC01 resistance assays, and HIV-1 DNA concentration assays are required earlier based on the findings of the interim analysis of plasma HIV-1 RNA levels described in Section 9.5.2, these specimens will be requested for shipment as needed. Alternative specimen shipping arrangements may be specified by the protocol team as needed. Detailed shipping instructions will be provided in the LPC.

After all primary, secondary, and other evaluations are performed, any remaining samples will be retained for exploratory evaluations. After all exploratory evaluations are performed, residual specimens may be of interest for future research use. Infants' parents or legal guardians will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Parents may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of infant study participation.

6.17.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the CMC and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Section 9.5.

Unless otherwise noted, the specifications of this section apply to infants in both study arms.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the CMC if unexpected concerns arise. Refer to Section 8.1 for a listing of adverse events requiring notification to the CMC within 72 hours of site awareness of the event.

Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Chair and Co-Chair, Medical Officers, Immunologist, Virologist, Pharmacologist, Statisticians, Data Managers, Clinical Trials Specialists, and at least one international Protocol Investigator. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events, study product administration, cART regimens, and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.1.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the composition and role of the SMC in monitoring this study.

7.2 Safety-Related Data Collection

For this study, the term adverse event is used to refer to any untoward medical occurrence identified in an enrolled infant, which does not necessarily have a causal relationship with the study product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after enrollment in the study, whether or not related to the study product. **This definition of adverse event will be applied to infants in both arms of this study, beginning at the time of randomization.** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease identified prior to randomization will be considered a pre-existing condition.

For infants in both study arms, pre-existing conditions and adverse events identified in this study will be source documented and entered into eCRFs as reactogenicity outcomes, abnormal laboratory test results, signs, symptoms, or diagnoses, as described below. The severity of all pre-existing conditions and adverse events identified among infants in both study arms will be graded as described in Section 7.3.3. For infants in Arm 1, the relationship of all adverse events to VRC01 will be assessed as described in Section 8.1.

Reactogenicity outcomes: The reactogenicity assessments described in Section 6.16 will be performed at Entry and Weeks 2, 6, and 10, and on the six days following each of these visits. For infants in Arm 1, local injection site reactions and systemic signs and symptoms will be assessed. For infants in Arm 2, systemic signs and systems will be assessed. All findings from these assessments will be entered into eCRFs.

Laboratory test results: The results of all protocol-specified screening and entry laboratory tests that are performed in real time at site laboratories will be entered into eCRFs. During follow-up, through Week 16, all grade 1 or higher results will be entered into eCRFs. Thereafter, all grade 2 or higher results will be entered. The same eCRF data entry is required for infants in both study arms.

Signs, symptoms, and diagnoses: All signs, symptoms, and diagnoses identified from 30 days prior to entry (or from birth for infants who are less than 30 days of age at entry), up until the time of randomization, will be entered into eCRFs as pre-existing conditions. During follow-up, through Week 16, all grade 1 or higher signs, symptoms, and diagnoses will be entered into eCRFs. Thereafter, all grade 2 signs, symptoms, and diagnoses will be entered into eCRFs. All diagnoses will be entered consistent with the relevant diagnosis appendix (available at www.frontierscience.org). The same eCRF data entry is required for infants in both study arms.

Throughout follow-up, for infants in both study arms, the following will be further evaluated, with additional data entered into Event Evaluation eCRFs (refer to the study-specific MOP for more information on these eCRFs):

- Grade 3 or higher laboratory test results, signs, symptoms, and diagnoses
- Laboratory test results, signs, symptoms, and diagnoses that meet criteria for EAE reporting
- Laboratory test results, signs, symptoms, and diagnoses that result in deferral or discontinuation of study product administration
- Laboratory test results, signs, symptoms, and diagnoses that result in any change of cART regimen (including ARV holds, replacements, discontinuations, additions, and dose modifications)

Through Week 16, the eCRFs referenced above must be entered within 48 hours of availability of the relevant clinical findings and laboratory test results at the site. Thereafter, these eCRFs may be entered within standard timeframes for other eCRFs, unless otherwise requested by the CMC.

7.3 Expedited Adverse Event (EAE) Reporting

EAEs will be reported only for infants randomized to Arm 1 of this study, as only these infants are exposed to study product (VRC01).

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at:
http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at:
http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID Clinical Research Management System Support via email at CRMSSupport@niaid.nih.gov. Questions may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office via email at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 EAE Reporting Requirements for this Study

EAEs will be reported only for infants in Arm 1 of this study, as only these infants will be exposed to study product (VRC01).

The serious adverse event (SAE) reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

In addition to all SAEs, grade 3 or higher serum sickness, grade 3 or higher urticarial or other hypersensitivity reactions, and grade 4 injection site reactions must also be reported as EAEs in this study.

The study product for which expedited reporting is required is VRC01.

7.3.3 Grading Severity of Events

For infants in both study arms, adverse events will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, dated March 2017, which is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables

The only exceptions to the above apply to grading of axillary measured fever, injection site pain/tenderness, and malnutrition, which will be graded as follows:

Axillary Measured Fever

Grade 1	37.4 to < 38.0° C
Grade 2	38.0 to < 38.7° C
Grade 3	38.7 to < 39.4° C
Grade 4	≥ 39.4° C

Injection Site Pain/Tenderness

Grade 1	Mild reaction to light touch with no or minimal limitation of movement of limb
Grade 2	Persistent crying (up to one hour) with no or light touch, or significant limitation of movement of limb
Grade 3	Persistent crying for more than one hour or interference with ability to sleep or eat
Grade 4	Inconsolable crying for more than two hours

7.3.4 EAE Reporting Period for this Study

For infants randomized to Arm 1, the EAE reporting period begins at the time of first VRC01 administration and continues through the protocol-specified end of follow-up (i.e., through the date of the Week 48 visit).

After the above-specified period, only suspected, unexpected, serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual, will be reported if the study staff become aware of such events on a passive basis (e.g., from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

All adverse events identified in this study will be source documented consistent with the policies and procedures referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3).

For infants in Arm 1, source documentation will also include the relationship of each event to study product, assessed as follows:

Related There is a reasonable possibility that the event may be related to VRC01

Not related There is not a reasonable possibility that the event may be related to VRC01

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual, referenced in Section 7.3.1 above.

For infants in both study arms, all adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of the event. Grade 3 or 4 laboratory tests should be repeated for confirmation as soon as possible and within three working days. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards. Additional evaluations beyond those indicated in Appendix I may be performed at the discretion of the site investigator to determine the etiology of an adverse event and/or further assess its severity or relationship to study product (if applicable). When applicable, management will include referral to non-study sources of further evaluation and treatment.

Refer to Sections 8.1.1 and 8.1.2 for further guidance on management of adverse events. When management requires consultation with the CMC, the CMC should be contacted as soon as possible and within 72 hours of site awareness of the event. Site investigators must notify the CMC of all of the following as soon as possible and within 72 hours of awareness:

- Grade 1 or higher serum sickness
- Grade 1 or higher urticarial or other hypersensitivity reaction
- Any grade 3 or higher event assessed as related to study product
- Any grade 3 or higher adverse events assessed as related to the infant's cART regimen that persist for two weeks.

Note: Version 2.1 of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events defines serum sickness as a disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea. Generally, it is expected that several of these signs and symptoms should be present to substantiate a diagnosis of serum sickness and ─ consistent with the instruction above to notify the CMC of all grade 1 or higher serum sickness ─ all diagnoses should be made in consultation with the CMC.

8.1.1 General Adverse Event Management

Adverse events other than those listed in Section 8.1.2 should be managed consistent with the following guidance:

- **Grade 1 or 2 clinical and laboratory events** should be re-evaluated consistent with Section 6 and the Schedule of Evaluations in Appendix I or additionally at the discretion of the site investigator.

- **Grade 3 or 4 clinical events, and confirmed grade 3 or 4 laboratory events** should be re-evaluated as follows:

  – For grade 3 or 4 events occurring from the time of randomization through Week 10, re-evaluation should occur weekly until improvement to grade 2 or lower. Thereafter, re-evaluation should occur every two weeks until resolution (return to baseline, i.e., grade at study entry) or stabilization.

  – For grade 3 or 4 events occurring after Week 10, re-evaluation should occur no less frequently than every two weeks until resolution (return to baseline) or stabilization.

  For any grade 3 or 4 event that does not return to resolve (return to baseline) within four weeks after the date of onset of the event, the CMC should be consulted for further guidance on the frequency of re-evaluation and overall management of the event.

Refer to Sections 8.2 and 8.3 for further information on deferral and discontinuation of study product administration, respectively.

8.1.2 Event-Specific Adverse Event Management

The following types of adverse events should be managed consistent with the guidance provided in the event-specific tables in this section:

- Injection site reaction
- Urticaria or other hypersensitivity reaction
- Serum sickness
- Elevated ALT, total bilirubin, and creatinine values
- Decreased absolute neutrophil counts

INJECTION SITE REACTION		
SEVERITY	**VRC01 MANAGEMENT**	**FOLLOW-UP**
Grade 1 or 2	Continue administration of VRC01 doses. Use alternate injection site until event resolves to less than Grade 1	• Evaluate at subsequent visits per SoE.
Grade 3, resolves within two hours	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • If CMC and site investigator agree, may administer subsequent VRC01 dose.
Grade 3, persists longer than two hours	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Provide immediate clinical management per site investigator and subsequently in consultation with CMC. • If no alternative etiology is identified, permanently discontinue VRC01. • If alternative etiology identified and CMC agrees, may administer subsequent VRC01 dose. If grade 3 injection site reaction recurs, permanently discontinue VRC01.
Grade 4	Permanently discontinue VRC01.	• Contact CMC within 72 hours. • Provide immediate clinical management per site investigator and subsequently in consultation with CMC.

URTICARIA OR OTHER HYPERSENSTIVITY REACTION		
SEVERITY	**VRC01 MANAGEMENT**	**FOLLOW-UP**
Grade 1, 2, 3, 4	Stop VRC01 administration. Defer VRC01 until event reviewed with the CMC.	• Contact CMC within 72 hours. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • Provide immediate clinical management per site investigator (see study-specific MOP for guidance) and subsequently in consultation with CMC. • If diagnosis confirmed and assessed by either site investigator or CMC as related to VRC01, permanently discontinue VRC01. • If diagnosis not confirmed or definite alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs, permanently discontinue VRC01.

SERUM SICKNESS		
SEVERITY	**VRC01 MANAGEMENT**	**FOLLOW-UP**
Grade 1	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • Provide immediate clinical management per site investigator and subsequently in consultation with CMC. • If diagnosis confirmed and assessed by either site investigator or CMC as related to VRC01, permanently discontinue VRC01. • If diagnosis not confirmed or possible alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs at any grade, permanently discontinue VRC01.
Grade 2	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Assess for alternative cause. • Provide immediate clinical management per site investigator and subsequently in consultation with CMC. • If diagnosis confirmed and assessed by site investigator or CMC as related to VRC01, permanently discontinue VRC01. • If diagnosis not confirmed or probable alternative cause identified and has event has resolved and CMC agrees, may administer subsequent next VRC01 dose. If event recurs at any grade, permanently discontinue VRC01.
Grade 3 or 4	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Assess for alternative cause. • Provide immediate clinical management per site investigator and subsequently in consultation with CMC. • If diagnosis confirmed and assessed by site investigator or CMC as related to VRC01, permanently discontinue VRC01. • If diagnosis not confirmed or definite alternative cause identified and event has resolved and CMC agrees, may administer subsequent VRC01 dose. If event recurs at any grade, permanently discontinue VRC01.

