P1112
Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

DAIDS Study ID #11903

This file contains the current IMPAACT P1112 protocol, which is composed of the following documents, presented in reverse chronological order:

- Letter of Amendment #1, dated 10 June 2020
- Clarification Memorandum #1, dated 31 March 2020
- Protocol Version V4.0, dated 06 November 2018

Letter of Amendment #1 for:

IMPAACT P1112
Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

Version 4.0, dated 6 November 2018

DAIDS Study ID #11903
IND #113,611

Letter of Amendment Date: 10 June 2020

Table of Contents

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT P1112 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for IMPAACT P1112. If the IMPAACT P1112 protocol is amended in the future, applicable contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT P1112
Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

DAIDS Study ID #11903

Version 4.0, Letter of Amendment #1
Letter of Amendment 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 Council 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)

Summary of Modifications and Rationale

This LoA updates the protocol team roster and incorporates the contents of protocol Clarification Memorandum (CM) #1.

Section A of this LoA includes the protocol team roster updates.

Section B of this LoA incorporates the contents of CM #1, which was issued on 31 March 2020 to safeguard the health and well-being of study participants in the context of circulating SARS-CoV-2 and the associated COVID-19 pandemic. CM #1 provided operational flexibility for conducting study visits and procedures when needed to ensure, when possible, completion of protocol-specified study product dosing for participants in Dose Group 5 Cohort 2 and, for all participants, to prioritize the conduct of clinically and scientifically important evaluations, particularly those evaluations planned to be conducted within 24 weeks of the last dose of study drug and at Week 96. Consistent with the instructions provided in CM #1, implementation of Section B of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT P1112 Protocol Team will determine when, in the future, the guidance in Section B is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

Implementation

Updates of the protocol team roster are shown in Section A of this LoA, using strikethrough for deletions and bold type for additions where applicable. Operational guidance for conducting study visits and procedures during the COVID-19 pandemic is provided in Section B of this LoA; conventions for use of strikethrough and bolding do not apply in this section.

A. Updates of Protocol Team Roster

To reflect current membership, the protocol title page and protocol team roster are updated as follows:

Protocol Title Page

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NICHD Medical Officer:	~~Rohan Hazra, MD~~ **Sai Majji, PhD**
Clinical Trials Specialist**s**:	Charlotte Perlowski, MSPH ~~Patricia Morgan, MS, PA~~ **Emily Brown, MA**

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B. Operational Guidance from Protocol CM #1, dated 31 March 2020

This CM provides operational guidance to study sites from the IMPAACT P1112 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and should contact the Protocol Team (impaact.teamp1112@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

Visit Scheduling

- Sites should utilize the allowable visit windows currently specified in the protocol V4.0 to permit continued completion of in-person visits through 24 weeks after the last dose of study drug and at Week 96. Sites should consider current or anticipated operational disruptions or closures when scheduling visits and should schedule visits early or late in the allowable window, as appropriate. Visits conducted outside of the allowable window would also be preferred to completely missed visits.
- Effective with the issuance of this CM, for Dose Group 5 Cohort 1, the allowable window for visits beyond 24 weeks after the last dose of study drug and prior to Week 96 (i.e., visits at Week 36, Week 48, Week 60, Week 72, and Week 84 for all Dose Group 5 Cohort 1 participants) are broadened to ±6 weeks. The current V4.0 protocol-specified visit windows remain the target for these visits, and sites are encouraged to continue scheduling within these target windows whenever possible.

- Effective with the issuance of this CM, for Dose Group 5 Cohort 2, the allowable window for visits beyond 24 weeks after the last dose of study drug and prior to Week 96 (i.e., visits at Week 48, Week 60, Week 72, and Week 84 for all Dose Group 5 Cohort 2 participants and also the visit at Week 36 for Dose Group 5 Cohort 2 participants who do not receive a dose of study drug at Week 12) are broadened to ±6 weeks. The current V4.0 protocol-specified visit windows remain the target for these visits, and sites are encouraged to continue scheduling within these target windows whenever possible.

Prioritization of Study Visit Procedures

- Sites with full capacity to conduct in-person study visits at the study clinic through 24 weeks after the last dose of study drug and at Week 96 (to confirm end-of-study HIV infection status) should continue to do so in full compliance with the protocol.
- Sites with limited capacity to conduct in-person study visits at the study clinic through 24 weeks after the last dose of study drug and at Week 96 should prioritize:
  - administration of study drug at Week 12 to Dose Group 5 Cohort 2 participants who have not had complete cessation of breastfeeding, if the site is reasonably confident that the completion of the subsequent safety and other assessments will be possible.
  - conduct of laboratory evaluations per the "priority for blood samples" listings in the protocol Schedules of Evaluations. If it is not possible to perform these tests consistent with the site's approved Protocol Analyte List (PAL), tests may be performed in alternative settings using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).
- Sites may also conduct study visits, in full or in part, beyond 24 weeks after the last dose of study drug and prior to Week 96, off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with parents/guardians to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately trained and qualified to immediately manage any adverse events and/or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, study staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee, as needed.
- Sites with no ability to conduct in-person study visits, either at the study clinic or off-site, should consider whether any study procedures can be conducted remotely (e.g., by telephone). Evaluations should be prioritized as follows (as applicable for the individual participant and scheduled study visit in question):
  1. Medical history taking
  2. Review of any injection site reactions

Study Drug Supply

- No changes in procedures for preparing, dispensing, or administering study product (VRC07-523LS) are planned. These procedures must be performed on-site to ensure adherence to product temperature requirements. In addition, study product must be administered in a clinical setting to ensure appropriate management in the rare event of an acute hypersensitivity reaction.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1112.

- Documentation should be entered in participant study charts in real-time should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Non-standard provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Similar guidance will be provided for documentation of use of alternate laboratories or alternate laboratory assays. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.

Clarification Memorandum #1 for:

IMPAACT P1112

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

Version 4.0, dated 6 November 2018

DAIDS Study ID #11903
IND #113,611

Clarification Memorandum Date: 31 March 2020

Summary of Clarifications

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT P1112 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) pandemic.

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, institutional review board/ethics committee (IRB/EC) approval of this CM is not required by the Division of AIDS prior to implementation. However, given the context of the COVID-19 pandemic and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to ensure, when possible, completion of protocol-specified study product dosing for participants in Dose Group 5 Cohort 2 and, for all participants, to prioritize the conduct of clinically and scientifically important evaluations, particularly those evaluations planned to be conducted within 24 weeks of the last dose of study drug and at Week 96.

Implementation of this CM is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with IMPAACT Network leadership and the study Sponsor, the IMPAACT P1112 Protocol Team will determine when, in the future, the guidance provided in this CM is no longer applicable. When such a determination is made, study sites will be formally notified and instructed to inform their IRBs/ECs.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT P1112.

Implementation

This CM provides operational guidance to study sites from the IMPAACT P1112 Protocol Team. The Protocol Team acknowledges that the extent to which site operations may be disrupted by the COVID-19 pandemic may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and should contact the Protocol Team (impaact.teamp1112@fstrf.org) with any questions or concerns regarding this CM or management of study participants.

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IMPAACT P1112

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

(DAIDS ID Document ID # 11903)

A Multicenter, Domestic and International Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials (IMPAACT) Network

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
The National Institute of Mental Health (NIMH)

IND# 113,611

The IMPAACT Prevention Scientific Committee Chair: Lynda Stranix-Chibanda

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Protocol Vice Chair:	Elizabeth McFarland, MD
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Version 4.0
06 November 2018

All questions concerning this protocol should be sent via e-mail to impaact.teamP1112@fstrf.org. Remember to include the participant's PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to impaact.teamP1112@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material should be submitted via the DAIDS Protocol Registration System (DPRS): https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration or can be sent via e-mail to epr@tech-res.com. For Expedited Adverse Event (EAE) questions, e-mail DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 1-301-897-1709 or fax 1-800-275-7619 or 301-897-1710. To order study agent, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at rando.support@fstrf.org.

IMPAACT P1112 PROTOCOL TEAM ROSTER

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DAIDS Study ID #11903

Version 4.0
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)

GLOSSARY OF TERMS

AE	Adverse Event/Adverse Experience
AIDS	Acquired Immune Deficiency Syndrome
ANA	Antinuclear antibody activity
aPTT	Activated Partial thromboplastin time
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area-Under-the-Curve
CAP	College of American Pathologists
CDR	Complementarity Determining Regions
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DNA	Deoxyribonucleic Acid
DPRS	DAIDS Protocol Registration System
EAE	Expedited Adverse Event
EIA	Enzyme Immunoassay
EC	Ethics Committee
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAART	Highly active antiretroviral therapy
HBIG	Hepatitis B immune globulin
HIV	Human Immunodeficiency Virus
IC50	Half maximal inhibitory concentration
Ig	Immunoglobulin
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IRB	Institutional Review Board
IV	Intravenous
LPC	Laboratory Processing Chart
mAb	Monoclonal antibody
MTCT	Mother to child transmission
N	Number (typically refers to participants)
NAT	Nucleic Acid Testing
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
NVP	Nevirapine
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PID	Patient Identifier

PK	Pharmacokinetic
PRO	Protocol Registration Office
PROM	Premature rupture of membranes
PTT	Partial thromboplastin time
RE	Regulatory Entity
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
RSV	Respiratory syncytial virus
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event/Serious Adverse Experience
SC	Subcutaneous
SDAC	Statistical and Data Analysis Center
SHIV	Simian Human Immunodeficiency Virus
SMC	Safety Monitoring Committee
SUSAR	Suspected, Unexpected Serious Adverse Reactions
TCID	Tissue Culture Infectious Doses
$T_{1/2}$	Half-life
UNAIDS	United Nations AIDS Organization
VRC	Vaccine Research Center
VRC01	Human monoclonal antibody (VRC-HIVMAB-060-00-AB)
VRC01LS	Human monoclonal antibody (VRC-HIVMAB-080-00-AB)
VRC07-523LS	Human monoclonal antibody (VRC-HIVMAB075-00-AB)
WHO	World Health Organization

SCHEMA

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1-Exposed Infants

DESIGN: Open-label, dose-escalating, Phase 1, multicenter trial of VRC01 (VRC-HIVMAB-060-00-AB), VRC01LS (VRCHIVMAB080-00-AB), and VRC07-523LS (VRC-HIVMAB075-00-AB)

SAMPLE SIZE: N=79 mother-infant pairs, 13 per Dose Groups 1, 2 and 3; 20 per Dose Groups 4 and 5 (10 per each cohort)

Description of Dose Groups		
	N	**Dose of VRC01, VRC01LS, or VRC07-523LS**
Dose Group 1	13	20 mg/kg SC X1 VRC01
Dose Group 2	13	40 mg/kg SC X1 VRC01
Dose Group 3	13	40 mg/kg SC for initial dose 20 mg/kg SC monthly of VRC01 for at least 6 months (24 weeks) and no more than 18 months (72 weeks) while breastfeeding
Dose Group 4	10 10	Cohort 1: Non-breastfeeding Single dose at birth of VRC01LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose at birth of VRC01LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100 mg VRC01LS at Week 12 to be administered SC if the infant has not achieved complete cessation of breastfeeding
Dose Group 5	10 10	Cohort 1: Non-breastfeeding Single dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100 mg VRC07-523LS at Week 12 to be administered SC if the infant has not achieved complete cessation of breastfeeding

POPULATION: Infants born to HIV-1-infected women who meet all maternal inclusion and no maternal exclusion criteria and who are ≥ 36 weeks gestation; ≥ 2kg birth weight; and meet the study definition of increased risk of HIV infection. Additional exclusion criteria for infants also apply (see Section 4). The mothers are enrolled as well, but only the infants receive the VRC01/VRC01LS/VRC07-523LS immunization(s) and are followed on the study. All infants receive prophylactic antiretroviral therapy (ART) treatment per local standard of care.

REGIMEN: Infants in Dose Group 1 received a single VRC01 (human monoclonal antibody) 20 mg/kg subcutaneous injection less than 72 hours after birth.

Dose Group 2 opened after 13 infants had been accrued into Dose Group 1 and 6 of those had been immunized, completed 28 days of follow-up and passed a safety assessment. Infants in Dose Group 2 received a single subcutaneous VRC01 dose of 40 mg/kg less than 72 hours after birth.

Dose Group 3 opened after 6 infants in Dose Group 2 had been immunized, completed 28 days of follow-up and passed a safety assessment. Infants in Dose Group 3 received a subcutaneous VRC01 dose of 40 mg/kg less than 5 days after birth for the initial dose and 20 mg/kg SC monthly. There have been and will be formal safety reviews of data from adult and pediatric protocols of VRC01 (from P1112 database and most recent safety reports available from other protocols) every 6 months beginning after the first participant in Dose Group 3 reaches the Week 24 milestone.

In Dose Group 4, infants enrolled into one of two separate cohorts: Dose Group 4, Cohort 1 opened after Version 3.0 was released and safety data – as shown in **Error! Reference source not found.** – was reviewed and revealed no signal. Dose Group 4: Cohort 2 (breastfeeding) opened after six infants in Dose Group 4, Cohort 1 were immunized, completed 28 days of follow-up, and passed a safety assessment. Non-breastfeeding infants in Dose Group 4, Cohort 1 received a single subcutaneous VRC01LS dose (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and less than 72 hours after birth. Breastfeeding infants in Dose Group 4, Cohort 2 received subcutaneous VRC01LS (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and no longer than 5 days after birth for the initial dose and a second dose (100 mg) at Week 12 if the infant has not achieved complete cessation of breastfeeding. Complete

cessation of breastfeeding is defined as no exposure to breastmilk for 28 days.

In Dose Group 5, infants will enroll into one of two separate cohorts: Cohort 1 (non-breastfeeding) or Cohort 2 (breastfeeding). Non-breastfeeding infants in Dose Group 5, Cohort 1 will receive a single subcutaneous VRC07-523LS dose (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and less than 72 hours after birth. Breastfeeding infants in Dose Group 5, Cohort 2 will receive subcutaneous VRC07-523LS (< 4.5 kg: 80 mg; ≥ 4.5 kg: 100 mg) as soon as possible and no longer than 5 days after birth for the initial dose and a second dose (100 mg) at Week 12 if the infant has not achieved complete cessation of breastfeeding. Complete cessation of breastfeeding is defined as no exposure to breastmilk for 28 days. Dose Group 5, Cohort 1 will open as soon as Version 4.0 has been released and interim safety data – as shown in **Error! Reference source not found.** – have been reviewed and reveal no signal. Dose Group 5, Cohort 2 will open as soon as six infants in Dose Group 5, Cohort 1 have been immunized, completed 28 days of follow-up, and passed a safety and PK assessment.

There will be formal safety reviews of data from adult and pediatric protocols of VRC01LS and VRC07-523LS (from the P1112 database and most recent safety reports available from other protocols) approximately every six months to coincide with the already occurring reviews described above.

TREATMENT DURATION:

VRC01: One day for Dose Groups 1 and 2.

VRC01: For Dose Group 3, all have received monthly doses for at least 6 months. Infants who continue to receive breastmilk will receive monthly doses through the complete cessation of breastfeeding up to a maximum of 72 weeks (19 doses).