ELEVATED ALT, TOTAL BILIRUBIN, OR CREATININE		
SEVERITY	**VRC01 MANAGEMENT**	**FOLLOW-UP**
Grade 1 or 2	Continue administration of VRC01 doses.	• Evaluate at subsequent visits per SoE or more frequently at the discretion of site investigator.
Grade 3	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Repeat test within 3 working days. • If repeat test result is ≤ Grade 2, manage as per Grade 2. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • If possible alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer subsequent VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01. • If no possible alternative cause identified, permanently discontinue VRC01.
Grade 4	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Repeat test within 3 working days. • If repeat test result is ≤ Grade 2, manage as per Grade 2. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • If probable alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer the next VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01. • If no probable alternative cause identified, permanently discontinue VRC01.

DECREASED ABSOLUTE NEUTROPHIL COUNT		
SEVERITY	**VRC01 MANAGEMENT**	**FOLLOW-UP**
Grade 1 or 2	Continue administration of VRC01 doses.	• Evaluate at subsequent visits per SoE or more frequently at the discretion of site investigator.
Grade 3	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Repeat test within 3 working days. • If repeat test result is ≤ Grade 2, manage as per Grade 2. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • If possible alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer subsequent VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01. • If no possible alternative cause identified, permanently discontinue VRC01.
Grade 4	Defer VRC01 until event reviewed with CMC.	• Contact CMC within 72 hours. • Repeat test within 3 working days. • If repeat test result is ≤ Grade 2, manage as per Grade 2. • Assess for alternative cause; treat the underlying illness or remove the likely causative agent. • If probable alternative cause identified and event has resolved to <Grade 3 and CMC agrees, may administer the next VRC01 dose. If event recurs at Grade 3 or higher, permanently discontinue VRC01. • If no probable alternative cause identified, permanently discontinue VRC01.

8.2 Deferral of Study Product Administration

The specifications of this section apply only to infants randomized to Arm 1.

At each study product administration time point, the site investigator or designee must confirm infant eligibility to receive study product based on review of medical history, physical examination findings, and prior laboratory test results.

For the types of adverse events listed in Section 8.1.2, study product administration must be deferred consistent with the guidance provided in the event-specific tables in that section.

For all other types of adverse events, if any of the following are present on the scheduled day of study product administration, administration must be deferred, and the CMC should be consulted on next steps:

- Any grade 3 or higher adverse event (sign, symptom, diagnosis, or laboratory test result)
- Any other significant medical condition that, in the opinion of the investigator, would make it unsafe to administer study product or make it difficult to assess for subsequent product-related adverse events

Following required consultation with the CMC, and improvement or resolution of the exclusionary condition (if applicable), study product may be administered. Whenever possible, infants should be re-scheduled to return to the clinic for product administration within the allowable visit window. If the allowable window elapses, the site investigator should consult with the CMC, which may approve product administration after the allowable window.

Infants who miss one or more scheduled administrations of study product will remain in follow-up and will ideally complete all visits, subsequent study product administrations, and evaluations specified in Section 6 and Appendix I.

8.3 Discontinuation of Study Product Administration

The specifications of this section apply only to infants randomized to Arm 1.

Administration of study product will be permanently discontinued in the event that:

- The infant's parent or legal guardian refuses further study product administration or evaluations required to monitor safety following study product administration
- The infant does not receive the study Entry (Week 0) dose of VRC01 within 14 days after initiation of cART.
- The infant experiences an adverse event requiring permanent discontinuation of study product per the event-specific tables in Section 8.1.2.
- The infant experiences a grade 3 or higher adverse event that is assessed as related to study product and, in consultation with the CMC, is determined to require discontinuation of study product administration.

- The site investigator determines that further administration of study product would not be in the best interest of the infant (consultation with the CMC is encouraged but not required prior to final determination)

Note: For infants who experience a grade 3 or higher adverse event, and for whom study product administration is approved to continue following improvement/resolution of the event, if the same grade 3 or higher adverse event recurs after subsequent study product administration, no further study product will be administered, unless there is an alternative explanation for the recurrence of the event and the CMC approves further study product administration.

Infants who are permanently discontinued from administration of study product will remain in follow-up and will complete all visits and evaluations specified in Section 6 and Appendix I.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I/II, multisite, two-arm, randomized, controlled, open-label study to evaluate the safety and antiviral activity of VRC01 among HIV-1-infected infants initiating cART within 12 weeks of birth. A total of 68 infants are expected to be enrolled at study sites located in Botswana, Brazil, Haiti, Malawi, South Africa, Zimbabwe, and the US. Enrolled infants will be randomly assigned in a 1:1 ratio to either receive VRC01 (Arm 1) or to not receive VRC01 (Arm 2). Infants assigned to receive VRC01 will be administered subcutaneous injections (40 mg/kg) at study Entry (Week 0) and Weeks 2, 6, and 10. Enrolled infants will be followed for 48 weeks with safety, pharmacokinetic, and antiviral activity evaluations performed throughout the duration of follow-up as specified in Section 6 and Appendix I.

Infants' mothers may optionally enroll in this study for purposes of one-time blood collection at the time of infant study entry, but mothers will not receive VRC01, will not undergo any other study evaluations, and will not be followed after blood collection at study entry.

As this is a relatively small study, only relatively large differences in safety and efficacy will be detectable between arms.

9.2 Outcome Measures

Note: The numbering of outcome measures in this section corresponds to the numbering of the study objectives in Section 2. Additional exploratory outcome measures will be defined after completion of the primary, secondary, and other analyses described in Section 9.6.

The primary and secondary outcome measures listed in Section 9.2.1 and 9.2.2 below will be addressed in the study's primary statistical analysis plan, which will define the content of the primary analysis report. This report will form the basis for the primary study publication and results reporting to ClinicalTrials.gov. Outcomes of interest for other objectives (intended for subsequent publications) are listed as other outcome measures in Section 9.2.3.

9.2.1	Primary Outcome Measures
9.2.1.1	• Grade 3 or higher adverse events including reactogenicity outcomes, abnormal laboratory test results, signs, symptoms, and diagnoses occurring from randomization through Week 14
9.2.1.2	• Change of HIV-1 DNA concentration in PBMCs from baseline (Week 0) to Week 14
9.2.2	**Secondary Outcome Measures**
9.2.2.1	• Pharmacokinetic parameters of VRC01 in the plasma at Weeks 2, 6, 10, 14, and 16 (Arm 1 only; see Section 10 for more details)
9.2.3	**Other Outcome Measures**
9.2.3.1	• Grade 3 or higher adverse events including reactogenicity outcomes, abnormal laboratory test results, signs, symptoms, and diagnoses occurring from randomization through Week 48
9.2.3.2	• Detection of antibodies against VRC01 at Weeks 14, 24, and 48 (binary outcome, Arm 1 only)
9.2.3.3	• Time from study entry to first plasma HIV-1 RNA below 40 copies/mL
9.2.3.4	• Change of HIV-1 DNA concentration in PBMCs from baseline (Week 0) to Weeks 24 and 48 • Change of HIV-1 RNA concentration in PBMCs (multiply-spliced and unspliced) from baseline (Week 0) to Weeks 14, 24, and 48 • Concentration in PBMCs of inducible HIV-1 RNA measured by TILDA at Weeks 24 and 48
9.2.3.5	• ADCC activity against viral isolates (expressed as antibody titers) at Weeks 14, 24, and 48 • Neutralization against viral isolates (expressed as antibody titers) at Weeks 14, 24, and 48

9.3 Randomization

Infants will be randomized in a 1:1 ratio to the two study arms using the permuted block method and stratified by whether the infant's initial cART regimen included an integrase inhibitor. In the event that twins (or other multiplets) are enrolled, both (all) infants will be randomized to the same arm. Randomization will not be balanced within each site, as some sites may have small numbers of participants.

9.4 Sample Size and Accrual

Sixty-eight infants are planned to be enrolled, with approximately 34 in Arm 1 and 34 in Arm 2, in order to have at least 20 infants per arm who are evaluable for the primary antiviral activity outcome at Week 14. Infants will be considered evaluable for this analysis based on an as-treated population who receive at least the first scheduled dose of VRC01 dose (Arm 1) and do not interrupt cART for more than three consecutive days prior to the Week 14 visit (Arm 1 and Arm 2). Infants who are not considered evaluable will not be replaced.

All enrolled infants will be included in safety analyses.

Enrollment is anticipated to be completed within one year after the first infant is enrolled in the study.

9.4.1 Safety

For the primary safety objective, Table 5 summarizes the probability of observing at least one adverse event (AE, as defined in Section 9.2.1) with 10, 20, 25, 34, and 40 participants and a variety of hypothetical event probabilities. For example, assuming the hypothetical probability of an adverse event in the Arm 1 is 0.05, with a sample size of 34, the probability of observing at least one participant with an adverse event will be 0.83.

Table 5
Probability of Observing at Least One Adverse Event with Sample Sizes of 10, 20, 25, 34, and 40 Infants within an Arm and Hypothetical Adverse Event Probabilities

Sample Size	True Probability of an AE	Probability of Observing at Least One AE
10	0.01	0.10
	0.03	0.26
	0.05	0.40
	0.07	0.52
	0.09	0.61
20	0.01	0.18
	0.03	0.46
	0.05	0.64
	0.07	0.77
	0.09	0.85
25*	0.01	0.22
	0.03	0.53
	0.05	0.72
	0.07	0.84
	0.09	0.91
34*	0.01	0.29
	0.03	0.64
	0.05	0.83
	0.07	0.92
	0.09	0.96
40	0.01	0.33
	0.03	0.70
	0.05	0.87
	0.07	0.95
	0.09	0.98

**Sample sizes of 25 and 34 are used to power the study for the primary objective of antiviral activity (please see section on antiviral activity below)*

Table 6 provides 95% confidence intervals (CIs), based on the Wilson Score method, on the adverse event probability for various observed adverse event numbers across sample sizes of 10, 20, 25, 34, and 40 infants. For example, if an adverse event is observed in 5 out of 34 infants, based on the 95% CI, these data are consistent with an adverse event occurring with a probability between 0.10 and 0.36. The resulting CI is also relevant if no adverse events are observed. Notably, observing no events among 34 infants is consistent with a probability of an adverse event of 0 to 0.10.

Table 6
95% Confidence Intervals for the Probability of an Adverse Event with Sample Sizes (and Adverse Event Numbers) of 10, 20, 25, 34, and 40 infants within an Arm

Sample Size	Number of Events	Proportion with an Event	95% CI Lower Bound	95% CI Upper Bound	Width
10	**0**	0	0.00	0.28	0.28
	1	0.1	0.02	0.40	0.39
	2	0.2	0.06	0.51	0.45
	3	0.3	0.11	0.60	0.50
	4	0.4	0.17	0.69	0.52
	5	0.5	0.24	0.76	0.53
20	**0**	0	0.00	0.16	0.16
	2	0.1	0.03	0.30	0.27
	4	0.2	0.08	0.42	0.34
	6	0.3	0.15	0.52	0.37
	8	0.4	0.22	0.61	0.39
	10	0.5	0.30	0.70	0.40
25*	**0**	0	0.00	0.13	0.13
	2	0.1	0.03	0.28	0.24
	4	0.2	0.09	0.39	0.30
	5	0.2	0.09	0.39	0.30
	10	0.4	0.23	0.59	0.36
	15	0.6	0.41	0.77	0.36
34*	**0**	0	0.00	0.10	0.10
	4	0.1	0.04	0.24	0.21
	5	0.2	0.10	0.36	0.26
	10	0.3	0.17	0.47	0.29
	15	0.5	0.34	0.66	0.32
40	**0**	0	0.00	0.09	0.09
	4	0.1	0.04	0.23	0.19
	10	0.25	0.14	0.40	0.26
	15	0.4	0.26	0.55	0.29
	20	0.5	0.35	0.65	0.30

**Sample sizes of 25 and 34 are used to power the study for the primary objective of antiviral activity (please see section on antiviral activity below)*

9.4.2 Antiviral Activity

The antiviral activity analysis is powered on the primary assessment of an average change from baseline (Week 0) to Week 14 in HIV-1 DNA concentration in PBMCs (log_{10} HIV-1 DNA copies per million PBMCs) between arms.

Data from the IMPAACT P1030 study [9] were reviewed to provide an estimate of the mean and standard deviation (SD) in the change from baseline to Week 14 in log_{10} HIV-1 DNA copies per million PBMCs (referred to as log_{10} HIV-1 DNA copies) for the sample size and power calculations for detecting a difference in the mean change between arms.

P1030 was a multicenter, phase I/II, open-label, single arm trial of LPV/r for treatment of 31 HIV-1-infected infants in which the pharmacokinetic properties of LPV/r were established. HIV-1 DNA data were available on 24, 20, 20, and 16 participants at Week 0 (baseline) and 24, 48, and 96 weeks, respectively, after cART initiation. In P1030, HIV-1 DNA measurements were not assayed during the weeks between baseline and Week 24, so there are no data for Week 14, the primary evaluation time point for this study. Therefore, these calculations are based on data from 20 participants with available HIV-1 DNA copies per million PBMC measurements both at baseline and data at the nearest available time point (Week 24).

In P1030, the mean (SD) log_{10} HIV-1 DNA copies measurements at baseline was 3.16 log_{10} (0.7 log_{10}) HIV-1 DNA copies, and all infants had detectable HIV-1 DNA copies. The mean (SD) log_{10} HIV-1 DNA copies change from baseline to Week 24 was 0.88 (0.34) log_{10} HIV-1 DNA copies for the 20 participants with data both at baseline and week 24.

Based on these estimates, sample size and power calculations for this study consider a range of possible differences of mean changes between two arms from baseline to Week 14 of 0.75, 1.0, and 1.5 and SD of change of 0.5 to 2.0 log_{10} HIV-1 DNA copies. Evaluable sample sizes of 10, 20, 30, and 40 participants per arm (20, 40, 60, 80 total for two arms) were considered to power the study. Calculations are based on the two-sided t-test with pooled variances for the primary outcome of antiviral activity comparison between arms with a 5% significance level (Table 7). Assuming a SD of 1.0, the study would have 87% power to detect a difference in mean change of HIV-1 DNA of 1.0 log_{10} copies between two arms with a sample size of 20 analyzed participants per arm (40 total for two arms). A difference of 1.0 log_{10} would be considered a meaningful difference.

Incorporating a non-parametric adjustment to use the Wilcoxon rank sum test, the necessary sample size per arm is 21 (using a relative efficiency ratio of 0.95). Adjusting for 20% missing data at baseline and/or at Week 14 due to VRC01 or cART discontinuation, loss-to-follow-up, missed visits or potential problems with the samples, the sample size per arm should be 25 infants per arm (50 total for two arms).

Furthermore, data on the effect of VRC01 on viremia in HIV-1-infected adults [12], indicate that a proportion of the viremic adults treated with VRC01 had virus that resisted neutralization by VRC01. An additional analysis will restrict the comparison between arms to infants with susceptible (not resistant) virus, as identified through testing planned to be performed after study completion. To provide adequate statistical power for this analysis, and assuming that up to 25% of infants may be identified with virus that is resistant to VRC01 neutralization at entry, the final selected sample size of 34 infants per arm represents a 25% increase from the 25 per arm noted above (25/0.75).

Table 7
Power to Detect a Difference Between Arms in
Mean Change of Log_{10} HIV-1 DNA Copies per Million PBMCs at Week 14

Standard Deviation	Mean Difference	Sample Size per Arm	Power
0.50	0.75	10	0.89
		20	>0.99
		30	>0.99
		40	>0.99
	1.00	10	0.99
		20	>0.99
		30	>0.99
		40	>0.99
	1.50	10	>0.99
		20	>0.99
		30	>0.99
		40	>0.99
	2.00	10	>0.99
		20	>0.99
		30	>0.99
		40	>0.99
1.00	0.75	10	0.36
		20	0.64
		30	0.81
		40	0.91
	1.00	10	0.56
		20	0.87
		30	0.97
		40	0.99
	1.50	10	0.89
		20	>0.99
		30	>0.99
		40	>0.99
	2.00	10	0.99
		20	>0.99
		30	>0.99
		40	>0.99
1.50	0.75	10	0.19
		20	0.34
		30	0.48
		40	0.60
	1.00	10	0.29
		20	0.54
		30	0.72
		40	0.84
	1.50	10	0.56
		20	0.87
		30	0.97
		40	0.99
	2.00	10	0.80
		20	0.98
		30	>0.99
		40	>0.99

Table 7
Power to Detect a Difference Between Arms in
Mean Change of Log_{10} HIV-1 DNA Copies per Million PBMCs at Week 14

Standard Deviation	Mean Difference	Sample Size per Arm	Power
2.00	0.75	10	0.12
		20	0.21
		30	0.30
		40	0.38
	1.00	10	0.19
		20	0.34
		30	0.48
		40	0.60
	1.50	10	0.36
		20	0.64
		30	0.81
		40	0.91
	2.00	10	0.56
		20	0.87
		30	0.97
		40	0.99

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard procedures described in the IMPAACT Manual of Procedures. Included in these standard procedures is monthly review of participant accrual and retention by the IMPAACT Management Oversight Group. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, participant safety, pharmacokinetics, and antiviral activity across sites is provided below.

9.5.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones and quality of study conduct.

The Protocol Team will closely monitor participant accrual based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. For any site that is delayed in completing the study activation process or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will monitor participant retention in a manner similar to participant accrual. On behalf of the Protocol Team, the CMC will monitor adherence to study product regimen and other key indicators of the quality of study conduct (e.g., data quality, data and specimen completeness) based on reports generated by the SDMC and will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will provide information on adverse events reported in the eCRF database for Arm 1 and Arm 2, including abnormal laboratory test results, signs, symptoms, and diagnoses. For infants in Arm 1, local injection site reactions will also be listed. The CMC will review data at the infant level, and data listings will include information on receipt of VRC01 and cART. Therefore, the CMC will be unblinded to participant random assignments.

The CMC will review safety data reports via conference call or other meeting at least monthly and — in addition to the site investigator — will assess the relationship of reported adverse events to the study product according to the categories of attribution provided in Section 8.1. In addition to individual adverse event listings, data reports will include the cumulative number and frequency of grade 2 or higher adverse events assessed as related to VRC01. At the time of each review, the DAIDS Medical Officer will also review any EAEs reported for infants in Arm 1 (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the eCRF database. The CMC will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern.

The CMC will also monitor whether any of the safety-related triggers for SMC review specified in Section 9.5.2 are met. If so, the CMC will rapidly review the triggering events and notify the SMC that an *ad hoc* review is required. The CMC will likewise request SMC review of any other safety concerns that may be identified throughout the course of the study.

In addition to the routine reviews described above, given that the VRC01 dosing regimen specified for this study has not previously been administered to infants, an interim safety analysis will be performed when the first five infants in Arm 1 have completed their Week 3 visits. This analysis will include all adverse events for all infants enrolled in the study at the time of the analysis. The CMC will review these data prior to SMC review; participant accrual will continue pending the SMC's review unless a safety-related trigger for SMC review (see Section 9.5.2) is met.

Pharmacokinetics

The regimen of VRC01 administered in this study is expected to maintain targeted concentrations of VRC01. To confirm that targeted concentrations are being achieved, an interim analysis will be performed when six infants randomized to Arm 1 have received the first two scheduled doses of VRC01 and have specimens available for PK analysis through Week 6. The CMC will review the dose evaluation data as soon as available and provide the data — along with a recommendation as to whether dose adjustment appears to be indicated — for independent review by the SMC. See Section 9.5.2 for further information about this SMC review and Section 10 for further information on the clinical pharmacology plan.

Antiviral Activity

The CMC will monitor plasma HIV-1 RNA levels as a real-time measure of antiviral activity. The SDMC will generate individual RNA profiles for each infant and summary descriptive statistics for the change from baseline (Week 0) across arms for routine review by the CMC.

9.5.2 Monitoring by the SMC

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures. The composition of the SMC will include the SMC Chair; IMPAACT Chair or Vice Chair; IMPAACT Cure Scientific Committee Chair or Vice Chair; representatives of the IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center; and representatives of NIAID and NICHD.

The first SMC review of this study is expected at the time of the interim safety analysis, which will be performed when the first five infants in Arm 1 have completed their Week 3 visits. The first regularly scheduled SMC review will occur after the first 50% of participants are enrolled or at 12 months after the first site is activated to initiate the study (whichever comes first); regular reviews will then be scheduled annually. SMC reviews may also occur on a more frequent or *ad hoc* basis if any issues or concerns arise, or if requested by the SMC. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

Reports prepared for the SMC will present data by blinded study arm; codes will also be provided to permit unblinding at the discretion of the SMC.

Study Progress and Quality of Study Conduct

The SMC will monitor study progress and the quality of study conduct through review of the same types of data reports as the Protocol Team and CMC. As noted above, however, reports prepared for the SMC will present data by blinded study arm.

Participant Safety

The SMC will monitor participant safety through review of the same types of safety data reports as the CMC; however, data will be made available to the SMC by blinded study arm when possible (data on local injection site reactions will not be blinded). For *ad hoc* or triggered safety reviews, more limited data may be provided, focusing on the events that triggered the reviews.

As indicated above, the SMC will review an interim safety analysis when the first five infants in Arm 1 have completed their Week 3 visits. This analysis will include all adverse events for all infants enrolled in the study at the time of the analysis; the SMC will additionally focus on safety-related trigger events (listed below). If trigger 1 or trigger 2 is met, or if other safety-related concerns warranting a change of study design are identified, accrual into the study and administration of study product will be paused.

Triggered SMC reviews will occur in the following scenarios:

1. Any infant in Arm 1 dies or has a Grade 4 adverse event that is judged by the CMC to be related to the study product (excluding neutropenia, anemia, and fever)
2. Three or more infants in Arm 1 have a Grade 3 or higher adverse event that is judged by the CMC to be related to the study product (excluding neutropenia, anemia, and fever)
3. After at least 25 participants have been enrolled, 20% (across arms) have Grade 3 or higher adverse events

Because Grade 3 and higher neutropenia and anemia are common among infants on ART, and Grade 3 and higher fever is common due to inter-current illnesses, these events will not be counted in scenarios (1) and (2). These events will be counted in scenario (3).

If either scenario (1) or scenario (2) occurs, accrual into the study and administration of study product will be paused, and an SMC review will take place within seven days. If scenario (3) occurs, accrual into the study and administration of study product will not be paused, and an SMC review will take place within seven days.

In the event of any other event or trend of concern identified by the CMC, an SMC review may be requested, and the CMC may choose to pause participant accrual and administration of study product pending the outcome of the SMC review.

Following any pause, participant accrual and administration of study product may be resumed if recommended by the SMC. If resumption is not recommended, no further participants will be enrolled and no further study product will be administered, but all enrolled participants will continue follow-up per protocol, unless otherwise advised by the SMC.

Given the relatively small study sample size, the information available for safety decisions will be imperfect. Two types of sampling errors are possible:

1. In a group where the true rate of adverse events is too high to warrant increased exposure to VRC01, the sample data may pass the safety guidelines;
2. In a group where the true rate of adverse events is low enough that further exposure to VRC01 is warranted the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical "true adverse events" rates that could occur if the study product were used extensively among the participant population. The hypothetical situations presented in Table 8 range from conditions under which VRC01 would cause a high incidence of severe and life threatening adverse events to conditions under which severe adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations, it is assumed that a sample of 25 infants is drawn from the participant population, receives VRC01, and that the safety guidelines specified above are followed.