VRC01LS: All infants in Dose Group 4 received a single dose at birth. Infants in Dose Group 4, Cohort 2 will receive a second dose at Week 12 if they have not achieved complete cessation of breastfeeding.

VRC07-523LS: All infants in Dose Group 5 will receive a single dose at birth. Infants in Dose Group 5, Cohort 2 will receive a second dose at Week 12 if they have not achieved complete cessation of breastfeeding.

NOTE: It is expected that serum levels will remain detectable for > 1 month after the final dose of VRC01 and at least 6 months after the final dose of VRC01LS or VRC07-523LS.

STUDY DURATION:

Dose Groups 1 and 2: minimum of 48 weeks
Dose Group 3: 96 weeks
Dose Group 4: 96 weeks
Dose Group 5: 96 weeks

OBJECTIVES:

Primary: In HIV exposed infants at increased risk for peripartum or breastfeeding HIV transmission:

1. To assess safety of single subcutaneous dose (20 mg/kg or 40 mg/kg) of VRC01 (Dose Groups 1 and 2).
2. To determine pharmacokinetic profile of single dose, subcutaneous VRC01 (Dose Groups 1 and 2).
3. To assess safety of monthly subcutaneous doses of VRC01 (Dose Group 3).
4. To determine pharmacokinetic profile of monthly subcutaneous doses of VRC01 (Dose Group 3).
5. To assess safety of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2).
6. To determine pharmacokinetic profile of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2).
7. To assess safety of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2).

8. To determine pharmacokinetic profile of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2).

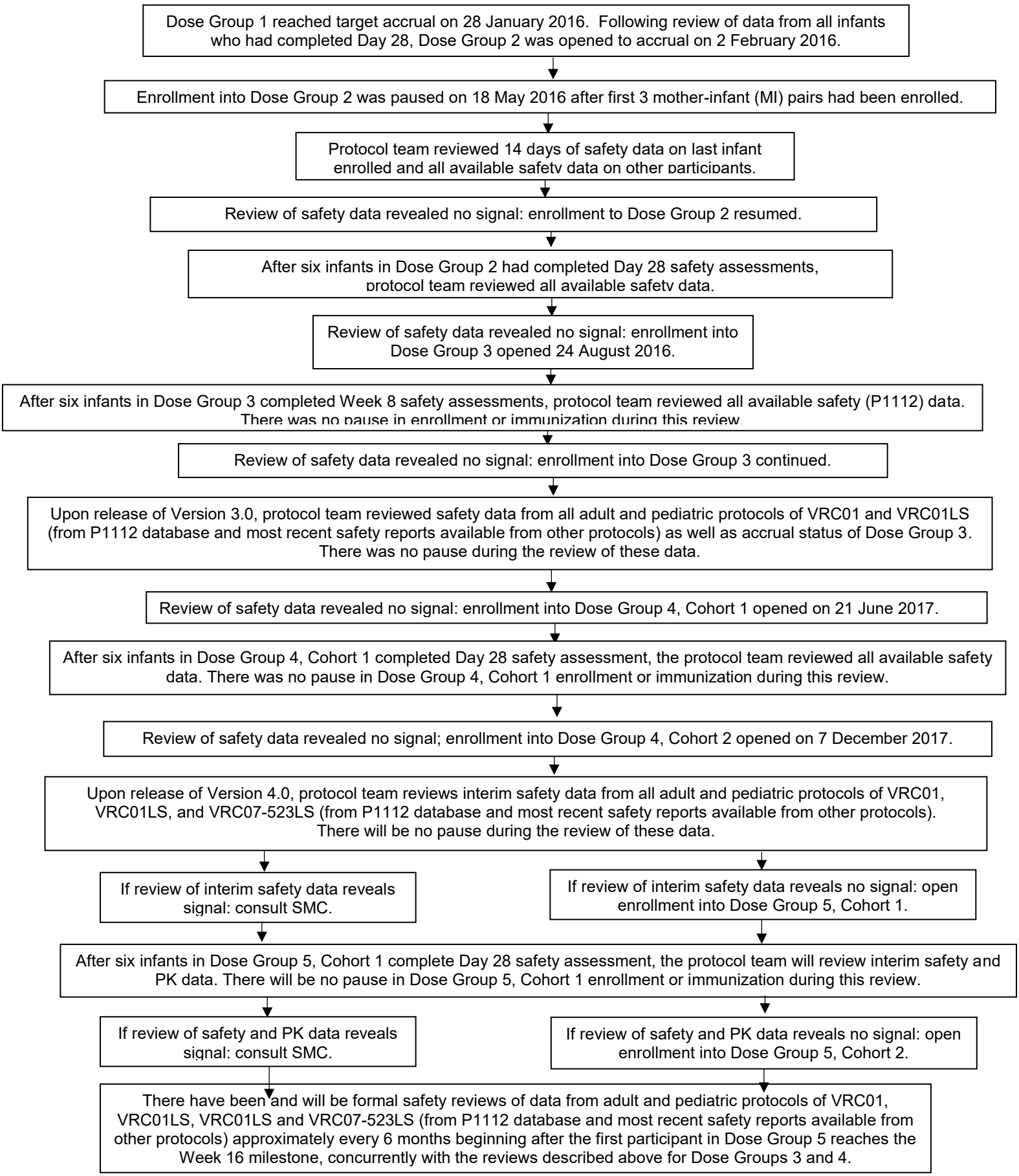
Secondary:

1. To examine the anti-VRC01 antibody production following immunization.
2. To examine the anti-VRC01LS antibody production following immunization.
3. To examine the anti-VRC07-523LS antibody production following immunization.

Exploratory:

1. To assess the amount of VRC01/ VRC01LS/ VRC07-523LS in oral secretions.
2. If one or more infants are determined to be HIV-infected, to describe the neutralization sensitivity of the infant and maternal virus and the amount of HIV-1 provirus and plasma HIV-1 RNA (measured in copies/mL), after receipt of VRC01, VRC01LS, or VRC07-523LS.
3. To assess neutralizing ability of serum before and after receipt of the antibody.

Figure 1: Overview of Study Design



1 INTRODUCTION

1.1 Background

In the United States and other resource rich countries, the risk of Mother to Child Transmission (MTCT) of Human Immunodeficiency Virus-1 (HIV) has been dramatically reduced through the combination of wide scale testing for HIV during pregnancy, treatment of all pregnant HIV-infected women with highly active antiretroviral therapy (HAART), provision of cesarean section if the pregnant woman has active viral replication, administration of antiretroviral therapy to the infant for the first six weeks of life, and formula feeding. With all these measures, 1% or less of HIV-exposed infants will become HIV-infected. However, in resource poor countries prevention of transmission is not so successful, resulting in continued MTCT of HIV to 260,000 infants each year [1]. A partial list of factors that contribute to ongoing transmission in this setting include late diagnosis of maternal HIV infection, sometimes as late as the intrapartum period; lack of universal access to HAART during pregnancy; continued need to breast feed at least through the first year of life in most of the developing world; and limited access to maternal HAART or nevirapine (NVP) for the breastfeeding infant.

In the United States, while transmission has been significantly reduced, HIV MTCT continues to occur. Review of these transmission events allows identification of infants at highest risk of perinatal transmission and, therefore, the most likely to benefit from additional interventions that might further reduce the risk of intrapartum transmission of HIV. Data on ongoing transmission in the US comes in part from the US Centers for Disease Control and Prevention Enhanced Perinatal Surveillance in 15 U.S. jurisdictions. In a study evaluating transmission risk in 2005-2008 in 8,054 births to HIV-infected mothers, 179 infants (2.2%) were diagnosed with HIV infection [2]. The odds of having an HIV-infected infant were higher among HIV-infected women who were tested late, had no antiretroviral (ARV) medications, abused illicit substances, breastfed, or had lower CD4 cell counts. In another report of nearly 8,600 births to HIV-infected women reported to the CDC, 8% of women did not receive prenatal care; of those with prenatal care, 3% did not receive HIV testing during pregnancy; of those with HIV testing, 6% did not receive ARV prophylaxis or treatment during pregnancy; of those who received antenatal therapy, 5% did not receive ARV drugs during labor and delivery [3]. In a study of 707 women receiving HAART during pregnancy, overall transmission was 1.6%; MTCT was directly correlated with HIV viral load nearest delivery and duration of HAART during pregnancy and CD4 count near delivery were correlated with viral load [4]. A number of studies have demonstrated that duration of ARV prophylaxis during pregnancy is significantly associated with the risk of MTCT [4, 5]; in the European Collaborative Study, MTCT was significantly related to insufficient antenatal HAART, defined as no or <13 days of HAART [4]. An additional important risk factor for transmission in the U.S. is acute HIV infection during pregnancy in women with initially negative HIV tests [6]. Finally, the number of women with HIV infection giving birth in the U.S. has increased by approximately 30% since the year 2000 to approximately 9,000 annually, which can result in increased perinatal transmission secondary to these missed opportunities for prevention [3]. Thus, infants born to mothers with late diagnosis of HIV, receiving no antiretroviral drugs or short duration of HAART, or detectable viral load at delivery, are at particularly high risk of HIV transmission in the U.S. as well as in developing countries.

Globally, transmission resulting from breastfeeding is a major challenge to reducing rates of MTCT. Breastfeeding carries a significant risk of HIV transmission: without antiretroviral therapy to mother or infant, transmission risk over the first year of life is between 5 and 15% [7-9]. The risk can be reduced by exclusive breastfeeding, rather than mixed feeding, in the first six months and provision of antiretroviral therapy during the time of breastfeeding to either mother or infant. Recommended therapy to prevent breast milk transmission includes either HAART to the mother or NVP to the infant during the period of breastfeeding. However, even with treatment, breast milk transmission occurs in approximately 2 to 3% of infants [7, 8].

Breastfeeding continues in spite of the transmission risk primarily because breast milk provides a substantial survival advantage in low resource settings. In a meta-analysis conducted by the World Health Organization (WHO) collaborative study team, breastfeeding in the first two months of life provided a 6-fold reduction in infectious disease mortality [10]. This benefit diminished over time but remained significant throughout the first year of life with a 1.4-fold decrease in mortality due to infectious diseases attributable to breastfeeding in months 9-11. Thus, even with the risk of HIV transmission, in many low resource settings, breastfeeding still provides the best opportunity for a child to remain alive and HIV-infection free. Therefore, it remains critically important to identify means whereby infants may be further protected from HIV during the time of breastfeeding.

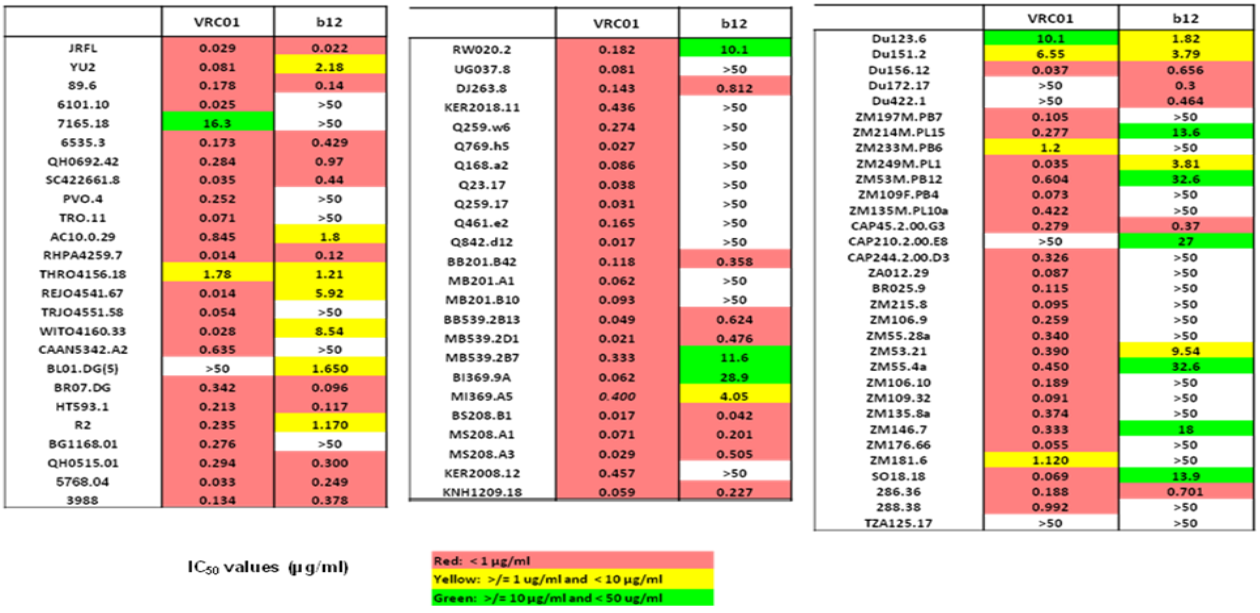
Administration of pre-formed antibodies, also known as passive immunization, can provide protection from infection or disease if protection is mediated through antibodies. Evidence increasingly suggests that antibody, in particular neutralizing antibody, has the potential to prevent infection with HIV [11-15]. Further, passive antibody has been successfully used to prevent disease caused by other viral infections in children. Infants born to women with hepatitis B who receive a single dose of hepatitis B immune globulin (HBIG) are protected against transmission in the intrapartum period [16] and infants at risk for serious respiratory syncytial virus (RSV) who receive monthly doses of the monoclonal antibody (mAb), palivizumab (Synagis®), have a reduced risk of serious RSV illness during the first few months of life [17]. These two examples highlight viral infections that can be prevented with administration of polyclonal and monoclonal antibody and suggest the possibility that passive antibody might prevent mother to child transmission of HIV.

While previous studies of monoclonal antibodies (mAb) to prevent MTCT of HIV have been proposed, the studies were not implemented because there was no antibody product with broad, cross clade neutralization ability that also lacked anti-self-reactivity. Recently, investigators in the Vaccine Research Center (VRC) at the National Institutes of Health (NIH) have described a broadly neutralizing mAb, VRC01 [18, 19]. 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 and neutralizes more than 90% of a diverse panel of tier 2 viruses (Table 1). Antibody levels of 50 µg/mL neutralize (IC_{50}) 91% of isolates tested and more than 70% are neutralized by 1 µg/mL. In comparison, the mAb b12, [19-21] which was the prior gold standard for broad neutralization, achieved an IC_{50} at 50 µg/mL against <50% of tier 2 isolates. Potency breadth curves (

Figure 2) demonstrate broad and potent neutralization against a panel of 179 viruses. Further, there is no evidence that VRC01 is auto- or poly-reactive as demonstrated by antinuclear antibody (ANA) reactivity, anticardiolipin assay, or prolongation of the activated partial thromboplastin time (aPTT) [22]. Additional experiments, outlined in the Investigator's Brochure (IB), detail extensive immunohistochemical studies performed on 38 types of tissue for adults and 21 types of tissue from neonates demonstrating no cross reactivity with any tissue type (IB). Anti-self properties limited the development of earlier "broadly" neutralizing anti-HIV monoclonal antibodies such as 2F5 and 4E10 [23]. Based on the potent and broad neutralizing activity as well as the in vitro safety profile, VRC01 holds tremendous promise as a therapeutic agent to further reduce HIV transmission in infants.