For example, Table 8 shows that there is an 86% chance of meeting the safety review trigger for the SMC under conditions in which the true rate of Grade 4 adverse events or deaths is 5% and the rate of Grade 3 adverse events is 10%, and a 92% chance if the true rate of Grade 4 adverse events or deaths is 7% and the rate of Grade 3 adverse events is 10%. Assuming that VRC01 is associated with this extent of severe adverse events would be unacceptable, the 14% and 8% chance of not triggering an SMC safety review under these conditions, respectively, would represent sampling error.

The true rate of Grade 3 events would have to be over 10% to provide a strong probability of pausing the study when there are no Grade 4 events or deaths in Arm 1. This is considered acceptable, since a larger sample size would be needed to increase the probability of pausing the study at lower rates of Grade 3 events, and this would entail exposing greater numbers of children to VRC01, which may be either toxic or sub-therapeutic. (Accordingly, the probability of meeting study pausing guideline for SMC review would be lower for smaller sample sizes than the sample size of 25).

Table 8
Probability of Failing Safety Criteria (n = 25)

True Adverse Event Rates		
Grade 3 AE related to VRC01	**Grade 4 or death related to VRC01**	**Probability of meeting study pausing guideline for SMC review**
0.50	0.00	>0.99
0.50	0.01	>0.99
0.50	0.02	>0.99
0.50	0.05	>0.99
0.50	0.07	>0.99
0.25	0.00	0.97
0.25	0.01	0.98
0.25	0.02	0.98
0.25	0.05	0.99
0.25	0.07	>0.99
0.15	0.00	0.75
0.15	0.01	0.81
0.15	0.02	0.85
0.15	0.05	0.94
0.15	0.07	0.97
0.10	0.00	0.46
0.10	0.01	0.59
0.10	0.02	0.68
0.10	0.05	0.86
0.10	0.07	0.92
0.05	0.00	0.13
0.05	0.01	0.32
0.05	0.02	0.48
0.05	0.05	0.76
0.05	0.07	0.86
0.01	0.00	<0.01
0.01	0.01	0.22
0.01	0.02	0.40
0.01	0.05	0.72
0.01	0.07	0.84

True Adverse Event Rates		
Grade 3 AE related to VRC01	Grade 4 or death related to VRC01	Probability of meeting study pausing guideline for SMC review
0.00	0.01	0.22
0.00	0.02	0.40
0.00	0.05	0.72
0.00	0.07	0.84

Pharmacokinetics

The regimen of VRC01 administered in this study is expected to maintain targeted concentrations of VRC01. To confirm that targeted concentrations are being achieved, an interim analysis will be performed when six infants randomized to Arm 1 have received the first two scheduled doses of VRC01 and have specimens available for PK analysis through Week 6. The CMC will review the dose evaluation data as soon as available and provide the data — along with the CMC's interpretation of the data and recommendation as to whether dose adjustment appears to be indicated — for review by the SMC. If these data are available at the time of a routinely scheduled SMC review, they will be provided to the SMC at the time of that review; otherwise, they will be provided to the SMC with a request for an *ad hoc* review.

Antiviral Activity

When approximately 50% of participants have reached Week 14, the SMC will review data on plasma HIV-1 RNA levels as a measure of antiviral activity. The SDMC will first generate plasma HIV-1 RNA profiles for each infant and descriptive summary statistics for the change from randomization (Week 0) for each arm (blinded) for review by the SMC. If the SMC has concerns of lack of antiviral activity, prior to recommending changes to the study accrual plan or design, available specimens will be tested for (i) ARV drug concentrations, (ii) virus susceptibility to VRC01, and (iii) HIV-1 DNA concentrations in PBMCs. These results will be provided to the SMC for further consultation regarding continuing participant accrual or stopping accrual early.

If the above-described data are available at the time of a routinely scheduled SMC review, they will be provided to the SMC at the time of that review; otherwise, they will be provided to the SMC for an *ad hoc* review.

9.6 Analyses

A detailed statistical analysis plan will be developed and finalized before the first distribution of safety data for CMC review.

All statistical tests will be two-sided with a nominal significance level of 0.05.

In the event that twins or other multiplets are enrolled in the study, one of the multiplets will be randomly selected to be included in the analyses. Sensitivity analyses will be performed in which the selected infant will be replaced by the other sibling(s) to ensure that any choice would support the same overall results. Line listings will provide individual data from all infants.

9.6.1 Primary Analyses

Safety

All enrolled infants will be included in safety analyses.

For the primary safety analysis, Grade 3 or higher adverse events occurring after randomization cumulatively through Week 14 will be summarized. Descriptive analyses will consist of frequency distributions by type of event. For each infant, the worst grade of adverse event experienced will be summarized. Separate summaries and listings of deaths will also be provided. Estimates of Grade 3 or higher adverse event rates will be computed separately for each arm and bounded by 95% CIs, reflecting the precision of the estimates using the Wilson Score method. Death rates will also be computed separately for each arm and bounded by 95% CI.

Antiviral Activity

The primary analysis of antiviral activity will be an as-treated analysis, limited to evaluable infants who do not interrupt cART for more than three consecutive days prior to the Week 14 visit and, if randomized to Arm 1, who receive at least the first scheduled dose of VRC01.

Log-transformations will be applied to the primary antiviral activity outcome of HIV-1 DNA concentration in PBMCs. For values below the assay detection limit, a value of one half the lower assay limit will be imputed. The proportion of values below the assay limit will be summarized at each time point, if any.

The values and changes from baseline (Week 0) of HIV-1 DNA concentration in PBMCs will be tabulated and summarized graphically at each scheduled study visit by calculating 95% CI around the mean.

The primary analysis will compare the change in HIV-1 DNA concentrations in PBMCs from baseline to Week 14 between the two randomized arms, testing the null hypothesis of no difference in the distribution of change from baseline between the two arms, using a Wilcoxon rank sum test at a 5% significance level.

Infants will not be tested at screening to determine if their virus is resistant to neutralization by VRC01. However, an additional analysis of the primary outcome will exclude infants whose baseline virus is resistant to VRC01 neutralization, as identified at the time when HIV-1 DNA concentrations are determined.

Sensitivity analyses will be conducted using the last available time point before Week 14 if HIV-1 DNA concentration in PBMCs is missing at Week 14.

9.6.2 Secondary Analyses

Refer to Section 10 for a detailed description of the planned analyses of the PK of VRC01.

9.6.3 Other Analyses

Safety

Analyses of the safety outcome through Week 48 will parallel the analysis approach of the primary safety outcome.

The same summaries for the safety outcome for Arm 1 will also be provided for Arm 2. Additional analyses will compare the adverse event probabilities by arm with Fisher's exact test with the mid-p option (as-treated and intent-to-treat analyses). Injection reactions will be excluded when comparing safety between arms. In another safety analysis, Grade 3 or higher adverse events that are judged by the CMC to be related to study product at any time cumulatively through Week 14 will also be summarized for Arm 1.

VRC01 tolerability will be summarized by the number of participants who prematurely discontinue the study product along with the reasons for discontinuation. Probabilities and 95% CIs will be estimated.

Antiviral Activity

Analyses of the antiviral activity outcomes — changes at Week 24 and Week 48 — will parallel the analysis approach of the primary antiviral activity outcome. For analyses of inducible HIV-1 RNA at Weeks 24 and 48, in the event that specimen collection volumes at baseline do not permit evaluation of changes from baseline to Week 24 or Week 48, TILDA results for the two randomized arms will be compared at each time point (rather than comparing changes from baseline).

Time to event outcomes (e.g., time to viral load <40 copies/mL) for both arms will be estimated using the method of Kaplan-Meier. Time-to-event distributions will be compared with log-rank tests, and differences between arms will be assessed by the Cox proportional hazards model.

Other analyses will additionally include sensitivity analyses of the primary outcomes, in particular restricting the VRC01 analysis set to those who received all four injections; intent-to-treat analyses; and analyses with alternative censoring and imputation methods.

An analysis of within-participant change will be evaluated by comparing post-VRC01 measurements with pre-VRC01 measurements in all participants who received at least one infusion of VRC01 using a Wilcoxon signed rank test at 5% significance level.

Other Outcomes

The estimated probabilities of participants with a measurable level of antibody to VRC01 will be presented along with an exact 95% CI.

The absolute values and changes of laboratory test results for different measures of HIV-1 reservoir size, ADCC activity, and virus neutralization will be summarized graphically at each scheduled visit by calculating 95% CI around the mean.

Analyses will parallel the analysis approach of the antiviral activity outcomes.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objective

The pharmacology objective of this study is to determine the pharmacokinetics (PK) of a regimen of four doses of VRC01 (40 mg/kg per dose) administered subcutaneously to HIV-1-infected infants initiating cART within 12 weeks of birth.

10.2 Pharmacology Data

Data expected to be used for PK analyses include the following: demographics (sex and age); height and weight; VRC01 dosing details (date, time, dose administered, administration location); and sample collection details (date and time of collection). For each infant randomized to Arm 1, seven samples are expected to be collected for PK evaluations, at study Entry (Day 0) and Weeks 2, 6, 10, 14, and 16. Samples collected at Entry and Weeks 2, 6, and 10 will be collected prior to VRC01 dosing. All sample collection data will be documented in LDMS.

Assay Location: Plasma samples will be shipped to the NIAID Vaccine Immune T-Cell and Antibody Laboratory (NVITAL) where they will be assayed for concentrations of VRC01.

Assay Methods: All assay methods will be immune-based, standardized with a filed Methods Report, and performed under Good Clinical Laboratory Practice conditions at NVITAL.

Reporting of Assay Data: Real-time PK evaluations will not be performed in this study. Assay data are expected to be evaluated at two time points:

- An interim PK analysis will be undertaken when six infants randomized to Arm 1 have received two doses of VRC01 and have specimens available for analysis through Week 6. At this time, all PK samples collected from all infants thus far will be shipped and assayed at NVITAL. These results will be compared to those predicted from IMPAACT P1112 with an emphasis on VRC01 concentrations, and their variability, prior to dosing at Weeks 2 and 6. As described in section 9.5, results will then be reported to the CMC and SMC for purposes of assessing whether a dose adjustment may be indicated.

- A final PK analysis will be undertaken after study completion. All remaining PK samples will be shipped and assayed at NVITAL after completion of follow-up. All VRC01 concentration data (including data from the interim analysis) will be combined for final analysis and final results will be reported to the Protocol Team.

10.3 Pharmacology Study Design, Modeling, and Data Analysis

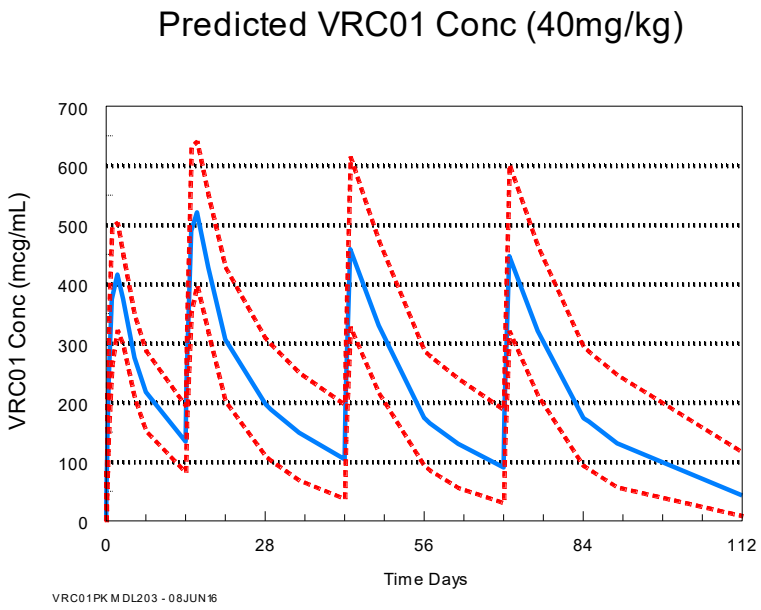
PK samples will be collected from all infants randomized to Arm 1 at the time points listed above. At each time point, 1-2 mL of whole blood will be collected to yield 0.4-1.0 mL of plasma.