Two groups have evaluated the ability of monoclonal antibodies to neutralize early infant virus and both showed that VRC01 was a potent inhibitor, neutralizing 18/23 infant isolates in one study [24] and six of seven early infant isolates in a second study [25], demonstrating that VRC01 is capable of neutralizing early, transmitted virus.

Table 1: Breadth and Potency of VRC01 neutralization of tier 2 virus



	VRC01	b12
JRFL	0.029	0.022
YU2	0.081	2.18
89.6	0.178	0.14
6101.10	0.025	>50
7165.18	16.3	>50
6535.3	0.173	0.429
QH0692.42	0.284	0.97
SC422661.8	0.035	0.44
PVO.4	0.252	>50
TRO.11	0.071	>50
AC10.0.29	0.845	1.8
RHPA4259.7	0.014	0.12
THRO4156.18	1.78	1.21
REJO4541.67	0.014	5.92
TRJO4551.58	0.054	>50
WITO4160.33	0.028	8.54
CAAN5342.A2	0.635	>50
BL01.DG(S)	>50	1.650
BR07.DG	0.342	0.096
HT593.1	0.213	0.117
R2	0.235	1.170
BG1168.01	0.276	>50
QH0515.01	0.294	0.300
5768.04	0.033	0.249
3988	0.134	0.378

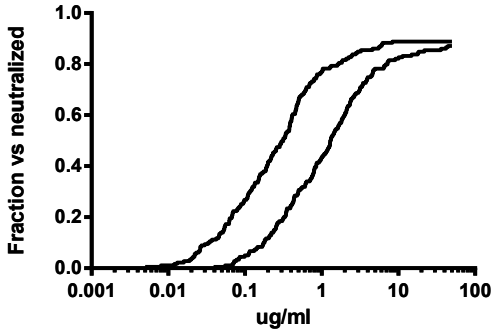
	VRC01	b12
RW020.2	0.182	10.1
UG037.8	0.081	>50
DJ263.8	0.143	0.812
KER2018.11	0.436	>50
Q259.w6	0.274	>50
Q769.h5	0.027	>50
Q168.a2	0.086	>50
Q23.17	0.038	>50
Q259.17	0.031	>50
Q461.e2	0.165	>50
Q842.d12	0.017	>50
BB201.B42	0.118	0.358
MB201.A1	0.062	>50
MB201.B10	0.093	>50
BB539.2B13	0.049	0.624
MB539.2D1	0.021	0.476
MB539.2B7	0.333	11.6
BI369.9A	0.062	28.9
MI369.A5	*0.400*	4.05
BS208.B1	0.017	0.042
MS208.A1	0.071	0.201
MS208.A3	0.029	0.505
KER2008.12	0.457	>50
KNH1209.18	0.059	0.227

	VRC01	b12
Du123.6	10.1	1.82
Du151.2	6.55	3.79
Du156.12	0.037	0.656
Du172.17	>50	0.3
Du422.1	>50	0.464
ZM197M.PB7	0.105	>50
ZM214M.PL15	0.277	13.6
ZM233M.PB6	1.2	>50
ZM249M.PL1	0.035	3.81
ZM53M.PB12	0.604	32.6
ZM109F.PB4	0.073	>50
ZM135M.PL10a	0.422	>50
CAP45.2.00.G3	0.279	0.37
CAP210.2.00.E8	>50	27
CAP244.2.00.D3	0.326	>50
ZA012.29	0.087	>50
BR025.9	0.115	>50
ZM215.8	0.095	>50
ZM106.9	0.259	>50
ZM55.28a	0.340	>50
ZM53.21	0.390	9.54
ZM55.4a	0.450	32.6
ZM106.10	0.189	>50
ZM109.32	0.091	>50
ZM135.8a	0.374	>50
ZM146.7	0.333	18
ZM176.66	0.055	>50
ZM181.6	1.120	>50
SO18.18	0.069	13.9
286.36	0.188	0.701
288.38	0.992	>50
TZA125.17	>50	>50

Clade B (N=25) **Clade A** (N=24) **Clade C** (N=32)

Figure 2: Breadth Potency Curves for VRC01 Data.

Left curve: IC_{50}
Right curve: IC_{80}



1.1.1 Pre-clinical in vivo data supporting product and dose selection

A series of experiments were conducted in male and female rhesus macaques to determine VRC01 levels in serum and secretions after IV and SC dosing and the ability of VRC01 to protect animals from simian-human immunodeficiency virus (SHIV) challenge. The first study determined plasma concentrations up to 28 days after IV or SC administration of 40mg/kg of pre-GMP VRC01 in female rhesus macaques. The plasma concentration of VRC01 at day 14 exceeded 50 µg/mL in 7/8 animals and 10 µg/mL in 7/8 animals (IB). In addition, detectable concentrations were measured in rectal, vaginal, and nasal secretions. The challenge-protection experiments were then completed in rhesus macaques using virulent chimeric SHIV which contains the HIV envelope in an SIV background. The first experiment included groups of male rhesus macaques infused IV with research-grade VRC01 5 or 20 mg/kg or control human IgG. At 2 days post-infusion animals were challenged intrarectally with 300 tissue culture infectious doses (TCID) 50 of SHIV SF162P3. All four animals infused with 20 mg/kg remained uninfected whereas two of four infused with 5 mg/kg had confirmed infection and three of four animals in the control group became infected.

A similar study was conducted in female macaques but for this experiment all animals received IV VRC01 20mg/kg or control human IgG and the challenge was performed via the intravaginal route. Again, all four animals infused with VRC01 remained uninfected, whereas three of four animals infused with control human IgG were infected.

To extend these findings another challenge-protection study was conducted using a different SHIV and a larger number of animals. Groups of at least 4 male rhesus macaques were administered a single dose of research-gradeVRC01 IV at 20 (n=6), 5 (n=6), 1.25 (n=4) or 0.3 (n=16) mg/kg. Fourteen controlled animals received human IgG. At day 2 post infusion, all animals were challenged intrarectally with 1mLof SHIV-Ba-L virus that had a TCID50 titer of 12,800/ml in Tzm-bl cells. All animals infused with 20, 5 and 1.25 mg/kg VRC01 were protected from infection with SHIV-Ba-L; 7 out of 16 animals infused with 0.3 mg/kg were

protected; in contrast, all 14 animals that received a control human IgG were infected after the challenge with SHIV-Ba-L. One hundred percent protection from SHIV-Ba-L challenge was demonstrated at 20, 5 and 1.25 mg/kg dose of VRC01 administered IV.

In the final challenge-protection experiment conducted by Nancy Haigwood, seven newborn *M. mulatta* received a single SC dose of VRC01 followed by a single high dose oral challenge with SHIV SF162P3 24 hours later. This animal model was previously shown to result in acquisition of infection in 100% of challenged animals. In this experiment, one of five animals that received 5 mg/kg had breakthrough infection and zero of two animals that received 20 mg/kg were infected.

Although there has been a great increase in the understanding of the biological events occurring during HIV transmission in humans, there is much that is not yet known. Non-human primate (NHP) models using various strains of SIV and SHIV have been developed, refined, and improved over years to more closely mimic the known events of HIV transmission [26]. The NHP models provide important data about transmission and potential efficacy of prevention interventions. However, a fully predictive animal model is not available and animal data have sometimes failed to predict the results of human trial [27]. On the other hand, careful design of animal models recapitulated the result of a failed HIV candidate vaccine in a human trial indicating the potential to provide predictive results [28, 29]. NHP transmission studies are the best available pre-clinical model but proof of efficacy must be determined in human trials [26, 27].

VRC01LS was produced from VRC01 through modification by site-directed mutagenesis to increase its binding affinity for the neonatal Fc receptor (FcRn), and the resulting antibody was designated VRC01LS. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region far outside of the antigen-combining site [30]. Other than the two amino acid difference, VRC01LS is structurally identical to VRC01. As a result of its enhanced FcRn function, VRC01LS has an extended half-life in both serum and mucosal tissue compared to VRC01 and improved protection against primate SHIV infection [31].

VRC07-523LS was derived from VRC-01 through cloning and structure-guided optimization techniques designed to produce an antibody with greater potency, breadth and half-life. The increased neutralization potency *in vitro* and prolonged half-life of VRC07-523LS correlate with improved protection against SHIV infection *in vivo* in animal studies, suggesting a potential clinical advantage in humans for preventive and/or treatment of HIV. Like VRC01 and VRC01-LS, VRC07-523LS is targeted against the HIV-1 CD4 binding site. The mutations that together define the 523 designation are a glycine to histidine mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG, thus increasing plasma

half-life. The resulting product has significantly increased potency and breadth compared to VRC01 or VRC01LS (Table 2).

VRC07-523LS is 5- to 8-fold more potent than VRC01, with an inhibitory concentration IC50 <50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades and IC50 <1 mcg/mL against 92% of HIV-1 viruses tested and displays minimal levels of autoreactivity. VRC07-523LS was shown to have a prolonged half-life over VRC07 by about 2-fold. *In vivo* proof-of-concept studies showed that VRC07-523LS is about 5-fold more potent than VRC01-LS in rhesus macaques [32].

Table 2: Potency and Breadth of HIV-1 Neutralization of VRC01 and VRC07-523LS (Development-Grade Material)

Color shading represents potency as follows:

<.100
.100-1.00
1.00-10.0
>10.0

		IC50 (µg/mL)		IC80 (µg/mL)	
clade	virus	VRC01	VRC07-523LS	VRC01	VRC07-523LS
A	KER2018.11	0.701	0.232	1.920	0.992
A	Q23.17	0.075	0.023	0.257	0.111
A	Q769.h5	0.027	0.003	0.166	0.024
A	RW020.2	0.159	0.024	0.535	0.125
AC	6540.v4.c1	>50	>50	>50	>50
AD	Q168.a2	0.108	0.026	0.385	0.175
AE	C1080.c3	1.360	0.050	7.010	0.539
AE	CNE59	0.567	0.036	2.260	0.205
AE	TH966.8	0.062	0.006	0.675	0.045
AG	DJ263.8	0.042	0.001	0.392	0.010
B	6101.10	0.066	0.005	0.205	0.042
B	Bal.01	0.034	0.0007	0.165	0.008
B	BG1168.01	0.647	0.097	2.970	0.351
B	CAAN.A2	1.410	0.213	4.460	0.719
B	JRCSF.JB	0.246	0.019	0.939	0.131
B	JRFL.JB	0.014	0.0006	0.074	0.002
B	PVO.04	0.418	0.041	1.380	0.233
B	THRO.18	1.700	0.330	13.100	4.920
B	TRJO.58	0.080	0.017	0.258	0.090
B	TRO.11	0.455	0.069	1.430	0.223
B	YU2.DG	0.057	0.003	0.203	0.032
C	CNE58	0.154	0.017	0.527	0.069
C	DU156.12	0.087	0.004	0.271	0.031
C	DU172.17	>50	0.071	>50	0.565
C	DU422.01	>50	6.990	>50	>50
C	ZA012.29	0.491	0.103	2.370	0.495
C	ZM106.9	0.285	0.017	0.876	0.145
C	ZM55.28a	0.306	0.020	1.090	0.109
D	57128.vrc.15	>50	0.193	>50	2.470
G	X1632.S2.B10	0.033	0.0008	0.287	0.013

1.1.2 Study Product

Detailed descriptions of the products are contained in their respective IBs, which will be provided to all registered sites.

1.1.3 Product Development

The present study is one in a series of planned studies that will ultimately result in sufficient clinical data to allow a larger efficacy trial to occur in infants exposed to HIV at delivery and through breastfeeding. The first studies to be conducted have occurred in adults in the US. The studies are summarized in Table 3 below. Two Phase I studies of VRC01 occurred in HIV positive and HIV negative adults, respectively, to confirm safety and PK in both populations [33, 34]. These were dose-escalating up to 40mg/kg. Similarly, safety and PK studies of VRC01LS [35] and VRC07-523LS have been completed in adults. The studies were conducted at the NIH VRC and had data available prior to enrollment of infants into IMPAACT P1112. Additional studies are now enrolling large numbers of adult subjects into studies of each of these monoclonals in adults for prevention and treatment of HIV (Table 3).

The present study is the initial infant study and it will be conducted at sites in the US and in Africa. Further infant studies will be conducted through IMPAACT in settings where breastfeeding of infants remains the best option for infants born to HIV-infected women. This is a Phase I safety study that may position IMPAACT to conduct a large efficacy study depending on the results of an ongoing study in adults.

Table 3: Planned or completed studies of VRC01, VRC01LS and VRC07-523LS

Study	Study Design	Participant Population	Dosage (mg/kg) route x numbers of administrations	Target Accrual VRC01 or VRC01LS/placebo
VRC 601 (Completed)	Phase 1, 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 Pharmacokinetics (PK) and viral phenotype	23 (up to 5 per dose group; 11 in 40 mg/kg)
VRC 602 (Completed)	Phase 1, 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 PK	23/5 (5 per dose group)
IMPAACT P1112 (the present study)	Phase 1, open label, dose escalation of VRC01 and VRC01LS	Newborn infants of HIV-infected mothers (US and African sites)	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 wks for minimum of 24 weeks and no more than 72 weeks while breastfeeding Dose Group 4: VRC01LS SC at ≤ 5 days of life and then at Week 12 if still breastfeeding. 80mg < 4.5kg; 100mg ≥ 4.5kg (in addition to standard perinatal ARV prophylaxis for all arms) Safety assessed and PK done to assess target trough.	59/0 (13 per dose group)
HVTN 104 (Completed)	Phase 1, multicenter randomized trial, Group 1 and Group 2 are open-label VRC01 and Group 3 is double-blind, placebo controlled.	HIV-uninfected volunteers aged 18 to 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 1: 20/0 Group 2: 20/0 Group 3 (double blind): 20/0 Group 3 (placebo controlled): 0/4
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	1268/634
HVTN 704/HPTN 085 (Ongoing)	Phase 2b, multicenter randomized trial, double-blind, placebo controlled VRC01	HIV-uninfected adults	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
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 (Closed to follow-up)	Phase 1, open label VRC01	HIV-infected adults	40 mg/kg IV x 3 doses; One each on days 0, 21, and 42	15/0
IMPAACT 2008 (Ongoing)	Phase I/II, multicenter randomized trial, open label VRC01	HIV-infected infants age 0-120 days	Arm 1: 40mg/kg/dose SC at Weeks 0, 2, 6, 10 with cART provided outside the study Arm 2: cART with cART provided outside the study	34/34
15-I-01040 (Completed)	Phase I/II, open label VRC01	HIV-infected adults	40mg/kg IV x 3-8 doses, given on days -3, 14, 28, and monthly up to 6 months.	10/0
RV397 (Completed)	Phase II single center randomized placebo controlled trial of VRC01	HIV-infected adults, acutely treated	Arm 1: 40mg/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 40mg/kg VRC01 IV at Week 0 Arm 3: Single infusion of 40mg/kg VRC01 IV at Week 0 and ART at Week 1	24 (8 per arm)
HVTN 116 (Ongoing)	Phase I, open label (VRC01 and VRC01LS)	HIV-uninfected adults	Group 1: 10 mg/kg VRC01 IV at Month 0, 2, 4 and 6 Group 2: 30 mg/kg VRC01 IV at Month 0, 2, 4 and 6 Group 3: 30 mg/kg VRC01LS IV at Month 0, 3 and 6 Group 4: 30 mg/kg VRC01 IV at Month 0 Group 5: 30 mg/kg VRC01LS IV at Month 0	101/0
VRC 606 (Closed to follow-up)	Phase 1, open label, dose escalation of VRC01LS	HIV-uninfected adults	Group 1: 5 mg/kg VRC01LS IV on Day 0 Group 2: 5 mg/kg VRC01 SC on Day 0 Group 3: 20 mg/kg VRC01LS IV on Day 0 Group 4: 40 mg/kg VRC01 IV on Day 0 Group 5: 5 mg/kg VRC01LS SC on Day 0, Week 12 and Week 24 Group 6: 20 mg/kg VRC01LS IV on Day 0, Week 12 and Week 24	40/0
VRC 607/A5378 (Ongoing)	Phase 1, open label, single dose VRC01LS and VRC07-523LS	HIV-1-infected adults	40 mg/kg IV x 1 dose	10-20/0
VRC 605 (Ongoing, closed to accrual)	Phase 1, open label, dose escalating VRC07-523LS	HIV-uninfected adults	Group 1 1mg/kg IV Group 2 5mg/kg IV Group 3 5mg/kg SC Group 4 20mg/kg IV Group 5 40mg/kg IV Group 6 5mg/kg SC on Month 0, 3, and 6 Group 7 20mg/kg IV on Month 0, 3, and 6	Groups 1-5: 3/0 Groups 6-7: 5/0
HVTN127/HPTN087 (Ongoing)	Randomized Phase 1 Trial to Evaluate the Safety and PK of VRC07-523LS, Multiple Doses, Routes, and Dosing Schedules	HIV-uninfected adults	Group 1 2.5mg/kg IV at weeks 0, 16, 32, 48, 64 Group 2 5 mg/kg IV at weeks 0, 16, 32, 48, 64 Group 3 20mg/kg IV at weeks 0, 16, 32, 48, 64 Group 4 2.5mg/kg SC 0, 16, 32, 48, 64 Group 5 5mg/kg SC at 0, 16, 32, 48, 64 Group 6 2.5 mg/kg IM at weeks 0, 16, 32, 48, 64	20/0 per group Group 6: 20/4