VRC01 concentrations will be presented for each time point and the frequency of achieving trough concentrations greater than 20 and 50 mcg/mL at Week 2, 6, 10 and 14 will be calculated. The median, mean, and standard deviation of the concentrations will also be calculated from evaluable samples at each time point. Evaluable samples are defined as those with adequate

volume and integrity to yield accurate concentration results, with associated accurate dosing and sample time data.

It is expected that the VRC01 pharmacokinetic parameters and their variability observed in this study will be similar to those observed in IMPAACT P1112. The observed VRC01 concentrations will be compared to those observed in P1112 as well as those observed in adults. Specifically, the geometric mean and 90% CI for the Week 6 concentrations, which are expected to be the lowest observed concentrations in this study, will be generated. Based on currently available data from infants and adults, the Week 6 concentrations are predicted to fall within the range of 20-70 mcg/mL, as shown in Figure 2.

Figure 2
Predicted VRC01 Concentrations:
Median and 5th-95th Percentile



10.4 Pharmacokinetic Analysis

Given the sparse nature of the PK data being collected, non-compartmental pharmacokinetic analysis will not be performed. However, population pharmacokinetic analyses using the computer program NONMEM will be conducted on the VRC01 pharmacokinetic data to determine VRC01 apparent clearance (CL/F). Other compartmental PK parameters will be estimated to the extent possible. Both one and two compartment pharmacokinetic models with first order absorption will be assessed based on existing pharmacokinetic studies of subcutaneously administered VRC01. Prior analysis in adults suggests a two compartment model will be needed to characterize the VRC01 pharmacokinetics in infants. However, due to the limited early sampling in this study, the absorption rate constant (KA) and distribution parameters (V1/F and Q/F) may be leveraged with infant PK parameter estimates from IMPAACT P1112 to enhance estimation of CL/F in this study.

The population analysis will generate estimates for apparent volumes of distribution (V1/F and V2/F), inter-compartmental clearance (Q/F), CL/F and absorption rate constant KA. Given the small number of infants in this study, the population pharmacokinetic analysis will not include an exploratory covariate analysis to assess clinical factors as fixed effects associated with VRC01 pharmacokinetic parameters, except for study (P1112 versus 2008). Infant size will be included using standard allometric scaling.

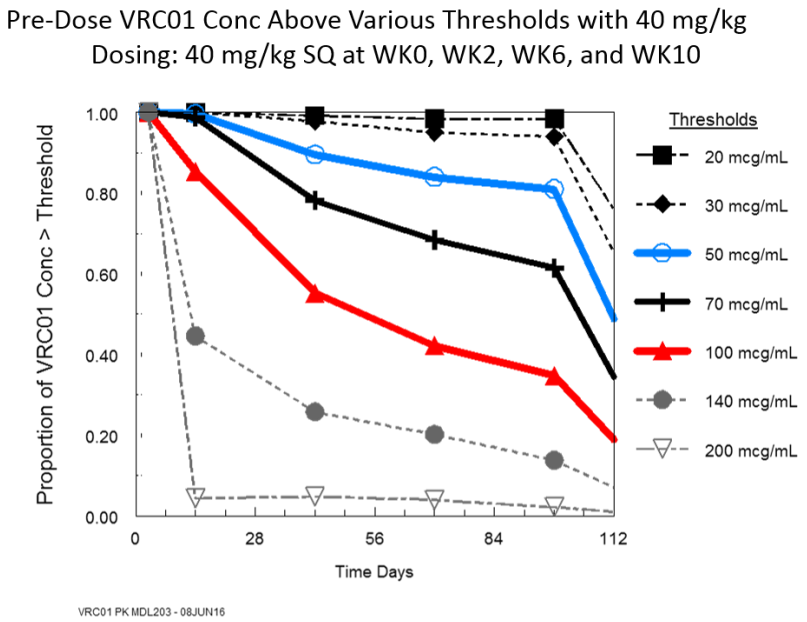
The population analysis will be used to quantify unexplained between-infant PK variability. Final model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population model parameters will be assessed using bootstrapping to generate 95% CIs for parameter estimates. Post-hoc empiric Bayesian estimates of individual infant pharmacokinetic parameters will be generated. The final population PK model and the study dosing regimen (40 mg/kg subcutaneously administered x 4) will be used to assess the ability of the regimen to achieve and maintain target VRC01 concentrations through Monte Carlo simulations with at least 5000 virtual infants.

This study is not powered for a stand-alone population PK analysis that can generate a complete set of PK parameters. However, the PK variability in pre-dose VRC01 concentrations following subcutaneous administration in studies 601 and 602 was approximately 40%. Assuming similar variability in this study, and with 34 infants receiving VRC01 in this study, the precision of the pre-dose concentration in this study is expected to generate a 95% CI of ± 15% of the observed mean. While population PK studies do not lend themselves to classical power calculations, based on PK studies of similar size, the 238 PK samples collected from 34 infants in this study are expected to yield precise estimates of the population estimate for VRC01 CL/F.

10.5 Anticipated Outcomes

It is expected that VRC01 exposure (Week 6 concentrations) will be consistently above 20 mcg/mL and frequently above 50 mcg/ml, as shown in Figure 3.

Figure 3
Expected VRC01 Concentrations



11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.5, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled mother-infant pairs, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 11.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at www.frontierscience.org.

11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at:
www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study products for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the VRC, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, OHRP, and other applicable regulatory entities. Records must be kept on site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID of NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at: www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, paper-based CRFs (if used), eCRFs medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

13 HUMAN SUBJECTS PROTECTIONS

13.1 IRB/EC Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed, and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

13.2 Vulnerable Participants

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Infants enrolled in this study are considered vulnerable participants per 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children and assess the justification for their inclusion in the study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2 and the risk category assigned by the IRB/EC determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

13.3 Informed Consent

Refer to Section 4.5 and the study-specific MOP for further information on informed consent procedures for this study. Refer to Appendices II-V for sample informed consent forms.

Written informed consent for infant study participation will be obtained from each infant's mother or legal guardian before any study-specific procedures are performed. The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the randomized nature of the study design and the unproven efficacy of VRC01. Regardless of random assignment, mothers or legal guardians will be extensively counseled on the importance of adherence to the infant's cART regimen for viral suppression and other long-term treatment goals.

As part of the informed consent process, mothers (or legal guardians) will be asked whether they agree to collection of infant blood specimens for primary, secondary, other, and exploratory evaluations. Mothers or legal guardians must agree to this in order for infants to participate in the study; however, genetic testing of these specimens may be declined. Similarly, collection of residual CSF for exploratory evaluations may be declined.

The mothers of enrolled infants will also be asked to consent to collection of their own blood for exploratory evaluations. This consent is optional; it is not required for infant study participation. In addition, genetic testing of maternal specimens may be declined.

Separately, mothers (or legal guardians) will be asked whether they agree to storage and future research testing of specimens remaining after all protocol-specified primary, secondary, other, and exploratory testing has been completed. Future research testing of residual specimens may be declined with no impact on other aspects of infant study participation. This informed consent process should ideally be conducted at study screening or entry visits; however, if this is not possible logistically, or if more time is needed for a mother (or legal guardian) to decide whether to provide or decline consent for future research testing, this process may be completed at any time up until the Week 6 visit.

As indicated above, it is generally expected that the consent of one parent (or legal guardian) will be sufficient for infant participation in this study. However, consenting requirements at each site will depend on the IRB/EC risk determination described in Section 13.2; all IRB/EC requirements will be followed.

Should the consenting parent (or legal guardian) of an enrolled infant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study product should be administered (if applicable) and no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from the infant's authorized guardian, as defined locally. Study sites may continue to provide care for the infant as needed and appropriate (outside of the study) consistent with the local standard of care, but no study-specific procedures (outside of the standard of care) may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued infant study participation, the infant must be terminated from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 13.2), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

Administration of VRC01 transiently reduced plasma HIV levels in adults when given without cART [12] and thus may reduce plasma HIV levels when given in combination with initiation of cART. Although it is hypothesized that administration of VRC01 may attenuate HIV reservoir formation and lead to lower concentrations of HIV-infected cells in peripheral blood, there may be no direct benefit to infants who take part in their study. Likewise, there may be no benefit to mothers who take part in this study. Information learned in this study may, however, be of benefit to infants born to HIV-infected mothers in the future.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of VRC01.

Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, and (rarely) infection at the site where the needle is inserted.

VRC01 has not previously been administered to HIV-infected infants, but has been administered to both HIV-infected and HIV-uninfected adults. It also has been administered to newborn HIV-exposed infants. As indicated in Section 1.2, VRC01 has generally been well-tolerated by all study populations to date. Among infants, only mild to moderate local reactions following subcutaneous administration of VRC01 have been observed to date, and no other adverse events attributable to VRC01 have been identified. Experience with VRC01 in adults also indicates a generally mild risk profile, with few and mild to moderate local reactions at the site of administration and mild systemic reactions including malaise, myalgia, fatigue, headache, and nausea observed in some study participants. In addition, mild to severe urticarial reactions have been observed rarely.

In general, administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness, and the generation of antibodies; however, these reactions are rare and more often associated with mAb targeted to human proteins or with the use of murine monoclonal antibodies. In this regard, as VRC01 is targeted to a viral antigen and is a human monoclonal antibody, it is expected to have a low risk of such side effects. Typically, the side effects of mAbs are mild but may include fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. 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.

There is a theoretical risk that receiving VRC01 might affect sensitivity to ARVs that work through entry or fusion inhibition; however, these are third-line ARVs that are not approved for use in infants or young children. There is also a theoretical risk that receipt of VRC01 could lead to viral resistance to VRC01, thereby limiting its use in the future for a given infant, and possibly also conferring cross-resistance to other antibodies that target the CD4 binding site. This risk is minimized, however, through the use of VRC01 in combination with cART.

These types of reactions may be observed in infants in this study, and there may be other risks that are not currently known.

13.6 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

13.7 Privacy and Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2. If any photographs of observed reactions are taken, standard precautions will be followed to ensure that participant privacy and confidentiality are protected.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) will be identified by PID only. Likewise, communications between study staff and Protocol Team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password-protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.9 Management of Incidental Findings

Site clinicians will inform infants' parents or legal guardians of all clinically meaningful physical exam findings and laboratory test results, including hematology and chemistry test results, CD4/CD8 cell counts, and HIV-1 RNA levels. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

The results of protocol-specified pharmacokinetic, virologic, and immunologic assays are not planned to be provided to infants' parents or guardians, as these are considered research tests that are not expected to be relevant to clinical care and management. If, however, new information becomes available during the course of the study indicating that the results of any of these assays are of clinical relevance, the results of these assays will be provided. Additional results disclosure may also occur if determined to be in the best interest of study participants based on the outcome of SMC reviews as described in Section 9.5.2.

13.10 Management of New Information Pertinent to Study Participation

Infants' parents or legal guardians will be provided any new information learned over the course of the study that may affect their willingness to allow their infants to continue receive VRC01 (if in Arm 1) or to remain in follow-up in the study.