1.1.4 Product Safety

Preclinical:
A series of experiments have been conducted to assess anti-self properties and toxicities in laboratory animals of both study products. These studies are described in detail in the respective IBs. To briefly summarize; antiphospholipid characteristics were assessed by two different methods. The first method utilized a luminescent assay to measure binding of VRC01 to cardiolipin. While another anti-HIV mAb demonstrated strong binding to cardiolipin, neither Synagis (an FDA-approved mAb), nor VRC01 reacted with cardiolipin. In a separate experiment, anti-Phospholipid characteristics were evaluated by measuring impact on activated partial thromboplastin time (aPTT). Again, VRC01 was compared to 4E10 and Synagis and again, antiphospholipid activity was seen for 4E10 but not for Synagis or VRC01.

Anti-nuclear antigen reactivity was assessed with a commercial lupus kit (anti-ANA). Unlike other anti-HIV neutralizing mAb, VRC01 does not react with nuclear antigens.

In an additional experiment, binding to a human cell line was assessed via immunohistochemistry. In this experiment, fluorescently-labeled VRC01 does not bind Hep-2 cells.

In experiments to evaluate the potential for human autoreactivity, VRC01LS was assessed for anti-phospholipid reactivity, anti-nuclear antigen reactivity, binding to a human epithelial cell line (HEp-2) by immunohistochemistry, and potential "off target" binding to protein arrays microchips precoated with 9400 full-length human proteins: all experiments showed no clinically significant autoreactivity. In an assessment of potential "off target" binding in a human Tissue Cross-Reactivity study VRC01LS and VRC01 variably stained cytoplasm and cytoplasmic granules in epithelial and/or decidual cells in several human tissues. The findings were judged of no toxicologic significance for mAb as the cytoplasmic compartment is not available to mAb in vivo [36, 37].

As previously noted, VRC01 and VRC01LS differ by only two amino acids. As a result of these changes, binding to the neonatal Fc receptor (FcRn) is increased resulting in an extended half-life in both serum and mucosal tissue compared to VRC01 and improved protection against primate SHIV infection [31]. VRC01LS has similar in vitro neutralization potency and breadth when compared to VRC01 (wild type). VRC01LS is found at higher concentrations in macaque rectal secretions, as well as rectal and vaginal tissues. When administered IV at a single dose of 10 mg/kg to rhesus macaques, VRC01LS persisted up to 70 days in rectal tissues, while VRC01 was no longer detectable after 28 days.

In preclinical experiments in macaques, after a single dose of VRC01LS was administered intravenously (IV) at doses from 0.02 to 20 mg/kg (n=26), or subcutaneously (SC) at a dose of 10 mg/mL (n=6), there was no indication of local reactogenicity, anaphylactoid reaction, or any systemic disease (based on clinical symptoms). In a series of experiments, VRC01LS was compared to VRC01 in ability to

protect from challenge in male and female macaques. In all experiments, VRC01LS demonstrated a longer half-life (increased about 3-fold), persistent levels in GI tract and other mucosal surfaces, and improved ability to protect from infection.

To summarize the VRC01LS preclinical data, VRC01 and VRC01LS are similar with VRC01LS displaying improved pharmacokinetics, identical or improved antiviral effects, and no unexpected cross reactivity in any of the neonatal human tissues examined (VRC01LS IB, Version 3.0, dated 21 August 2017).

In other pre-clinical safety studies, VRC07-523LS demonstrated slight reactivity to phospholipids and a small subset of nuclear antigens, minimal reactivity with HEp-2 cells, and no impact on aPTT by binding phospholipids. In studies of potential "off target" binding in a GLP tissue cross-reactivity study with normal adult human and rat tissue, VRC07-523LS staining of cytoplasmic and extracellular elements was similar between the human and Sprague-Dawley rat tissues examined. According to ICH S6(R1), monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicologic significance. In further "off target" binding studies in human tissue, VRC07-523LS staining was observed in cytoplasm, cytoplasmic granules, and/or perinuclear cytoplasm of various neonatal human tissues. No membrane specific binding was observed suggesting that there is no cross-reactivity of toxicologic concern.

Pharmacokinetics Study in Sprague-Dawley Rats:
A single-dose IV and SC PK 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 U.S. 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 PK study, a cohort of rats received VRC01 on day 1 at 4 mg/kg and 40 mg/kg by the IV route of administration and at 40 mg/kg by the SC route of administration. Each of these 3 groups contained 9 male and 9 female rats. VRC01 levels in serum were determined using an enzyme-linked immunosorbant assay (ELISA) with samples collected pre-dose from each animal and from an additional 3 males and 3 females to provide untreated control serum. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following time points: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in a dose-proportional exposure. The terminal elimination phase half-life (t1/2) was about 10 days, with clearance (Cl) of approximately 20 ml/day/kg and volume of distribution (Vd) that was about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. VRC01 administration by the SC route resulted in mean peak serum levels at 7 days for males or 3 days for female animals. The maximum serum concentration (C_{max}), and area under the concentration-time curve to the last time point (AUC_{last}) values were lower when 40 mg/kg was administered by the SC route compared with the IV route. The bioavailability of 40 mg/kg VRC01 administered by the SC route was estimated to be 31.4% (males) and 42.3% (females). After the peak concentration of VRC01 was

achieved in the SC group, the serum levels decreased much more rapidly from 7 to 14 days than they did in the IV groups, and VRC01 concentrations in the SC group were not quantifiable at time points after 14 days. These data indicate that clearance of VRC01 in rats was markedly enhanced when it was administered by the SC route. The development of antidrug antibodies that contribute to an increased rate of clearance is often observed in preclinical safety studies of protein-based test articles when they are not tested in the species of origin. Although immunogenicity was not examined in this study, the presence of such antibodies might have possibly contributed to the increased rate of clearance of VRC01 after SC administration that was observed in this study [10, 11].

Repeat Dose Toxicity Study:
A repeat dose IV and 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 U.S. 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 the proposed human studies.

To bridge the preclinical proof-of-concept studies performed with research-grade VRC01 to the clinical product, the neutralization profiles of all materials used in the preclinical studies were generated against a panel of up to five strains of HIV-1. The virus panel included the four strains (3 HIV isolates and 1 murine leukemia virus variant isolate (SVA.MLV) negative control) tested in the viral neutralization assay used for release testing of the clinical product. All clinical drug substance and drug product lots of VRC01 were found to have equivalent or better neutralizing potency when compared to the research-grade materials.

Administration of VRC07-523 LS at repeat doses up to 400 mg/kg/dose IV or SC was well tolerated in Sprague-Dawley Rats and most findings were reversible and no longer seen at the end of the recovery period.

Clinical Studies:
Phase I clinical trials of VRC01 and VRC01LS are currently underway. Completed studies include first-in-humans dose escalation studies for safety, tolerability, and PK of VRC01 in HIV-1-infected (VRC 601) [33] and HIV-1-uninfected (VRC 602) adults [34]. Both the IV and SC routes of administration have been evaluated. A clinical trial (HVTN 104) evaluating serial dosing using several different IV or SC doses with different dosing schedules, for prevention of HIV-1 is completed [38, 39]. Studies of multiple doses of VRC01 to reduce markers of HIV-1 persistence in chronically infected, cART-treated HIV-1-infected adults are underway or completed (A5340, NIH 15-I-0140, A5342) [40], as is a study of the efficacy of VRC01 administration during ART interruption in adults (RV 397) [41] and another study of VRC01 for treatment during acute HIV-1 infection in adults is underway (RV 398).

VRC 601 was the first study of the VRC01 mAb in HIV-1-infected participants [33]. 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, and in total, 23 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 [33].

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 [33]. 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 antiretroviral 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 [33].

VRC 602 was the first study of the VRC01 mAb in HIV-1-uninfected adults [34]. 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 (5mg/kg, 20mg/kg, 40 mg/kg) and one double-blinded, placebo-controlled group for SC administration (5mg/kg). Cumulatively, 23 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 [34]. 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.

Data from ACTG A5340 demonstrated maintenance of viral suppression for 4 weeks in HIV-infected VRC01 recipients following ART interruption. There was a modest delay, overall, in the return of viremia compared to historical controls [40].

Further study of 88 adults at low risk for HIV infection (50% female) demonstrated favorable safety and PK profiles when the antibody was administered at varying doses over a prolonged period of time in study HVTN 104 [42]. Participants were followed for 32 weeks after their first VRC01 administration and received a total of 249 IV infusions

and 208 SC injections, with no serious adverse events, dose-limiting toxicities, nor evidence for anti-VRC01 antibodies observed.

As of February 2018, studies of VRC01 have now enrolled more than 800 adult volunteers with over 2500 doses. 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. In Phase 2 trials (still blinded), there have been 22 related AEs of mild or moderate severity in 15 participants (two AEs of change in sleep pattern, two AEs of hypogeusia (decreased ability to taste), five AEs of urticaria, and one event each of wheals and erythema-left upper arm/right calf/under right breast, urticaria of upper limbs, urticaria of the face, infusion site pruritus, generalized body itchiness, low neutrophil count, dizziness during infusion, lightheadedness, loose stools, dermatitis, headache, nausea and malaise). There has been one related severe (Grade 3) AE of urticaria in one participant (VRC01 IB, Version 8.0, dated 21 August 2017).

Given the potential for urticarial and/or allergic reactions after injections that may present with non-specific findings such as GI symptoms, clinicians should observe infants carefully following each injection and should manage any post-injection allergic/hypersensitivity reactions per site standard of care. In particular, clinicians should pay special attention to gastrointestinal symptoms (e.g., as part of post-injection observations and during contacts).

VRC 606 was the first in human dose-escalation study to examine safety, tolerability, dose, and pharmacokinetics of VRC-HIVMAB080-00-AB (VRC01LS) monoclonal antibody in healthy adults [35]. The first 37 volunteers who received administrations of VRC01LS had no serious adverse events (SAEs) or dose-limiting toxicities. Mild malaise and myalgia were the most common adverse events (AEs). There were six AEs assessed as possibly related to VRC01LS administration, and all were mild in severity and resolved during the study.

Regarding local reactions, VRC01LS administrations have been generally well tolerated. There was one instance of Grade 1 injection site reaction with persistent hyperpigmentation ongoing but improving at Day 28. Overall, three of 21 participants (14.3 %) who received VRC01LS IV and 14 of 18 participants (77.8%) who received VRC01LS SC and completed diary cards reported solicited local reactions in the week after product administration. These include 14 reports of mild local pain/tenderness. One participant in Group 5 (5 mg/kg SC) reported moderate pain, two participants (Group 5, 5 mg/kg SC and Group 6, 20 mg/kg IV) reported mild bruising, two participants in Group 5 (5 mg/kg SC) reported mild swelling, and two participants (Group 2 and Group 5, 5 mg/kg SC) reported mild redness.

Preliminary pharmacokinetic data from an ongoing clinical trial of VRC01LS in healthy adults shows increased persistence of antibody in participant sera with an elimination half-life of 71 +/- 18 days. The mean (+/-SD) serum concentration 12 weeks after one IV administration of 20 mg/kg or 40 mg/kg were 180 +/- 43 mug/mL (n = 7) and 326 +/- 35 mug/mL (n = 5), respectively, which supports the planned dosing interval of 12 weeks in

Dose Group 4, breastfed infants. See Section 1.2 and Section 9 of this protocol for rationale used in dose selection.

There is an ongoing study (VRC605) in adult participants to determine safety and PK of VRC07-523LS when administered intravenously or subcutaneously. To date, 26 participants have been enrolled and received one or more doses of between 1 mg/kg and 40 mg/kg. The preliminary PK results confirm the slower elimination and a longer half-life than "non-LS" bNAbs, but the half-life of VRC07-523LS is not as long as has been described for VRC01LS. However, due to the increased potency, the resulting ability of plasma to neutralize virus is similar or even slightly better with VRC07-523LS even at trough concentrations. The net result may be an antibody that can still be given very infrequently that has enhanced breadth compared to VRC01LS.

Twenty-five (25) of 26 subjects enrolled in VRC605 received at least 1 dose of VRC07-523LS (12 SC and 25 IV administrations). One participant withdrew prior to receiving the study product. There have been no SAEs and no safety pauses for AEs. Overall, 15 of 25 participants who received the product (60%) have had at least one AE with the maximum severity being Grade 1 for 7 participants, Grade 2 for six, Grade 3 for one and Grade 4 for one. The Grade 3 AE was for an elevated creatinine 56 days after the last product administration, most likely related to dehydration following exercise. The Grade 4 AE was for elevated liver enzymes likely related to starting a concomitant medication, fluoxetine, known to cause hepatoxicity, and was not related to VRC07-523LS. In summary, AEs were generally mild, and the few severe AEs were not likely related to study drug.