13.11 Post-Trial Access to Study Product

This Phase I/II study will provide information on the safety and antiviral activity of VRC01 for HIV-1-infected infants initiating cART. Based on the results of this study, other studies may be conducted in the future to further characterize the safety and efficacy of VRC01 for this population. Before such studies are completed, the efficacy of VRC01 and its risk-to-benefit ratio for this population remain unknown; therefore, VRC01 will not be immediately available after this study is completed. Should future studies demonstrate clinical benefit from use of VRC01, the VRC intends to develop the product so that it can be made available for appropriate indications.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The study product, VRC01, is provided by the NIAID Vaccine Research Center (VRC); however, the VRC is not involved in sponsorship or regulatory oversight of this study.

The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRB/EC, local IBC, and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs will be reviewed and approved by the DAIDS PRO, and sites 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.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are 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. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO, and sites 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, which is available on the RSC website:
http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, and non-US country and local regulations. Study implementation will also be guided by the IMPAACT Manual of Procedures, study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT web site: www.impaactnetwork.org.

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures.

14.5 Critical Event Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at:
www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring

14.6 ClinicalTrials.gov

This protocol is subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

16 REFERENCES

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Appendix I
IMPAACT 2008 Schedule of Evaluations: Screening through Week 14

Study Visit	Screen	Entry	Entry +3d	Week 1	Week 2	Week 2+3d	Week 3	Week 6	Week 6+3d	Week 7	Week 10	Week 10+3d	Week 11	Week 14
Visit Window	-30 d	Day 0	-1/+3 d	±3 d	±3 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d
Informed consent	X													
Maternal Evaluations *(for mothers of enrolled infants who consent to blood collection)*														
Stored plasma and PBMCs for exploratory evaluations		10 mL												
Stored serum for exploratory evaluations		10 mL												
Infant Evaluations														
HIV-related testing history	X	X												
Medical/medications history	X	X		X	X		X	X		X	X		X	X
ARV history	X	X			X			X			X			X
Immunization history	X	X			X			X			X			X
Feeding history	X	X			X			X			X			X
cART adherence assessment		X			X			X			X			X
Physical examination	X	X		X	X		X	X		X	X		X	X
VRC01 administration[1] (Arm 1 only)		***X***			***X***			***X***			***X***			
Reactogenicity assessment[2]		X	X	X	X	X	X	X	X	X	X	X	X	
Confirmatory HIV nucleic acid test (if needed)	0-3 mL													
Complete blood count with differential and platelets	1 mL			1 mL			1 mL			1 mL			1 mL	1 mL
ALT, AST, ALP, creatinine	1 mL			1 mL			1 mL			1 mL			1 mL	1 mL
CD4 and CD8 cell count and percentage[3]	1 mL													1 mL
HIV-1 RNA in plasma[4] (real time)		1 mL[4]		3 mL[4]				3 mL[4]			3 mL[4]			3 mL[4]
Urinalysis		X		X										X

Appendix I
IMPAACT 2008 Schedule of Evaluations: Screening through Week 14

Study Visit	Screen	Entry	Entry +3d	Week 1	Week 2	Week 2+3d	Week 3	Week 6	Week 6+3d	Week 7	Week 10	Week 10+3d	Week 11	Week 14
Visit Window	-30 d	Day 0	-1/+3 d	±3 d	±3 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d	-1/+3 d	±3 d	±7 d
Infant Evaluations (continued)														
Stored plasma and PBMCs for primary, secondary, and other evaluations		3-5 mL[5]			1 mL			1 mL			1 mL			5 mL
VRC01 level (plasma)		X			X			X			X			X
Anti-VRC01 antibodies (plasma)		X												X
HIV-1 DNA (PBMC)		X												X
HIV-1 RNA (spliced/ unspliced; PBMC)		X												X
HIV-1 RNA (inducible; PBMC)		X												
ADCC (plasma)		X												X
ARV levels (plasma, adherence)														X
Stored serum for neutralization assay		1 mL												1 mL
Stored plasma and PBMCs for exploratory evaluations[6]		0-2 mL[6]			X[6]			X[6]			X[6]			0-2 mL[6]
Cerebral spinal fluid storage for exploratory evaluations														
Total Infant Blood Volume	**3-6 mL**	**5-9 mL**	**—**	**5 mL**	**1 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**4 mL**	**—**	**2 mL**	**12-14 mL**

Appendix I
IMPAACT 2008 Schedule of Evaluations: Week 16 through Week 48

Study Visit	Week 16	Week 20	Week 24	Week 36	Week 48	Early D/C[7]	CSF Collection[8]
Visit Window	±7 d	±14 d	±14 d	±14 d	±14 d	NA	NA
Informed consent							
Maternal Evaluations ***(for mothers of enrolled infants who consent to specimen collection)***							
Stored plasma and PBMCs for exploratory evaluations							
Stored serum for exploratory evaluations							
Infant Evaluations							
HIV-related testing history							
Medical/medications history	X	X	X	X	X	X	X[8]
ARV history	X	X	X	X	X	X	
Immunization history	X	X	X	X	X	X	
Feeding history	X	X	X	X	X	X	
cART adherence assessment	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	
VRC01 administration (Arm 1 only)							
Reactogenicity assessment							
Confirmatory HIV nucleic acid test (if needed)							
Complete blood count with differential and platelets		1 mL	1 mL	0-1 mL[3]	0-1 mL[3]	1 mL[7]	
ALT, AST, ALP, creatinine		1 mL	1 mL				
CD4 and CD8 cell count and percentage[3]			1 mL	1 mL[3]	1 mL[3]	1 mL[7]	
HIV-1 RNA in plasma[4] (real time)	3 mL[4]		3 mL[4]	3 mL[4]	3 mL[4]	3 mL[4,7]	
Urinalysis			X			[X][7]	

Appendix I
IMPAACT 2008 Schedule of Evaluations: Week 16 through Week 48

Study Visit	Week 16	Week 20	Week 24	Week 36	Week 48	Early D/C[7]	CSF Collection[8]
Visit Window	±7 d	±14 d	±14 d	±14 d	±14 d	NA	NA
Infant Evaluations (continued)							
Stored plasma and PBMCs for primary, secondary, and other evaluations	1 mL		7 mL		7 mL	5-7 mL[7]	
VRC01 level (plasma)	X					X	
Anti-VRC01 antibodies (plasma)			X		X	X	
HIV-1 DNA (PBMC)			X		X	X	
HIV-1 RNA (spliced/ unspliced; PBMC)			X		X	X	
HIV-1 RNA (inducible; PBMC)			X		X		
ADCC (plasma)			X		X	X	
ARV levels (plasma, adherence)			X		X	X	
Stored serum for neutralization assay			1 mL		1 mL	1 mL[7]	
Stored plasma and PBMCs for exploratory evaluations[6]	X[6]		2 mL	5 mL	7 mL	2 mL[7]	2 mL[8]
Cerebral spinal fluid storage for exploratory evaluations							X[8]
Total Infant Blood Volume	**4 mL**	**2 mL**	**16 mL**	**9-10 mL**	**19-20 mL**	**13-15 mL**	**2 mL**

Appendix I Footnotes

1. At Entry and Weeks 2, 6, and 10, for infants in Arm 1, blood collection must precede administration of VRC01.
2. Refer to Section 6.16.
3. CD4 and CD8 cell counts and percentages are generally expected to require 1 mL of blood. At sites where a complete blood count (CBC) is needed to obtain both cell counts and percentages, 1 mL may be collected to perform the CBC at Week 36 and Week 48 (at other sites, the CBC is not required at these visits).
4. At Entry, collect 1 mL and dilute as needed to perform the HIV-1 RNA assay. At all other time points, collect 3 mL and process specimen for storage of PBMCs in addition to plasma for the RNA assay, if possible.
5. At Entry, collect 3 mL for storage for primary, secondary, and other evaluations if the infant weighs <3 kg; collect 5 mL if the infant weighs ≥3 kg.
6. At Entry and Week 14, collect 2 mL for storage for exploratory evaluations only if the infant weighs ≥ 3 kg at the visit; otherwise, do not collect any blood for exploratory evaluations at these visits. At Weeks 2, 6, 10, and 16, no additional blood is collected for exploratory evaluations but any plasma and PBMCs remaining from specimens collected for primary, secondary, and other evaluations will be stored for exploratory purposes (indicated with "X[6]").
7. Refer to Section 6.13. Infants who are withdrawn or terminated before completing the Week 24 Visit should have urinalysis performed and 5 mL of blood drawn for storage for primary, secondary, and other evaluations; infants who are withdrawn or terminated after the Week 24 Visit should not have urinalysis performed and should have 7 mL of blood drawn for storage for primary, secondary, and other evaluations. For all infants, laboratory evaluations that have been performed within the two weeks prior to the Early D/C Visit need not be repeated.
8. Refer to Section 6.12.

Appendix II
Sample Informed Consent Form for Infant Study Participation

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

Your baby is being asked to participate in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as you need to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide to have your baby participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [*insert site name*] are doing this study. The study is testing an experimental injection called **VRC01** in babies who have HIV. HIV is the virus that causes AIDS.

The study will include about 68 babies who are less than 12 weeks old from Botswana, Brazil, Haiti, Malawi, South Africa, Zimbabwe, and the United States. Babies will be in the study for about one year.

The person in charge of the study at [*insert site name*] is [*insert name of IoR*]. The United States National Institutes of Health are paying for the study.

1. The study is testing VRC01 in babies who have HIV.

The study will test the safety of VRC01 when given to babies who are starting treatment for HIV. It will also test the effect of VRC01 on the amount of HIV that can be found in babies' blood and blood cells.

VRC01 is an antibody against HIV. Antibodies are made by the immune system to fight infection. Antibodies can also be made in laboratories. VRC01 is made in a laboratory.

VRC01 has been tested in laboratory experiments and in animals and people. It has been tested in HIV-negative adults, HIV-positive adults, and babies born to HIV-positive mothers. Laboratory experiments have shown that VRC01 could help decrease the amount of HIV in the body. However, we are still in the early stages of testing VRC01 to find out what its effects may be. This will be the first study of VRC01 in babies who have HIV.

2. We do not know if VRC01 may be a useful treatment for HIV.

The study is a first step in testing VRC01 in babies who have HIV. All babies in the study will be taking anti-HIV medicines (ARVs). We do not know if VRC01 may be a useful treatment when given in addition to ARVs. The study will help us learn about that. ***While we are learning about VRC01, it is very important that babies keep taking ARVs. Taking ARVs is the best known way for people who have HIV to stay healthy.***

3. Only babies who qualify can participate in the study.

If you decide to have your baby join the study, we will first do some tests to see if your baby qualifies. More information about the tests is given in #5 (see below). If your baby qualifies, he or she will be entered in the study. If your baby does not qualify, he or she cannot be entered in the study.

4. It is your decision whether to join the study.

Deciding to have your baby join the study is voluntary (your choice). You are free to have your baby join or not join. If you decide to have your baby join, you can change your mind and take your baby off the study. Your decisions will have no effect on the medical care that your baby receives at this clinic. Your baby's access to services, and the benefits and rights he or she normally has, will not be affected.

Take your time and consider your decisions carefully. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, your baby should continue to receive standard medical care outside of the study. This includes childhood immunizations, ARVs, and other standard care and treatment for children with HIV. We will tell you where your baby can receive this care if needed.

Finding out if you and your baby qualify

5. We will ask questions, examine your baby, and test your baby's blood.

To find out if your baby qualifies for the study, we will:

- Review your baby's medical records.
- Ask about your baby's health and how you are feeding your baby.
- Ask about the ARVs and other medicines you (the baby's mother) and your baby have taken.
- Give your baby a physical examination.
- Draw your baby's blood (up to 6 mL or about 1 teaspoon) for tests. The tests will:
  - Check your baby's blood cells, liver, and kidneys.
  - Check your baby's CD4 and CD8 cells. These cells are part of the immune system, which is the part of the body that fights infections. HIV attacks CD4 cells, so it is important to check the number of these cells that can be found in the blood.
  - Confirm that your baby has HIV. There are certain HIV tests that are required for this study. If the required tests are not in your baby's medical records, we will do the tests that are needed.
- Talk with you about the study requirements and if your baby will be able to meet these requirements.