Two participants developed infusion reactions shortly after IV product administration. Specifically, one participant enrolled in the 40 mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. All symptoms resolved within 12 hours. Another participant in the 20 mg/kg IV group experienced three separate infusion reactions (n=2 moderate, n=1 mild) after each product infusion. The participant experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia, and arthralgia.

Four (25%) participants reported mild or moderate systemic reactogenicity symptoms three days after product administration. The reported symptoms were malaise (n=2 mild, n=1 moderate), myalgia (n=2 mild, n=1 moderate), mild headache (n=2), and moderate chills (n=2). Five of 8 subjects (62.5%) receiving VRC07-523LS SC reported mild systemic reactogenicity symptoms: malaise (n=3), myalgia (n=2), headache (n=3), chills (n=1), nausea (n=1), and joint pain (n=2).

Based on the PK and safety data available to date, the dose to be used in the present study is 80 mg (birthweight ≥ 2.0 to < 4.5 kg) and 100 mg (birthweight ≥ 4.5 kg), or approximately 18-40 mg/kg, administered subcutaneously (SC) as a single injection as close to birth as possible. This will be followed by a second 100 mg SC dose administered at Week 12 for infants still being breastfed.

1.1.5 Passive antibody safety in infants

Use of monoclonal antibodies to prevent infectious disease is a relatively recent development; however, passive polyclonal antibody products have been used for decades with excellent safety profiles. The following paragraphs will first outline data on polyclonal antibody products followed by monoclonal data.

Polyclonal products have been delivered to infants via the intravenous (IV), intramuscular (IM) and subcutaneous routes (SC) to prevent transmission of infections. Perhaps the best established and most frequently used product is hepatitis B immunoglobulin (HBIG) which is recommended as a single IM dose for all infants born to Hepatitis B antigen positive women in the US (and many other countries) [43]. This has been administered to thousands of infants as part of studies and as part of clinical care with few reported side effects. There is only one case report of an anaphylactic reaction in the literature [44]. In one study, HBIG was given by the SC route and found to also be safe and well tolerated [45]. Other polyclonal antibodies used in infants include Respigam®, Cytogam®, HIVIg, and IVIG. In a trial in which 500 women and their newborns received either HIVIg or IVIG, side effects in the women were uncommon and when they did occur, they were generally mild or moderate; only two women had severe side effects. In that trial, only two infants had toxicity thought to be related to study drug infusion, all graded as mild [46]. In a very large study of IVIG to prevent infection in preterm infants, the product was found to not decrease the risk of death or serious disability; however, product related adverse events were rare and no different in the IVIG group compared to placebo [47].

There is considerably less experience in the use of monoclonal antibodies in neonates and infants; however, the data that do exist support the safety of monoclonal antibody products and provide some information that helps to guide initial dosing. Currently, there are only two monoclonal antibody products FDA-approved to prevent an infectious disease: Palivizumab (Synagis®), an anti-RSV monoclonal antibody; and Raxibacumab, an anti anthracis toxin. While the latter is FDA-approved for children, there are no pediatric data available. The most extensive safety data come from use of Palivizumab and several other products which are not FDA-approved, outlined below.

Palivizumab is a humanized murine mAb directed against the F glycoprotein of RSV. This product is administered as a monthly 15 mg/kg intramuscular (IM) dose to infants at high risk of serious RSV disease during the RSV season. During the time of peak RSV activity (October through March) premature infants and others at high risk of severe disease may receive up to 6 doses of Palivizumab. In general, the series of Palivizumab doses are safe and well tolerated. The most frequently reported adverse events listed in the package insert are noted in Table 4; none occur more frequently in the Palivizumab recipients compared to placebo.

Table 4: Adverse Events Occurring at a Rate of 1% or Greater in Infants[†] Receiving Palivizumab or Placebo

Event	Palivizumab (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)
[†]Cyanosis (Synagis [9.1%]/placebo [6.9%]) and arrhythmia (Synagis [3.1%]/placebo [1.7%]) were reported during Trial 2 in CHD patients		

During the Palivizumab post-marketing period, severe thrombocytopenia, injection site reactions, and severe hypersensitivity reactions have been rarely reported. Because the reporting systems are voluntary, the actual incidence of such reactions cannot be determined. None of the reactions were fatal. It is not known whether the chimeric nature of Palivizumab (CDR3 region retained from original murine mAb on human IgG1 backbone) plays a role in these rare hypersensitivity reactions and whether treatment with a fully human mAb like VRC01 would result in similar reactions.

One theoretical concern with use of monoclonal antibodies is that the patient could develop their own antibody directed against the monoclonal and then either clear the monoclonal more rapidly over time (resulting in decreasing serum levels) or develop immune complex disease as the patient's antibody and the administered monoclonal antibody formed complexes. This possibility was previously evaluated when Palivizumab was administered and found not to occur. Similarly, this has been evaluated for the products described below and not found to occur.

Other monoclonal antibodies that have been administered to neonates or infants include pagibaximab (a human chimeric anti-staphylococcal mAb) [48, 49]; SB 209763 (a mouse humanized anti-RSV fusion protein) [50]; and motavizumab (a maturation variant of palivizumab) [51]. The above agents have been studied in preterm and term infants. In all cases, the mAb was generally well tolerated. The one safety concern that was raised was for the motavizumab which was administered to over 5,000 children. Nine of 3,000 (0.3%) children in one study of this product required treatment discontinuation due to a skin reaction; all in the treatment group (0 in placebo) and there was overall a higher incidence of skin AE in the treated group. A partial list of anti-infective monoclonal antibodies studied in adults includes KPBA-101 (anti *Pseudomonas*), CDA1, CDB1 (anti *C. difficile*) and others. The efficacy to prevent disease varies between the products but the safety profile is consistently good.

The excellent safety profile seen with anti-infective monoclonal antibodies is in direct contrast to the safety profile of monoclonal antibodies that have been developed to treat cancer and/or autoimmune disease. A review of the currently FDA-approved monoclonal antibodies (http://www.fda.gov/BiologicsBloodVaccines) lists 39 total products; 33 of which are used to treat cancer and or autoimmune disease. These agents carry a long list of side effects due to their anti-self-properties. In contrast, monoclonal antibodies that react with an infecting agent, rather than components of human tissue are consistently well tolerated and safe even when used in neonates. Given VRC01 documented lack of reactivity to human tissue, it is likely to be safe and well tolerated.

1.1.6 Monoclonal antibody dosing

The half-life ($T_{1/2}$) of antibodies depends on a variety of factors including the isotype (IgG vs IgM or IgA), the subclass (IgG1), the ongoing transudative losses in a patient, and patient age. In general, IgG antibodies have a half-life ($T_{1/2}$) in the range of 14 to 28 days. In a primate model, VRC01 has a $T_{1/2}$ of 10 days, and VRC01LS has a $T_{1/2}$ of about 30 days; however, clearance of a human mAb is expected to be increased in another animal species, therefore, it is anticipated that the $T_{1/2}$ will be substantially longer in humans. The $T_{1/2}$ of the human monoclonal Palivizumab in infants is 20 days. An initial pharmacokinetic study to determine $T_{1/2}$ of VRC01 in adults was completed prior to the initiation of the infant study. While the adult study will be useful in predicting half-life in infants, the absolute level of antibody needed for protection cannot be determined from those adult studies. Further, the half-life of VRC01 in infants may be somewhat different than that seen in adults. Therefore, the proposed trial is necessary to confirm the appropriate dosing interval to use in future multi-dose trials with this agent.

The PK results in HIV-infected and uninfected adults for VRC 601 and 602 have been published [33, 34] and are detailed in the IB. These results indicate that PK parameters are comparable in these two adult populations. The participants received one or two IV or SC doses at 28-day intervals.

In healthy adults receiving VRC01 20 and 40 mg/kg IV, maximum serum concentrations were 940±320 (n=8) and 1600±230 (n=5) mcg/ml, respectively, after the first infusion, and 1100±360 (n=5) and 1500±400 (n=5) mcg/ml after the second dose, respectively. At 20 and 40mg/kg, mean 28-day trough serum concentrations were 35±6.5 (n=8) and 57±19 (n=5), and 56±19 (n=5) and 80±40 (n=5) mcg/ml after the second dose, respectively. The overall clearance for all IV groups (n=18) was 0.016±0.0033L/h. In the HIV-infected participants at 20 and 40 mg/kg IV, maximum serum concentrations were 1000±340 (n=3) and 1500±340 (n=11), respectively, after the first infusion, and 1000±510 (n=3) and 1700±460 (n=2) mcg/ml after the second dose, respectively. At 20 and 40mg/kg, mean 28-day trough serum concentrations were 33±15 (n=3) and 30±16 (n=11) after the first dose, and 46±27 (n=3) and 65±57 (n=2) mcg/ml after the second dose, respectively. The overall clearance for the IV groups (n=20) was 0.024±0.006 L/h. There were not significant differences in the PK parameters for the viremic and non-viremic infected adults.

Evaluation of the SC route of administration in adults has been limited to the 5 mg/kg dose due to limitation on the volume that can be administered SC to adults. As expected, the peak concentrations are achieved later than IV, at 67 and 62 hours for the uninfected and infected adults, respectively. The C_{max} in plasma is higher for IV than SC dose (240±42 vs. 34±5 mcg/ml at a dose of 5mg/kg in the infected adults). However, the clearance and terminal half-life are similar between IV and SC. For the 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. Clearance (CL) following IV administration and apparent clearance (CL/F) following SC administration were similar suggesting good bioavailability (F) following SC administration.

For VRC01LS, the maximum serum concentrations in adults in VRC606 following IV administration of 20mg/kg and 40mg/kg were 1221±398 mcg/mL (n=8) and 2451±626 mcg/mL (n=3), respectively, with an overall half-life over 2 months. Following the single dose SC administration of VRC01LS 5 mg/kg, the C_{max} is reduced to levels about 25% of those seen following IV administration but the SC AUC is only reduced by about 20% compared to IV.

In preliminary PK studies of VRC07-523LS, adults who received 20 mg/kg (N=8) had a mean (± SD) day 28 concentration of 195 mcg/mL (+63) and a mean day 84 concentration of 37 mcg/mL (+5.5). While the levels at day 28 and 84 are lower than that seen with VRC01LS, due to the increased potency, it is expected that the ability of VRC07-523LS to neutralize virus will be similar or better than that of VRC01LS at these timepoints.

1.2 Rationale

UNAIDS estimates that almost 300,000 infants are newly HIV-infected each year, the vast majority due to mother to child transmission (MTCT). Measures to prevent transmission of HIV infection have improved dramatically leading to calls by UNAIDS and other organizations to eliminate new pediatric HIV infections by 2015. In spite of the successes, perinatal and breast milk transmission continues to occur. A substantial number of women are diagnosed and treated late in pregnancy resulting in higher rates of peripartum and early post-natal transmission even with maternal and/or infant antiretroviral therapy. Even with effective treatments for infants born to women with known infection, in high seroincidence regions, women will continue to transmit due to new maternal infections that occur after delivery. Studies show that acute maternal infection can occur in as many as 3% of women in high prevalence regions and the risk of transmission in the setting of acute infection is dramatically increased [52-56]. Protection of all infants will only be provided by vaccine that can be administered universally; however, a safe and effective vaccine capable of providing long-lasting protection is still not available. Recently, investigators at the United States National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center (VRC) at NIH have discovered monoclonal antibodies (mAbs) that have potent and broad neutralizing activity (<50 µg/ml) against over 90% of tier 2 (difficult to neutralize) viruses from a multiclade panel. This broad and potent neutralizing ability has the potential to prevent HIV transmission in a variety of settings but in particular, holds

tremendous promise in the prevention of MTCT of HIV. Therefore, the following study is proposed to provide initial safety and pharmacokinetic information on single and multiple dose mAb VRC01, VRC01LS, and VRC07-523LS when administered to infants at increased risk of peripartum and post-partum HIV transmission.

Single and multiple dose pharmacokinetic data from the present study will be used to select a dose regimen for repeated dosing that will be needed for protection during ongoing breast milk exposure. Protective efficacy will be determined in a future study which cannot begin until the present study determines a safe dose that provides a sufficient trough level. Demonstration that a neutralizing antibody prevents HIV transmission in humans would be a major milestone in the field of HIV prevention. Although ample data in animal models demonstrate protection with neutralizing antibody, this has yet to be studied in humans. Demonstration of efficacy will lead toward further development of mAb for use in prevention of MTCT and potentially for other post-exposure prophylaxis. It will also provide proof-of-concept for neutralizing antibody protection that will be important for design of active vaccines to induce immunity.

While VRC01LS is a very promising product with excellent breadth, potency and a very long half-life, the newer product VRC07-523LS has increased potency and increased breadth compared with either VRC01 product. Thus, if VRC07-523LS has a similar safety profile and a half-life that approaches that of VRC01LS, then it would be the preferred product to take into subsequent trials.

Product availability
Monoclonal antibody products currently available in the US are extremely expensive. Lower prices and ability to deliver in resource poor settings are made feasible by recent advances in technology which allow production of clinical grade monoclonal antibody products for dramatically reduced prices; as low as $200 per gram for cost-of-goods depending on the scale of production. Thus, if the appropriate dose of VRC01 is 40 mg/kg initially followed by 20 mg/kg monthly, total cost-of-goods for 6 months' therapy is <$100. If 30 infants need to be treated to prevent one infection, then the cost would be about $3,000 for each infection prevented, far lower than the estimated cost for 20 years of HAART. Estimated costs would be lower for a long-acting monoclonal, such as VRC01LS, for which fewer doses would be required for protection. It is often difficult to predict how products will be made feasibly available in resource-constrained settings; however, it is clear that the technology can be adapted to low cost production and that a product which is sufficiently effective could be made available to populations that need it. These arrangements cannot be guaranteed or even planned until further evidence of product efficacy is in hand.

Rationale for study population
The greatest risk for MTCT of HIV occurs in Africa and India, among infants who are being breastfed; however, we are proposing this initial study to also include non-breast-fed neonates in the US as well as at select international sites. In spite of the success in preventing most MTCT in the US and other countries where formula is a safe and affordable option and PMTCT regimens are available, there continue to be high risk

infants. The high-risk group includes infants born to women who seek care late in pregnancy, even as late as in labor, and who are, therefore, not treated until the intrapartum period. Risk of transmission in this setting, even with combination therapy to the infant is >5% [57]. Further, there are women who are known to be infected and on therapy but with ongoing viral replication due to poor adherence or resistant virus. These high-risk infants have the potential to benefit from a neutralizing monoclonal antibody.

The study product has the potential to decrease mother to child transmission of HIV in a variety of settings and this study is an initial step in the evaluation of the product. Ultimately, the target population that can benefit from a passive antibody would include infants both in the US and in resource poor countries. In the US, the target population would include high risk infants: that is, infants born to women who have replicating virus late in pregnancy, either due to late diagnosis, late presentation for care, poor medication adherence, or resistant virus. Worldwide, the target population would include infants with ongoing breast milk exposure who have a continued risk during the period of breastfeeding and around the time of weaning in spite of optimal ARV therapy. An added intervention such as this is necessary to eventually achieve a generation free of HIV.