These procedures will take about 2 hours. The results of your baby's blood tests will then be available within several days. We will review the results and all other information to determine if your baby qualifies for the study. We will schedule your baby to come back to the clinic when the results are available.

- If your baby does not qualify, we will tell you this. Your baby will not be entered in the study and we will tell you where your baby can go for any medical care or other services your baby may need.

- If your baby does qualify, he or she will be entered in the study.

Entering the study

6. If your baby qualifies, he or she will enter the study within a specified timeframe.

There are certain timeframes for when babies can enter the study. For example, babies must be less than 12 weeks old when they enter. We will explain the timeframes to you so you know what to expect.

On the day your baby enters the study, we will:

- Review your baby's medical records and ask about:
  - Your (the baby's mother's) and your baby's ARVs.
  - Your baby's health and other medicines.
  - How you are feeding your baby.
- Give your baby a physical examination.
- Collect your baby's urine for tests to check his or her kidneys.
- Draw your baby's blood (up to 9 mL or about 2 teaspoons) for tests including:
  - A test of the amount of HIV in your baby's blood. This is called your baby's "viral load." The viral load should decrease over time as your baby takes ARVs.
  - Tests of the effects of VRC01.

7. Babies will be placed in 1 of 2 groups on the day they enter the study.

Babies placed in one group will be given VRC01. Babies placed in the other group will not be given VRC01. To test the effects of VRC01, babies given VRC01 will be compared to babies not given VRC01.

Each baby will be placed a group at random, [like flipping a coin; *sites may insert a different example if preferred*]. Each baby has a 1-in-2 or 50% chance of being placed in the group that is given VRC01. The study staff cannot choose which group each baby is placed in. Babies' parents also cannot choose.

8. Babies in the VRC01 group will be given 4 injections.

Babies in the VRC01 group will be given the first injection of VRC01 when they enter the study. The other injections will be given 2, 6, and 10 weeks later. The injections will be given in the skin of the thigh. The amount of VRC01 given will depend on the baby's weight. The largest amount given will be about 4 mL (less than 1 teaspoon). If the full amount of VRC01 cannot be given in one injection, two injections will be given. Each injection is expected to take about 10-15 minutes.

Although babies in the VRC01 group are expected to be given 4 injections, we may not give injections to babies who are sick when injections are scheduled to be given. We may stop giving injections to any baby if we determine that more injections might be harmful. Babies who miss any injections will still stay in the study.

9. Babies in the VRC01 group will be checked for reactions to the injections.

After the first injection of VRC01, babies must stay in the clinic for at least 2 hours. During this time, study staff will check for reactions to the injection. After the other injections, babies must stay in the clinic for at least one hour.

[Here and in #19, sites may modify text regarding photographs if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.] If your baby has any reactions to VRC01, such as redness where VRC01 in injected, we may take a photo of the reaction. The photo will help the doctors working on the study assess the reaction.

10. All babies will have 13 scheduled visits over 1 year.

Starting 1 week after entering the study, babies will have 11 visits over 6 months. After that, babies will have 2 more visits, about 3 months apart. Each visit will take about 2 hours. At these visits, we will:

- Review your baby's medical records and ask about:
  - Your (the baby's mother's) and your baby's ARVs.
  - Your baby's health and other medicines.
  - How you are feeding your baby.
- Give your baby a physical examination.
- Collect your baby's urine for tests to check his or her kidneys.
- Draw your baby's blood for tests. The amount drawn will be up to 5 mL (about 1 teaspoon) while the baby is less than 3 months old, and up to 20 mL (about 4 teaspoons) as the baby ages to 6 and 12 months. At different visits, the tests will check your baby's:
  - Blood cells, liver, and kidneys.
  - CD4 and CD8 cells.
  - HIV viral load.

  Tests will also check the amount of VRC01 in the blood and the effects of VRC01.

Babies may have more visits if they are sick or need more tests to check on their health. Additional blood or urine may be drawn at these visits if needed.

11. Mothers or caregivers are asked to check on their babies.

After 4 of the study visits, you will be asked to take your baby's temperature and write down how your baby is doing. You will be asked to do this for 7 days after the visit when your baby enters the study, and for 7 days after the visits 2, 6, and 10 weeks later. For babies in the VRC01 group, these are the visits when VRC01 is given, but you will be asked to do this even if your baby is not given VRC01.

We will show you how to write down the information about your baby. After 3 days, we will telephone you to ask for the information you have written down. You can also come to the clinic with your baby or have a study staff member come to your home instead of having the telephone call. If your baby has any problems, you will be asked to bring him or her to the clinic.

12. If babies need a lumbar puncture, we will save spinal fluid for the study.

[here and below, sites may use locally appropriate terminology (e.g., "spinal tap") to refer to lumbar puncture]

A procedure called "lumbar puncture" is sometimes done when babies are sick. This procedure uses a needle to collect fluid from the baby's spine. The fluid is then tested to find out what may be causing the baby to be sick. No lumbar punctures will be done for this study. However, if your baby has a lumbar puncture outside of the study, we would like to save any spinal fluid that may be left over for tests. If you agree to this, the tests will look for HIV in the fluid. The tests may also look for other factors related to HIV and the immune system in the fluid.

If your baby has a lumbar puncture, and you agree to have the spinal fluid saved, we will ask you to bring your baby to the clinic. At this visit, we will:

- Review your baby's medical records
- Ask about your baby's health and medicines.
- Draw your baby's blood (2 mL or about half a teaspoon) for tests. The tests may look for HIV in the blood and blood cells. The tests may also look for other factors related to HIV and the immune system.

13. Different tests will be done at different laboratories.

We will do tests of your baby's urine, blood cells, liver, kidneys, CD4 and CD8 cells, and HIV viral load here at our laboratory. We will give you the results of these tests at the next scheduled visit or sooner if necessary. We will explain the results and give you counseling and referrals as needed.

Tests of the amount of VRC01 in the blood and of the effects of VRC01 will be done at different laboratories in the United States. Tests of spinal fluid will also be done in the United States. Some tests may be done while the study is ongoing, others after the study is completed. The results of these tests are for research purposes only. This means they are not expected to give any information relevant to your baby's health. The results will not be given to the study staff or to you.

If you agree, some of your baby's blood will be used for tests of his or her genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. For this study, only genes related to HIV, the immune system, and the effects of VRC01 will be tested. The results of these tests are for research purposes only and will not be given to the study staff or to you.

14. We may take your baby off the study early.

Babies are expected to stay in the study for about 1 year. However, we may take your baby off the study if:

- The study is stopped for any reason.
- We determine that your baby cannot meet the study requirements (for example, if you move away and cannot come to the clinic).
- We determine that staying in the study might harm your baby.

15. Please tell us if you wish to take your baby off the study.

You are free to take your baby off the study at any time for any reason. The care that your baby receives at this clinic will not be affected, but it is important that we know your decision. We will ask you to bring your baby to the clinic for one last visit. At this visit we will:

- Ask about your (the baby's mother's) and your baby's ARVs.
- Ask about your baby's health and other medicines.
- Ask about how you are feeding your baby.
- Give your baby a physical examination.
- Draw your baby's blood (about 15 mL or 3 teaspoons) for tests. The tests will check:
  - The baby's blood cells
  - The baby's CD4 and CD8 cells
  - The baby's HIV viral load
  - The effects of VRC01

If your baby has been in the study for less than six months, we will also collect urine for tests to check his or her kidneys.

We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

16. There is little risk from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to your baby. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

17. VRC01 is experimental.

This means we do not know if VRC01 is safe to use in people. We also do not know if VRC01 is useful as a treatment for HIV. VRC01 is being tested in research studies to learn more about it, and this study will help us learn about VRC01 in babies who have HIV.

VRC01 will be given as an injection in the skin. This kind of injection can cause stinging, itchiness, discomfort, pain, soreness, redness, bruising, swelling, or a small cut where the needle enters the skin. Rarely, this kind of injection can cause infection.

As of January 2017, more than 800 HIV-negative and HIV-positive adults have received VRC01 in research studies in the United States, Botswana, Malawi, South Africa, Zimbabwe, and other countries. Some people had mild or moderate reactions like itchiness, redness, or swelling where VRC01 was injected. Some people felt tired or had mild body discomfort, muscle or joint pain, headache, chills, or nausea after receiving injections. Some people had hives while VRC01 was being given or soon after VRC01 was given. In some cases, the hives were severe. One person had chest discomfort and one fainted. Some people had abnormal results on tests of their blood cells, liver, or kidneys. These came back to normal after a few days or weeks.

As of January 2017, 40 babies born to mothers who have HIV have received VRC01 in a research study being done by the IMPAACT network in the United States, South Africa, and Zimbabwe. Most of these babies had redness, swelling, or a small bruise where VRC01 was injected, which lasted for a short time. No other effects thought to be caused by VRC01 have been seen, and no serious health problems have occurred.

It is possible that babies who receive VRC01 in this study could develop "resistance" to VRC01 or other antibodies like VRC01. If resistance develops, the antibodies may not be effective in helping to control the baby's HIV. In this study, the risk of resistance is minimized by giving VRC01 with ARVs.

18. Other antibodies have caused other side effects.

Other antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies, most side effects happen within the first 24 hours including fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain. Rarely, some antibodies have caused serious reactions that may be life-threatening.

One type of serious reaction may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face. A second type of serious reaction may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, kidney problems, chest discomfort and shortness of breath. Rarely, antibodies used to treat other diseases have been linked to a blood disorder that interferes with blood clotting, cancer, damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies of VRC01. However, it is possible that babies in this study could have these types of reactions. Babies could also have other side effects or reactions that we do not yet know about.

We will closely check on babies in this study for side effects and reactions. Please contact the study staff if any of these problems or any other problems occur.

19. There could be risks of disclosure of your baby's information.

We will make every effort to keep your baby's information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, your baby's name will be written on some records. Despite our best efforts to keep your baby's information private, it is possible that your baby's information, including information about your baby's genes, could be obtained by someone who should not have it. If this were to happen, your baby could be treated badly or unfairly.

[Sites may modify this paragraph if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.] If we take photos of any reactions to VRC01, we will not photograph your baby's face. Photos will be labeled only with a code number (not with your or your baby's name). Photos will be kept securely with other information collected for the study. Photos also may be shared with other doctors working on the study. The other doctors may be here at *[site name]* or in other countries. These doctors will not be given your or your baby's name, and they will be required to keep the photos private and confidential. When the study is completed, the photos will be destroyed.

[*US sites, insert:* To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify your baby, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify your baby. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your baby's participation in the study to others, if you wish.]

Benefits of the study

20. There may be no benefit from being in the study.

By joining the study, your baby will be part of the search for new treatments for babies who have HIV. However, being in the study may not benefit your baby in any way.

Your baby will have regular visits here and frequent checks on his or her health. It is possible that the examinations and tests done in the study may help your baby stay healthy. If these procedures show that your baby may need medical care that cannot be provided through the study, we will tell you where you can go for the care your baby needs.

Other information about the study

21. There are no costs to you or your baby.

There are no costs to you or your baby for the study visits, injections, or procedures.

[*Insert information about compensation/reimbursement here*, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]

22. Your baby's study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- [i*nsert name of site IRBs/ECs*]
- [i*nsert name of site drug regulatory authority*]
- [i*nsert name of other site drug entities that may review records*]
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- The IMPAACT Network that is coordinating the study

The study staff and these groups are required to make every effort to keep study records private and confidential. Your baby's study information may be disclosed to other authorities if required by law. The results of the study may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally.

A description of this study will be available on www.ClinicalTrials.gov as required by United States Law. This website will not include any information that can identify your baby. At most, the website will include a summary of the results of the study. You can search this website at any time.

23. If your baby gets sick or injured, contact us right away.

Your baby's health is important to us. We will make every effort to minimize risks and protect your baby's well-being. It is possible, however, that your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study injections or other study procedures.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat your baby or tell you where you can you can get the treatment your baby needs. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through [site name or] the United States National Institutes of Health.

Who to contact

24. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [*insert name and telephone number of investigator or other study staff*].

- If you have questions about your baby's rights as a research participant or concerns about how your baby is being treated in the study:
  [*insert name and telephone number of IRB contact person or other appropriate person/organization*].

- If your baby has health or other problems that may be related to study participation:
  [*insert name and telephone number of investigator or other study staff*].

- If you want to take your baby off the study:
  [*insert name and telephone number of investigator or other study staff*].

Signatures

25. If you decide to have your baby join this study, please sign or make your mark below.

Before deciding whether to have your baby join this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected if you decide to have your baby join.

We will tell you any new information from this study or other studies that may affect your willingness to keep your baby in the study. You can ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for storage of residual CSF and for genetic testing].

Please write your initials or make your mark next to your choices:

_____ I agree to have my baby join this study

For storage of leftover spinal fluid:

_____ I agree to storage of leftover spinal fluid (if my baby has a lumbar puncture outside of the study)

_____ I do not agree to storage of leftover spinal fluid (if my baby has a lumbar puncture outside of the study)

For genetic testing:

_____ I agree to testing of my baby's genes related to HIV, VRC01, and the immune system

_____ I do not agree to testing of my baby's genes

_____
Name of Infant
(print)

_____	_____	_____
Name of Mother (or Legal Guardian; print)	Signature of Mother (or Legal Guardian)	Date
_____	_____	_____
Name of Witness (if applicable; print)	Signature of Witness	Date
_____	_____	_____
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Appendix III
Sample Informed Consent Form for Maternal Blood Collection and Testing

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

You are being asked to give blood for the research study named above.

This form gives information about giving blood for the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as you need to fully understand the information. We will ask you questions to see if we have explained the information clearly.

After you understand the information, if you decide to give blood for the study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [*insert site name*] are doing this study to test an experimental injection called VRC01 in babies. Because your baby is participating in the study, you are being asked to give blood for the study.

The person in charge of the study at this clinic is [*insert name of IoR*]. The United States National Institutes of Health are paying for the study.

1. The study is being done to test VRC01 in babies.

The study will test the effects of VRC01 when given to babies who have HIV. In the study, we will do laboratory tests of babies' blood to learn about these effects. We would also like to test the blood of babies' mothers to learn more about the effects of VRC01 in babies. For example, mothers have antibodies and other substances in their blood that are passed to their babies. It is possible that these substances could have an impact on the effects of VRC01 in their babies.

2. It is your decision whether to give your blood for the study.

Deciding to give blood for the study is voluntary. You are free to give blood or not. If you decide to give blood, you can change your mind at any time. Your decision will have no effect on your baby's participation in the study. Your decision will also have no effect on the medical care that you or your baby receive at this clinic. Your access to services and the benefits and rights you normally have will not be affected.

3. Mothers' blood will be collected on the day babies enter the study.

If you decide to give blood for the study, we will collect 20 mL (4 teaspoons) from your arm. The blood will be collected on the day your baby enters the study or within the next 7 days, if necessary.

4. Mothers' blood will tested at different laboratories.

Mothers' blood will be tested after all babies have completed the study. Different tests will be done at different laboratories in the United States. The results of these tests are for research purposes only. This means they are not expected to give any information relevant to your or your baby's health. The results will not be given to the study staff or to you.

If you agree, the blood that you give for this study could be used for tests of your genes. Your genes are passed to you from your birth parents. They affect how you look and how your body works. Differences in people's genes can help explain why some people get a disease while others do not. For this study, only genes related to HIV, the immune system, and the effects of VRC01 will be tested.

5. There is little risk from giving blood.

Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

6. There could be risks of disclosure of your information.

We will make every effort to keep your information private and confidential. Study records and blood samples will be kept in secure locations. All blood samples and most records will be labeled only with a code number. Your name will be written on some records but the results of your blood tests will not be kept with these records. Therefore, it is unlikely that anyone could find out the results of your tests linked to your name. Despite these efforts, it is possible that your information, including information about your genes, could be obtained by someone who should not have it. If this were to happen, you could be treated badly or unfairly. You could also feel stress or embarrassment.

[*US sites, insert:* To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.]

7. There may be no benefit from giving blood.

By giving blood, you will be part of the search for new treatments for babies who have HIV. However, giving blood is not expected to directly benefit you or your baby in any way.

8. There are no costs to you.

There are no costs to you for giving blood for this study.

9. Your records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- [i*nsert name of site IRB/EC*]
- [i*nsert name of site drug regulatory authority*]
- [i*nsert name of other site drug entities that may review records*]

- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- The IMPAACT Network that is coordinating the study

Like the study staff, these groups are required to make efforts to keep study records private and confidential. Your study information may be disclosed to other authorities if required by law.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

A description of this study will be available on www.ClinicalTrials.gov as required by United States Law. This website will not include any information that can identify you. At most, the website will include a summary of the results of the study. You can search this website at any time.

10. Please tell us if you change your mind about giving blood.

If you decide to give blood, and then change your mind, please tell us. We will destroy any of your blood that has not yet been tested.

11. If you are ill or injured, contact us right away.

Your health is important to us. We will make every effort to minimize risks and protect your well-being. It is possible, however, that you could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of giving samples for the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat you or tell you where you can you can get the treatment you need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through [site name or] the United States National Institutes of Health.

12. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study:
  [*insert name and telephone number of investigator or other study staff*].

- If you have questions about your rights as a research participant or concerns about how you are being treated in the study:
  [*insert name and telephone number of IRB contact person or other appropriate person/organization*].

- If you have health or other problems that may be related to study participation:
  [*insert name and telephone number of investigator or other study staff*].

- If you want to change your mind about giving samples for the study:
  [*insert name and telephone number of investigator or other study staff*].

Signatures

13. If you decide to give blood for this study, please sign or make your mark below.

Before deciding whether to give blood for study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you.

We will tell you any new information from this study or other studies that may affect your willingness to have your blood tested for the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing].

Please write your initials or make your mark next to your choice:

_____ I agree to give blood for this study and I agree to testing of my genes related to HIV, VRC01, and the immune system.

_____ I agree to give blood for this study but I do <u>not</u> agree to testing of my genes.

Name of Mother (print)	Signature of Mother	Date
Name of Witness (if applicable; (print)	Signature of Witness	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Appendix IV
Sample Informed Consent Form for Specimen Storage and Future Use: Infants

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

You have decided to have your baby join the study named above. As part of the study, your baby will have blood drawn. Your baby also may have spinal fluid collected. After your baby's samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether to allow extra samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your or your baby's participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your baby's extra samples will be kept in a repository.

[Sites should insert one of the two options show below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept [*sites may insert time limits here if required by local authorities*].

A repository is a secure facility that is used to store samples. The IMPAACT Network has repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples in a repository here at our laboratory. There is no limit on how long the samples will be kept [*sites may insert time limits here if required by local authorities*].

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, VRC01, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your baby's genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your baby's extra samples would only be used to look at genes related to HIV and the immune system.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your baby's health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your baby's study records.

4. There is little risk to your baby.

When extra samples are used for research, they are labeled with a code number only. To protect your baby's privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on whether your baby received VRC01 and the results of other tests related to VRC01 may also be linked to the samples.

There may be risks from tests of your baby's genes. If others found out the results of these tests, they could treat your baby badly or unfairly. However, this is almost impossible because the results will not be given to the study staff or to you, and will not be in your baby's study records.

5. There may be no benefit to your baby.

By allowing your baby's extra samples to be used for research, your baby will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit you or your baby in any way.

6. You will not be paid for use of your baby's samples.

There is no cost to you for use of your baby's extra samples. The samples will not be sold and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you.

7. Information from research using extra samples may be reviewed by groups that oversee the research.

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of the research done with extra samples may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally.

8. If you have any questions, concerns, or problems related to your baby's extra samples, use these contacts.

- If you have questions about use of your baby's extra samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you later change your mind about use of your baby's extra samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you have questions about your baby's rights as a research participant or concerns about how your baby is being treated in the study:
  [*insert name and telephone number of IRB contact person or other appropriate person/organization*].

Signatures

Before deciding whether to allow your baby's extra samples to be used for research, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing].

Please write your initials or make your mark next to your choice:

_____ I allow my baby's extra samples to be used for research on HIV, VRC01, the immune system, and other diseases. I also allow my baby's samples to be used for tests of his or her genes.

_____ I allow my baby's extra samples to be used for research on HIV, VRC01, the immune system, and other diseases. I do <u>not</u> allow my baby's samples to be used for tests of his or her genes.

_____ I do <u>not</u> allow my baby's extra samples to be used for any research.

Name of Infant (print)		
Name of Mother (or Legal Guardian; print)	Signature of Mother (or Legal Guardian)	Date
Name of Witness (if applicable; print)	Signature of Witness	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date

Appendix V
Sample Informed Consent Form for Specimen Storage and Future Use: Mothers

IMPAACT 2008
Phase I/II Multisite, Randomized, Controlled Study of Monoclonal Antibody VRC01 with Combination Antiretroviral Therapy to Promote Clearance of HIV-1-Infected Cells in Infants

Version 2.0, dated 29 May 2017

You have decided to have your blood drawn for the study named above with your baby. After your blood samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether to allow extra samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your or your baby's participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, your extra samples will be kept in a repository.

[Sites should insert one of the two options show below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept [*sites may insert time limits here if required by local authorities*].

A repository is a secure facility that is used to store samples. The IMPAACT Network has repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples in a repository here at our laboratory. There is no limit on how long the samples will be kept [*sites may insert time limits here if required by local authorities*].

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, VRC01, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at your genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your extra samples would only be used to look at genes related to HIV and the immune system.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your study records.

4. There is little risk to you.

When extra samples are used for research, they are labeled with a code number only. To protect your privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on whether your baby received VRC01 and the results of other tests related to VRC01 may also be linked to the samples.

There may be some risks from tests of your genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results will not be given to study staff or to you, and will not be in your study records.

5. There may be no benefit to you.

By allowing your extra samples to be used for research, you will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit you or your baby in any way.

6. You will not be paid for use of your samples.

There is no cost to you for use of your extra samples. The samples will not be sold and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you.

7. Information from research using extra samples may be reviewed by groups that oversee the research.

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research

The people who do research with the extra samples and the groups listed above are required to make efforts to information private and confidential.

The results of research done with extra samples may be presented publicly or published. However, no presentation or publication will use your name or identify you personally.

8. If you have any questions, concerns, or problems related to your extra samples, use these contacts.

- If you have questions about use of your extra samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you later change your mind about use of your extra samples:
  [*insert name and telephone number of investigator or other study staff*].

- If you have questions about your rights as a research participant or concerns about how you are being treated in the study:
  [*insert name and telephone number of IRB contact person or other appropriate person/organization*].

Signatures

Before deciding whether to allow your extra samples to be used for research, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

You do not give up any rights by signing this form.

[Insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing].

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_____ I allow my extra samples to be used for research on HIV, VRC01, the immune system, and other diseases. I do <u>not</u> allow my samples to be used for tests of my genes.

_____ I do <u>not</u> allow my extra samples to be used for any research.

Name of Mother (print)	Signature of Mother	Date
Name of Witness (if applicable; print)	Signature of Witness	Date
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff	Date