Risks and Benefits to Study Participants

The potential benefit of the product is the potential for further reduction of MTCT of HIV, when given in addition to standard of care ARV therapy. This is particularly true for VRC01LS and VRC07-523LS, which – because of the long half-life – might be easier to implement as a public health measure in countries where risk of transmission from breastfeeding is common. The potential for this benefit is supported by in vitro data (ability to neutralize) and non-human primate experiments, both outlined in greater detail in the background section of the protocol.

The potential risks of the product include risks of reactions at the local injection site or, in rare cases, systemic allergic reactions, such as urticaria observed in several adult study participants. Given the persistence of MTCT in the high-risk populations we are enrolling in the protocol, VRC01 offers a potential for benefit and, based on the available data from in vitro studies, animal studies, and studies of other monoclonal antibodies, appears to have an acceptable safety profile. VRC07-523 has a slight increase in auto-reactivity in in vitro studies, compared with VRC01. This auto-reactivity appears to be mild and did not result in adverse events in pre-clinical testing nor in initial clinical studies of adults. Further, the off-target binding assays displayed only intracytoplasmic binding and no membrane binding, suggesting that toxicity associated with that binding is unlikely.

Research participation should always be carefully considered, but for some women it may be challenging to make a decision about participation if they are just learning their HIV status or were not previously engaged in HIV care. When P1112 was first conceived, there were concerns that, for women who have not been regularly engaged in care, there may be loss to follow-up in the course of research. However, because it is the infants born to such women who have the greatest potential for benefit – as this group has a significant ongoing transmission risk in spite of use of aggressive ARV therapy once in care – P1112 was opened. Under Version 1.0, the study did not enroll infants born to

HIV-infected women with well controlled virus in Dose Groups 1 and 2 because such infants have a very low risk of HIV-transmission, thus less potential for benefit from the investigational product. In Version 2.0, with evidence of safety, the criteria for risk were modified for Dose Group 2 (Dose Group 1 had been fully enrolled), and Dose Group 3 was opened to infants with risk of transmission from breastfeeding. IMPAACT sites have successfully completed prior treatment trials requiring enrollment within 48 hours of birth of infants born to HIV-infected women who presented at near or at the time of delivery [57]. Conduct of P1112 has documented similar success with dosing within the protocol-specified timeframe for each dose group. Dose Group 4 and 5 Cohorts 1 enroll at both domestic and African sites to HIV-exposed non-breastfeeding infants; Cohorts 2 enroll at African sites to HIV-exposed infants at risk of transmission from breastfeeding.

There is a small risk of enrolling infants based on a maternal intrapartum rapid test results that is later determined to be a false positive test result. However, women who first test positive intrapartum are at extremely high risk for transmission and therefore, their infants are the most likely to benefit from aggressive intrapartum intervention including multidrug therapy. Most hospitals now offer, as standard of care, rapid intrapartum testing for women not tested during the current pregnancy or tested early in pregnancy but with other risk factors. Such products have good positive predictive value, especially when used in high risk populations. In a meta-analysis of Oraquick®, a popular rapid test, performed on blood samples that was reported recently in Lancet Infectious Diseases [58], specificity of the test was 99.91% and the positive predictive value in high prevalence populations was 98.5% and in low prevalence populations was 97.7%; therefore, we believe it is appropriate to allow sites to enroll women with positive rapid tests who are being approached to discuss strategies to reduce mother to child HIV transmission. However, in the Manual of Procedures (MOP), we will request that all sites work with their clinical and research labs to identify strategies to obtain confirmatory testing as rapidly as possible and if that confirmatory testing can be obtained rapidly, the sites are encouraged to review that test result before enrolling. However, requiring that second test result to be documented in all cases before enrollment will make it very difficult for the babies who are most likely to benefit to receive the drug rapidly; at the time it is most likely to help.

The women enrolled will likely have challenges with the burden of clinical care and study participation. The study sites are experienced in assisting these women with access to care for both themselves and their infants. Further, since the infants are by definition high risk, the infants will require very frequent medical evaluation for clinical care alone; therefore, the added burden of study participation is relatively small. The sites will be required to coordinate research visits with clinical care visits and whenever possible facilitate transportation or even complete some study visits in the patient's home, if the woman finds such home visits to be desirable. Women will be enrolled in the study as some of the history data needed to confirm infant eligibility will be gathered from maternal medical records (viral load, viral resistance for example) and maternal serum and PBMC will be collected and stored so that, if a transmission event occurs, we will be able to evaluate maternal virus transmitted and not transmitted with the infant isolate. However, women will not receive VRC01/VRC01LS/VRC07-523LS.

Consent
Asking for consent during labor and reconfirmation of consent (and the right to withdraw) after labor is not without precedent, nor is it ethically necessarily problematic. However, the protocol team and investigators will take further steps (detailed in MOP) to bolster participants' ability to give informed consent during a particularly difficult period. We will include the following steps:

1. The MOP will detail when and how women will be approached for consent antepartum and postpartum. Women who appear overly fatigued, in severe pain, or too inwardly focused to converse about the details of study participation will not be approached during labor.
2. Gatekeepers including the woman's primary OB provider and/or family members may be approached to ask if it is appropriate to approach a woman at that time; however, as family members may not be aware of the woman's HIV diagnosis, this strategy will only be employed if family members are aware of the diagnosis.

Whenever possible, women will be approached prior to onset of labor. For women who cannot be approached prior to labor (for whatever reason), consent will be obtained with great care and attention to the woman's ability to understand and consent. Further, she will be provided an opportunity to withdraw consent after she delivers the infant and before the dose of study medication is administered, if she chooses. There is a 72-hour window after delivery for Dose Groups 1, 2 and Cohort 1 of Dose Groups 4 and 5 and a five-day window for Dose Group 3 and Cohort 2 of Dose Groups 4 and 5 for women who would like more time to consider the study before consenting. This option must be balanced by the knowledge that the product is more likely to work the sooner it is administered after exposure (delivery).

Sites that intend to conduct home visits in lieu of clinic visits are expected to add detail about this to the site-specific informed consents.

Rationale for VRC01 dose selection in multi-dose groups
Doses up to 40 mg/kg have been tested in adults prior to the initiation of this study. Based on data from the adult studies (as described in "Clinical Studies"), from Palivizumab and other mAb, IC_{50} of tier 2 isolates, and the challenge-protection experiments conducted in primates we are projecting VRC01 doses of 20 and 40 mg/kg as sufficient to achieve a target trough (day 28) concentration of 50 µg/mL. For the multi-dose cohort (Dose Group 3), we have selected an initial (loading) dose of 40 mg/kg followed by monthly doses of 20mg/kg. Assessment of the PK of the initial infants receiving 20 mg/kg supports this approach. The team also considered available data from adults (ACTG A5340; 40/mg/kg IV first dose) [40]). Figure 3 shows VRC01 concentrations seen in P1112 infants (20mg/kg SC) and those seen in adults following 40mg/kg IV. In A5340, the 40mg/kg IV dose was well tolerated and achieved VRC01 concentrations approximately double those seen thus far in P1112 with the 20mg/kg SC dose. Thus, the team expects the Day 28 concentrations from P1112 Dose Group 2 (40mg/kg SC) to be in the range seen in current adult trials of intravenous VRC01 (40mg/kg) and, therefore, to the be appropriate starting dose for Dose Group 3.

Rationale for VRC01LS dose selection
VRC01LS offers some clear advantages over VRC01. Based on structural similarities, preclinical data, and initial adult data, VRC01LS is expected to have identical or improved antiviral effect and a safety profile similar to VRC01; however, given its dramatically improved half-life and preferential concentration at mucosal surfaces, it has the potential to improve delivery of the monoclonal antibody. Based on the adult PK data, modeling demonstrated that two doses (at birth and age 3 months) in an infant should result in serum levels above target (50 µg/mL) for six months or more. Because VRC01 and VRC01LS are structurally so similar, the PK and safety data from studies of VRC01 as well as studies ofVRC01LS (study VRC 606) have been considered in determining the dose for Dose Group 4. Based on the data available to date, weight-based dosing is planned: 80mg SC for infants weighing < 4.5kg at birth; 100 mg SC for infants weighing ≥ 4.5kg at birth. If the infant is still breastfeeding at Week 12, a second dose will be administered. Figure 4 below shows that, when VRC01LS is administered as a single 20mg/kg IV dose to healthy adults, average levels at day 84 are approximately > 180mcg/mL, well above the 30-day trough target used for VRC01.

Rationale for VRC07-523LS dose selection
VRC07-523LS demonstrates a shorter half-life than VRC01LS; however, much longer than that of VRC01 (Figure 5). The shorter duration is balanced by the greater potency; therefore, we anticipate that by administering the same dose as used for VRC01LS, we will have similar ability of serum to neutralize susceptible virus at these later time points. Since VRC07-523LS has greater breadth, then more viruses that the child is potentially exposed to should be neutralized.

It should be noted, however, that the dose needed to prevent infection is unknown, levels as low as 1 µg/mL neutralize more than 70% of tier 2 isolates, and the gradient between serum and relevant mucosal secretions is not known. Therefore, lower levels may be acceptable for moving these products into larger clinical trials.

PK modeling, described in more detail in Section 9, demonstrates how the doses selected for the present study are anticipated to achieve target concentrations. Briefly, based on preliminary adult data and data on VRC01LS PK in infants, modeling projects a median day 84 level in infants of 25 mcg/mL, assuming linear PK and no dose effect. This suggests that all infants will achieve or surpass our target level of 10 mcg/mL on day 84 (Figure 6).

Figure 3: Comparison of Infant SC 20mg/kg and Adult IV 40mg/kg of VRC 01

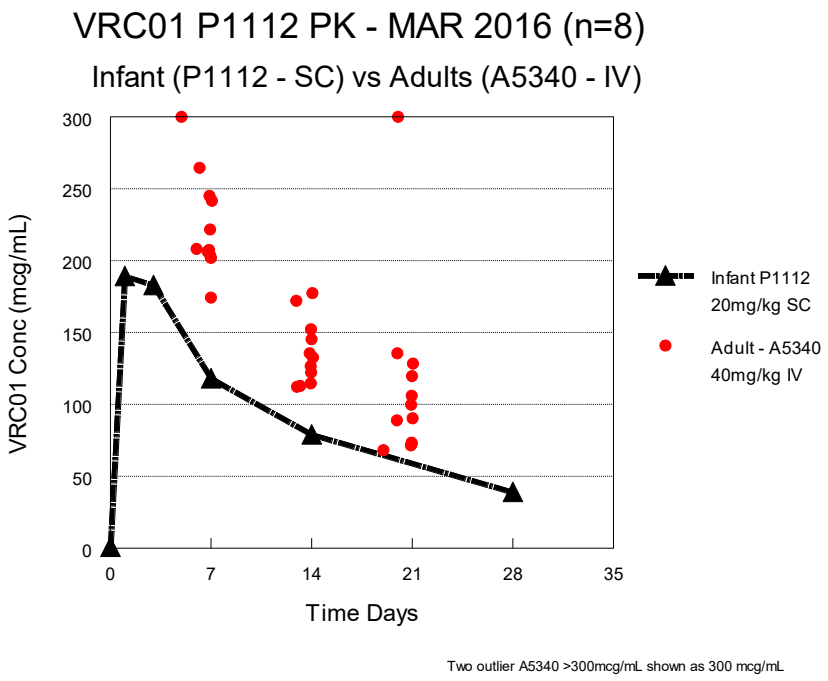


Figure 4: VRC01 and VRC01LS levels following IV administration in adults

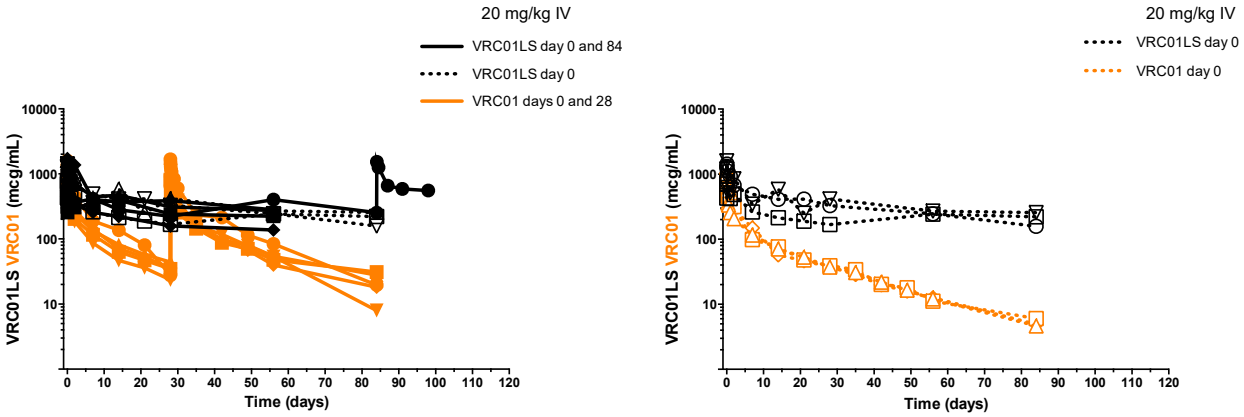


Figure 5: VRC01, VRC01LS and VRC07-523LS levels following IV administration of 20 mg/kg in adults

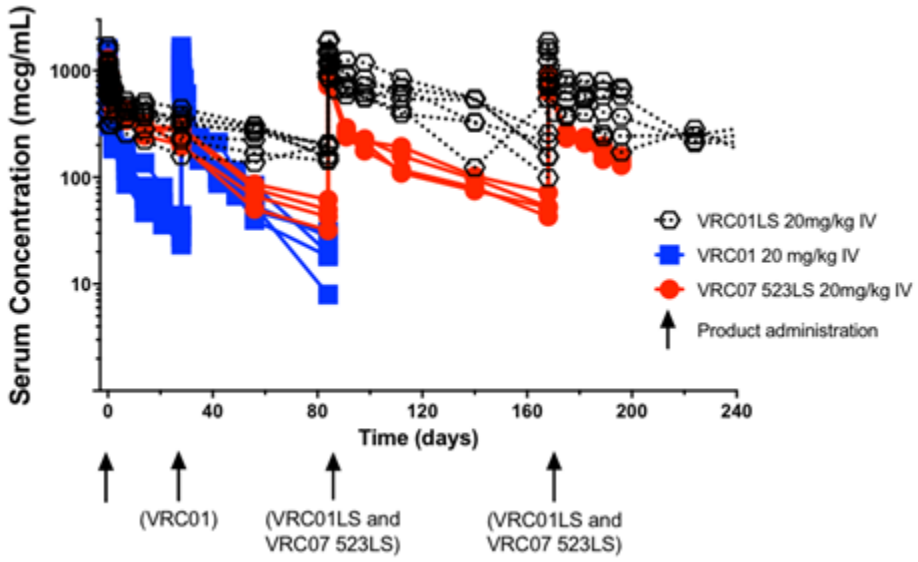
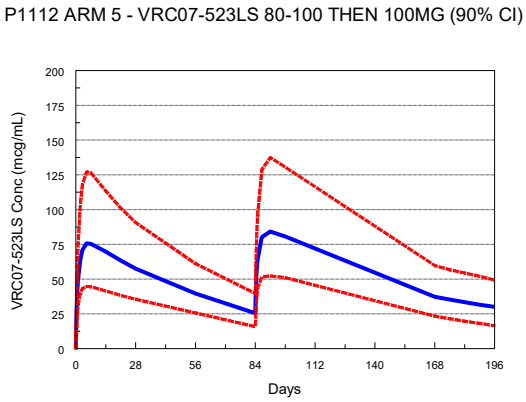


Figure 6: Modeling of VRC07-523LS levels



Study duration

The study duration of 48 weeks for Dose Groups 1 and 2 is warranted for the following reasons. First, in other intervention studies in which the infants receive HAART (instead of just ZDV monotherapy), detection of a positive HIV DNA or RNA may be delayed. While most infected children have an initial positive test result by 6 weeks of age, in the setting of HAART, the first positive may not be apparent until 10-12 weeks or even later. As children in the present study are by definition, high risk, it is likely that many will be receiving combination ARV. Further, we do not know what impact VRC01 VRC01LS, or VRC07-523LS will have on time to diagnosis; it may be that first infant positive test may not be apparent until weeks after the antibody is gone. In addition, we

know that maternal antibodies to HIV may be present in exposed infants for as long as 15 months and, in the international setting, it is common to use EIA or rapid antibody testing to confirm an infant is HIV negative. It is possible, even likely that some antibody will remain and may interfere with the infants' HIV antibody tests. Therefore, to confirm that infants who receive VRC01 become EIA and Western Blot negative by 12 months of age and to be certain that any infant infections are detected, the protocol team believes that 48 weeks of follow up is important for the children receiving a single dose of VRC01. If a child remains antibody positive on laboratory testing at 48 weeks, he/she will continue every 3 month follow up until antibody tests are negative. This is important to confirm that receipt of monoclonal antibody does not delay the time until when infants test negative on routine HIV antibody testing**.** Infants in Dose Groups 3 (multi-dose), 4 and 5 will be followed for 96 weeks.

Follow-up of infected infants
Two recent studies [59, 60] have demonstrated rapid and prolonged viral suppression of SHIV in primates after receipt of single or multiple monoclonal antibodies, prompting interest in evaluating monoclonal antibodies as a potential "cure" strategy. A third study demonstrated eradication of SHIV with administration of two antibodies within 24 hours of oral inoculation of infant macaques [61]. While the present study is not designed to test this potential, there is a possibility that one or more of the high-risk infants enrolled in this study may be HIV-infected either *in utero* or intrapartum. Therefore, it will be important to describe changes in replicating and integrated virus in such infants after receipt of VRC01. All such infants will receive ARV therapy as part of standard of care as determined by their treating physicians but will have additional virologic and immunologic evaluations and follow up as described in Section 6.6 and APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1].

2 STUDY OBJECTIVES

2.1 Primary Objectives

In HIV-exposed infants at increased risk for peripartum or breastfeeding HIV transmission:

2.1.1 To assess safety of single subcutaneous dose (20 mg/kg or 40 mg/kg) of VRC01 (Dose Groups 1 and 2).
2.1.2 To determine pharmacokinetic profile of single dose, subcutaneous VRC01 (Dose Groups 1 and 2).
2.1.3 To assess safety of monthly subcutaneous doses of VRC01 (Dose Group 3)
2.1.4 To determine pharmacokinetic profile of monthly subcutaneous doses of VRC01 (Dose Group 3).
2.1.5 To assess safety of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2).
2.1.6 To determine pharmacokinetic profile of one and two subcutaneous doses of VRC01LS (Dose Group 4, Cohorts 1 and 2).
2.1.7 To assess safety of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2).

2.1.8 To determine pharmacokinetic profile of one and two subcutaneous doses of VRC07-523LS (Dose Group 5, Cohorts 1 and 2).

2.2 Secondary Objectives

2.2.1 To examine the anti-VRC01 antibody production following immunization.

2.2.2 To examine the anti-VRC01LS antibody production following immunization.

2.2.3 To examine the anti-VRC07-523LS antibody production following immunization.

2.3 Exploratory

2.3.1 To assess the amount of VRC01/ VRC01LS/ VRC07-523LS in oral secretions

2.3.2 If one or more infants are determined to be HIV-infected, to describe the neutralization sensitivity of the infant and maternal virus and the amount of HIV-1 provirus and plasma HIV-1 RNA (measured in copies/mL), after receipt of VRC01, VRC01LS or VRC07-523LS.

2.3.3 To assess neutralizing ability of serum before and after receipt of the antibody.

3 STUDY DESIGN

This is an open-label, dose-escalating, Phase 1, multicenter study to determine the safety and pharmacokinetic parameters of subcutaneous VRC01, VRC01LS, and VRC07-523LS, three potent anti-HIV neutralizing monoclonal antibodies. VRC01 is administered in a single dose in 26 HIV-1-exposed infants (between birth and 72 hours of life in Dose Groups 1 and 2 and between birth and 5 days of life in Dose Group 3) and as monthly doses in 13 HIV-1-exposed breastfed infants. VRC01LS is administered in a single dose in 10 HIV-exposed non-breastfed infants at risk of infection between birth and 72 hours of life (Dose Group 4, Cohort 1) and in a single dose in 10 HIV-exposed breastfeeding infants between birth and five days of life (Dose Group 4, Cohort 2). A second dose of VRC01LS is given at 12 weeks of life in Dose Group 4, Cohort 2 if the infant has not achieved complete cessation of breastfeeding. VRC07-523LS is similarly administered in a single dose in 10 HIV-exposed non-breastfed infants at risk of infection between birth and 72 hours of life (Dose Group 5, Cohort 1) and in a single dose in 10 HIV-exposed breastfeeding infants between birth and five days of life (Dose Group 5, Cohort 2). A second dose of VRC07-523LS will be given at 12 weeks of life in Dose Group 5, Cohort 2 if the infant has not achieved complete cessation of breastfeeding.

Based on what is currently known about the pharmacokinetics of VRC01, the expectation is that this drug will be well tolerated in these infants and that a dose of 20 mg/kg will meet or exceed the target 28-day trough of 50 µg/mL in 50% of infants, while 40mg/kg will result in 90% of infants surpassing that trough level. The percentages of infants who meet these criteria will be estimated with considerable uncertainty given the small sample size. Table 7 in Section 8.6 provides CI around all potential results. For VRC01LS, it is expected that most infants who receive the initial dose will have levels of 50-100 µg/mL at Week 12. Based on the its shorter half-life in adults, levels of VRC07-523LS at 12 weeks in infants in Cohort 5 are expected to be lower than those of Cohort 4, in the range of 10-50 µg/mL.

The study is being conducted domestically in sites with a perinatal program and at select international sites and is open to a population of infants born to HIV-infected women at risk for intrapartum or postpartum HIV transmission. Factors that put the child at increased risk for mother-to-child HIV transmission include lack of or late maternal antiretroviral (ARV) drug administration during pregnancy or inadequate antepartum ARV drug administration (see inclusion criteria), active viral replication near the time of delivery, an intrapartum event that might increase risk of transmission such as prolonged or premature rupture of membranes (PROM) or exposure to breast milk (for Dose Group 3 and Cohort 2 of Dose Groups 4 and 5). Participation in Dose Group 3 and Cohort 2 of Dose Groups 4 and 5 will be limited to select sites in Africa, where breastfeeding is recommended for mothers living with HIV. Specific requirements are listed in inclusion/exclusion criteria (see Section 4). Mothers may be consented prior to delivery or shortly after delivery of their infants, but enrollment of the mother-infant pair will not proceed until the infant eligibility criteria have been confirmed. The first dose of the study product must be administered less than 72 hours after birth to infants in Dose Group 1, 2, 4 (Cohort 1) and 5 (Cohort 1) and before the end of Day 5 of life for Dose Groups 3, 4 (Cohort 2) and 5 (Cohort 2).

The approximate sample size of the study is 79 mother-infant pairs, 13 per Dose Groups 1, 2 and 3 and 10 per each of the cohorts in Dose Groups 4 and 5, to assure both that 30 infants receive VRC01 and 8 infants per cohort in Dose Group 4 receive VRC01LS and 8 infants per cohort in Dose Group 5 receive VRC07-523LS and that these infants complete:

- Day 28 evaluations for Dose Groups 1 and 2 and Cohort 1 of Dose Groups 4 and 5
- Week 24 for Dose Group 3
- Week 16 for Cohort 2 of Dose Groups 4 and 5

The mothers are enrolled as well, but only the infants receive the VRC01/VRC01LS/VRC07-523LS immunization and are followed on the study. All infants receive prophylactic ARV treatment per local standard of care, as prescribed by their clinician. Mothers are counseled on the importance of their own adherence to antiretroviral therapy for the entire duration of treatment to reduce the risk of mother-to-child transmission of HIV and on the importance of their infants receiving all standard prophylactic ARV regimens. In particular, they are informed that the study drug is not known to reduce risk of transmission. See **Error! Reference source not found.** for an overview of the study design.

The treatment regimen will be the following:

Dose Group 1
VRC01 (human monoclonal antibody) 20 mg/kg was given by subcutaneous (SC) injection one time to infants ideally within 24 hours but always less than 72 hours after birth. After 13 infants were accrued and 6 of those infants were immunized and completed the Day 28 evaluations and safety criteria described in section 8.5.1 have been passed; then

Dose Group 2
An additional 13 infants were enrolled and received a single 40 mg/kg SC dose of the same monoclonal antibody ideally within 24 hours but always less than 72 hours after birth.

Dose Group 3
After six infants in Dose Group 2 completed Day 28 safety assessments and safety criteria described in Section 8.5.1 had been passed, Dose Group 3 opened and enrolled concurrently with the remaining Group 2 participants. The 13 infants in this Dose Group received 40 mg/kg SC for the initial dose, then 20 mg/kg SC monthly for at least 24 weeks and no more than 72 weeks while breastfeeding. In Dose Group 3, while it is desirable for infants to receive the first dose ideally within 24 hours and less than 72 hours after birth, enrollment was allowed through Day 5 of life as these infants have an ongoing breastmilk transmission risk.

In all cases, the earlier the treatment is provided, the better; therefore, ideally enrollment would have been completed and study drug administered prior to 24 hours of life. However, given the challenges of obtaining informed consent and appropriate screening, enrollment and dosing up to 72 hours of life was and will be allowed for Dose Groups 1, 2, 4 (Cohort 1), and 5 (Cohort 1) and through Day 5 of life for Dose Groups 3, 4 (Cohort 2), and 5 (Cohort 2). (In all dose groups, if the dose is not administered within this stated window, the child may not receive the dose.)

Under Version 1.0, Dose Group 1 closed to enrollment on January 28th 2016. On February 2nd, Dose Group 2 was opened to enrollment and the dose escalated after 13 Group 1 infants had been randomized, all had completed 48-hour post immunization evaluations, and 10 had completed Day 28 evaluations. The protocol opened to Group 3 after at least 6 infants in Group 2 received the 40mg/kg dose, completed Day 28 evaluations and passed safety review. Dose Groups 2 and 3 have completed enrollment. We believed this sequential enrollment would be safe for the following reasons: 1) in adult studies to date, there have been no dose limiting toxicities even up to 40 mg/kg and 2) all infants will have received the 20 mg/kg dose and will have undergone initial post immunization monitoring; therefore, any acute severe reactions will have been identified. While adults will not have received 40mg/kg via the subcutaneous route, adults have received larger SC volumes (2-3 mL) and repeated doses without significant local reactions. In addition, we expected that if the SC dosing in the infants were to produce reactions not seen in adults, the events would most likely be acute reactions rather than long term (28-day events). Finally, in addition to an initial review of data through Week 8 on the first 6 infants to be enrolled in Dose Group 3, six-month reviews of all safety data from adult and pediatric protocols of VRC01 (from P1112 database and most recent safety reports available from the other protocols) commenced after the first infant enrolled into Dose Group 3 reached the 6-month milestone.

Dose Group 4

Upon release of Version 3.0, the protocol team reviewed all available safety and PK data as well as accrual data of Dose Group 3 on April 19, 2017. The safety data revealed no signal, and the team determined that Dose Group 4, Cohort 1 enrollment could begin as soon as study documents were updated per protocol V3.0 and site approvals were obtained. When the first six infants in Dose Group 4, Cohort 1 were immunized and completed 28 days of follow-up, the team reviewed all available safety data. There was no pause in Dose Group 4, Cohort 1 enrollment or immunization during this review. As the review of safety data revealed no signal, enrollment into Dose Group 4, Cohort 2 was opened.

All 20 (10 per cohort) of the infants in Dose Group 4 received an initial dose of VRC01LS SC at birth (within 72 hours for Cohort 1; within 5 days of life for Cohort 2). Infants in Dose Group 4, Cohort 2 will receive a second dose at 12 weeks if they have not achieved complete cessation of breastfeeding. In Cohort 2, while it is desirable for infants to receive the first dose within 24 hours or as soon as possible, enrollment will be allowed through Day 5 of life.

Dose Group 5
Upon release of Version 4.0, the protocol team will review interim safety and PK data (accrual data will not need to be reviewed, as Dose Group 4 was fully accrued as of February 1, 2018). If the safety data reveal no signal, Dose Group 5, Cohort 1 enrollment may begin as soon as study documents are updated per protocol V4.0 and site approvals are obtained. When the first six infants in Dose Group 5, Cohort 1 have been immunized and completed 28 days of follow-up, the team will review interim safety and PK data. There will be no pause in Dose Group 5, Cohort 1 enrollment or immunization during this review. If review of safety and PK data reveals no signal, enrollment into Dose Group 5, Cohort 2 will be opened.

All 20 (10 per cohort) of the infants in Dose Group 5 will receive an initial dose of VRC07-523LS SC at birth (within 72 hours for Cohort 1; within 5 days of life for Cohort 2). Infants in Dose Group 5, Cohort 2 will receive a second dose at 12 weeks if they have not achieved complete cessation of breastfeeding. In Cohort 2, while it is desirable for infants to receive the first dose within 24 hours or as soon as possible, enrollment will be allowed through Day 5 of life.

The description of the dose groups is presented in the table that follows, (Table 5).

Table 5: Description of Dose Groups

	N	Dose of VRC01/VRC01LS/VRC07-523LS
Dose Group 1	13	20 mg/kg VRC01 SC X1
Dose Group 2	13	40 mg/kg VRC01 SC X1
Dose Group 3	13	40 mg/kg VRC01 SC for initial dose 20 mg/kg VRC01 SC monthly for at least 24 weeks and no more than 72 weeks while breastfeeding
Dose Group 4	10 10	Cohort 1: Non-breastfeeding Single dose VRC01LS at birth administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose VRC01LS at birth administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100mg VRC01LS at Week 12 administered SC if complete cessation of breastfeeding not achieved.
Dose Group 5	10 10	Cohort 1: Non-breastfeeding Single dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Cohort 2: Breastfeeding Initial dose at birth of VRC07-523LS to be administered SC; dose is based on weight: < 4.5 kg: 80 mg ≥ 4.5 kg: 100 mg Second dose of 100 mg VRC07-523LS at Week 12 to be administered SC if the infant has not achieved complete cessation of breastfeeding

The product vials of VRC01 are formulated at 100 mg/mL. Thus, an average 3.5 kg infant would receive a 0.7 mL dose if in the 20 mg/kg dose group or a 1.4 mL dose if in the 40 mg/kg dose group. Doses > 1.0 mL may be administered as 1 or 2 separate injections, based on site preference. In Dose Group 4, VRC01LS is administered as an 80 mg (or 0.8 mL) dose to all infants < 4.5 kg birth weight, which is expected to be most children. The small number of children with birth weight ≥ 4.5 kg receive 100 mg (1.0 mL). Modeling suggests that using this dosing approach will achieve target plasma levels in 95% of infants. Infants in Cohort 2 of Dose Group 4 will receive a second dose of 100 mg at Week 12 if complete cessation of breastfeeding has not been achieved.

Likewise, in Dose Group 5, VRC07-523LS will be administered as an 80 mg (or 0.8 mL) dose to all infants < 4.5 kg birth weight, which is expected to be most children. The small number of children with birth weight ≥ 4.5 kg will receive 100 mg (1.0 mL). Modeling suggests that using this dosing approach will achieve target plasma levels in 95% of

infants. For VRC07-523LS, the target level at 12 weeks is 10 µg/mL or higher in most infants; 5-fold lower than that of VRC01LS. The lower target is appropriate considering the significant increased potency of the VRC07-523LS product. Infants in Cohort 2 of Dose Group 5 will receive a second dose of 100 mg at Week 12 if complete cessation of breastfeeding has not been achieved.

Maternal participants are evaluated at screening and enrollment. Infant participants in Groups 1 and 2 are followed for 48 weeks; infants in Group 3 are followed for 96 weeks; and infants in Groups 4 and 5 for 96 weeks. PK sampling, anti-VRC01Ab, and oral secretions are collected over the entire study period. Refer to Schedules of Evaluations in Appendices as follows: APPENDIX IA: Maternal Schedule of Evaluations (all dose groups) (Maternal); APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2) (Infant: Dose Groups 1 and 2); APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] (HIV infected infants, all dose groups); APPENDIX ID: Schedule of Evaluations (Dose Group 3) (Infant; Dose Group 3); APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding); APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding); APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding) (Infant: Dose Group 5, non-breastfeeding); and APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding)(Infant: Dose Group 5, breastfeeding) for a complete description of the clinical and laboratory evaluations to be performed.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Maternal Inclusion Criteria

4.1.1 Documentation of HIV infection.

Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. For this protocol, the results for sample #2 may be pending at the time of enrollment. Results documented in the clinical record from past testing may be used to satisfy the criteria for documentation of HIV-1 infection.

- Sample #1 may be tested by non-study clinical or PEPFAR programs. However, both the result and the assay date must be recorded in participant's charts. Source documentation (patient's medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.) must be available.
- Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operates according to GCLP guidelines and participates in appropriate external quality assurance program (for international sites).

Acceptable Tests

Sample #1 must be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes.

- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV nucleic acid amplification test specified in the MOP
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

Note: Confirmatory testing (Sample #2) may be pending at the time of enrollment of the mother-infant pair. If maternal confirmatory testing is negative and the infant has received the VRC01, VRC01LS, or VRC07-523LS immunization, the infant will be followed for safety as part of the study. If the infant has not received the VRC01, VRC01LS, or VRC07-523LS immunization, then the mother and infant will be removed from the study.

Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA confirmed by Western Blot OR immunofluorescence OR chemiluminescence
- One HIV nucleic acid amplification test specified in the MOP
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

4.1.2 Greater than or equal to 18 years of age.

4.1.3 Able and willing to provide signed informed consent for herself and her infant.

4.2 Maternal Exclusion Criteria

4.2.1 Prior participation in any HIV-1 vaccine trial.

4.2.2 Receipt of any other active or passive HIV immunotherapy or investigational product during this pregnancy. (Note that administration of FDA-approved antiretroviral drugs when used to treat disease or prevent mother to child transmission are <u>not</u> considered investigational).

4.2.3 Documented or suspected serious medical illness or immediate life-threatening condition (other than HIV infection) in the mother that may interfere with the ability to complete study requirements, as judged by the examining clinician.

4.3 Infant Inclusion Criteria

4.3.1 Born to an HIV-1-infected woman who meets all maternal inclusion/exclusion criteria listed above.

4.3.2 Gestational age, by best obstetrical, ultrasound, or infant exam, ≥36 weeks

4.3.3 Birth weight ≥ 2.0 kg.

4.3.4 Allowable infant age at the time of enrollment is dependent on the Dose Group and Cohort:

- Dose Groups 4 and 5 (Cohort 1): <72 hours of age, and anticipated availability to receive VRC01LS or VRC07-523LS immunization at less than 72 hours after birth.
- Dose Groups 4 and 5 (Cohort 2): ≤ 5 days of age, and anticipated availability to receive VRC01LS or VRC07-523LS immunization no more than 5 days after birth.

4.3.5 At increased risk of HIV acquisition defined as documentation of one or more of the following risk factors:

Dose Groups 4 and 5 (Cohort 1), only:

- Mother received no ART during pregnancy or mother began or reinitiated ART (after an interruption of >14 days), during the third trimester of pregnancy; or
- Mother with any detectable viral replication (HIV RNA above the limit of detection) at last measurement prior to delivery determined within 30 days of delivery; or
- Prolonged rupture of membranes (> 12 hours); or
- Mother with documented* 2-class resistant HIV infection, which may include historical documentation of lack of response

*Women who have a documented history of virologic failure while on NNRTIs but who had no resistance testing at the time of viral failure will be considered to have NNRTI documented resistance.

Dose Groups 4 and 5 (Cohort 2), only (African sites):

- Mother intends to breastfeed

4.4 Infant Exclusion Criteria

4.4.1 Receipt of any other active or passive HIV immunotherapy or investigational product other than the study vaccine (Note: Infant prophylaxis with any licensed ARV drugs clinically prescribed to prevent mother to child HIV transmission are not considered investigational).

4.4.2 Receipt of or anticipated need for blood products, immunoglobulin, or immunosuppressive therapy. This includes infants who require Hepatitis B

Immunoglobulin (HBIG) but does not require exclusion of infants who receive Hepatitis B vaccine in the newborn period.

4.4.3 Documented or suspected serious medical illness, serious congenital anomaly, or immediate life-threatening condition in the infant that may interfere with the ability to complete study requirements, as judged by the examining clinician.

4.4.4 Any requirement for supplemental oxygen beyond 24 hours of life or requiring supplemental oxygen at the time of the VRC01, VRC01LS, or VRC07-523LS dose.

4.4.5 Baseline laboratory results

- Hemoglobin < 12.0 g/dL
- Platelet count < 100,000 cells/mm^3
- Absolute neutrophil count: for infants ≤ 24 hours old, < 4000 cells/mm^3; for infants >24 hours old, < 1250 cells/mm^3
- SGPT (ALT) ≥ 1.25 times upper limit of age adjusted normal

4.4.6 Dose Groups 4 and 5 (Cohort 1), only: Infant is breastfeeding at time of enrollment or mother has indicated an intention to initiate breastfeeding. Note, if a child breastfed prior to known maternal diagnosis (in the case of a woman diagnosed in the intrapartum period), the child is still eligible as long as breastfeeding is stopped by the time the child is enrolled and there is no plan to resume breast milk feeding.

4.5 Concomitant Medication Guidelines

There are no prohibited medications; however, all concomitant medications must be recorded on the appropriate CRFs.

4.6 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol document and the consent form(s) approved, as appropriate, by their local Institutional Review Board (IRB) /Ethics Committee (EC), and any other applicable regulatory entity (RE). A Site Implementation Plan (SIP) will be required from each site participating in the study and the plan must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific

informed consent forms (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.

IMPAACT Operations Center notification of approval to begin enrollment is required before participants can be enrolled in this study. Participants meeting the study eligibility criteria will be enrolled through the Data Management Center Subject Enrollment System. Written informed consent for study participation must be obtained before any study related procedures are performed.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, 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 ICF(s) *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.

Written informed consent for study participation must be obtained before any study related procedures are performed. Mothers may be consented prior to delivery or shortly after delivery of their infants, but enrollment of the mother-infant pair will not proceed until the infant eligibility criteria have been confirmed.

Enrollment of participants onto the study will be done through the Subject Enrollment System (SES) on the Data Management Center website (at https://www.Frontierscience.org) under the Systems heading.

4.7 Co-enrollment Procedures

Co-enrollment into other observational studies is permitted but requires notification of the IMPAACT P1112 protocol team and appropriate maximum blood draw considerations. The NIH Clinical Center blood guidelines allow a maximum of 5ml/kg within 24 hours and 9.5 ml/kg drawn over an 8-week period.

Co-enrollment into IMPAACT P1110 and P1115 will not be permitted. Co-enrollment into other interventional studies will be considered on a case-by-case basis but will require written permission from both protocol teams.

5 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

5.1.1 Dose Group 1

VRC01 20 mg/kg subcutaneous injection ideally within 24 hours and less than 72 hours after birth.

5.1.2 Dose Group 2

VRC01 40 mg/kg subcutaneous injection ideally within 24 hours and less than 72 hours after birth.

5.1.3 Dose Group 3

VRC01 40 mg/kg subcutaneous injection for the initial dose, then 20 mg/kg subcutaneous injection monthly for at least 24 weeks and no more than 72 weeks while breastfeeding. Initial dose ideally within 24 hours and no more than 5 days of life.

5.1.4 Dose Group 4

- Cohort 1: VRC01LS subcutaneous injection, ideally within 24 hours and less than 72 hours of life. Dosing is weight-based: 80mg if birth weight < 4.5kg; 100mg if birth weight is ≥ 4.5kg. If birth weight is not available, may use weight at time of screening.
- Cohort 2: VRC01LS subcutaneous injection at entry (all participants) and at Week 12 if infant is still breastfeeding. Initial dose ideally within 24 hours and less than 5 days of life. Dosing will be weight based: 80mg if birth weight < 4.5kg; 100mg if birth weight is ≥ 4.5kg. If birth weight is not available, can use weight at time of screening. The second dose at Week 12 will be 100mg.

5.1.5 Dose Group 5

- Cohort 1: VRC07-523LS subcutaneous injection, ideally within 24 hours and less than 72 hours of life. Dosing will be weight-based: 80mg if birth weight < 4.5kg; 100mg if birth weight is ≥ 4.5kg. If birth weight is not available, may use weight at time of screening.
- Cohort 2: VRC07-523LS subcutaneous injection at entry (all participants) and at Week 12 if infant is still breastfeeding. Initial dose ideally within 24 hours and less than 5 days of life. Dosing will be weight-based: 80mg if birth weight < 4.5kg; 100mg if birth weight is ≥ 4.5kg. If birth weight is not available, can use weight at time of screening. The second dose at Week 12 will be 100mg.

Refer to the P1112 MOP for the weight band tables. Please note that these tables only apply to Dose Groups 1-3. Infants in Dose Group 4 and 5 receive either 80 or 100 mg as described above and in the MOP.

- Table 7-1: Product Volume by Weight Band to Achieve a 20 mg/kg Dose with Additional Volume to Add to Syringe to Fill Tubing Dead Space in Study-Supplied Infusion Set
- Table 7-2: Product Volume by Weight Band to Achieve a 40 mg/kg dose with Additional Volume to Add to the Syringe to Fill Tubing Dead Space.
- Table 7-3: Product Volume by Weight Band to Achieve a 20 mg/kg Dose with Additional Volume to Add to Each of Two Syringes to Fill Tubing Dead Space: *Administration with Two Syringes*

Dose volumes greater than 1 ml may be separated into two injections to be given successively depending on site policy or preference. In order to evaluate any potential site reaction, product should not be administered in the same thigh where the infant received hepatitis B or any other vaccination.

VRC01, VRC01LS, and VRC07-523LS are administered subcutaneously, by slow push in the thigh using a BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter. After the administration is completed, the sliding safety shield is to be manually activated.

5.2 Drug Formulation

5.2.1 VRC01: VRC-HIVMAB-060-00-AB

VRC01 is a recombinant human immunoglobulin G1 (IgG1) antibody produced in a Chinese Hamster Ovary (CHO) cell line in accordance with the current Good Manufacturing Practice (cGMP) regulations. VRC01 is manufactured for the VRC at the Vaccine Pilot Plant (VPP) operated by Leidos Biomedical Research, Inc. (formerly SAIC-Frederick, Inc.), Frederick, MD. VRC01 human monoclonal antibody is manufactured as a 100 mg/ml solution and provided in single-dose vials. VRC01 is supplied at a concentration of 100 ± 10 mg/mL in an isotonic, sterile solution; the fill volume used for P1112 is 2.25 ± 0.10 mL in a 3-mL glass vial. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. At the CRPMC, VRC01 is to be stored in a freezer at -35^{0}C to -15^{0}C. In clinical site pharmacies, VRC01 is to be stored in a freezer with a temperature range of -45^{0}C to -10^{0}C (-49^{0}F-14^{0}F). Dispense one BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter item number 367294 for each syringe dispensed.

5.2.2 VRC01LS: VRC-HIVMAB080-00-AB

VRC01LS is an IgG1, and the glycosylation pattern is derived from its production in a Chinese Hamster Ovary (CHO) mammalian cell line. The bulk lot of the drug substance was manufactured under cGMP using a stably transfected CHO cell line, purified, and the drug product vials were filled and labeled at the VRC, Vaccine Clinical Material Program operated by Leidos Biomedical Research, Inc., Frederick, MD. Each product vial contains 6.25 mL volume at a concentration of 100 mg/mL VRC01LS in formulation

buffer containing 25 mM Sodium Citrate, 50 mM Sodium Chloride, and 150 mM L-Arginine Hydrochloride at pH 5.8. At the CRPMC, VRC01LS is to be stored in a freezer at -35^{0}C to -15^{0}C. In clinical site pharmacies, VRC01LS is to be stored in a freezer with a temperature range of -45^{0}C to -10^{0}C (-49^{0}F to 14^{0}F). Dispense one BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter item number 367294 for each syringe dispensed.

5.2.3 VRC07-523LS: VRC-HIVMAB075-00-AB

VRC07-523LS is a broadly neutralizing human MAb targeted against the HIV-1 CD4 binding site. It was developed by VRC/NIAID/NIH and produced in a Chinese Hamster Ovary (CHO) DG44 cell line in accordance with the cGMP regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Frederick, MD. VRC07-523LS is a sterile, aqueous buffered solution filled into 10 mL or 3 mL single-dose glass vials. Each vial contains a volume of 6.25 ± 0.1 mL or 2.25 ± 0.1 mL at a concentration of 100 ± 10 mg/mL in formulation buffer composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8. At the CRPMC, VRC07-523LS is to be stored in a freezer at -35^{0}C to -15^{0}C. In clinical site pharmacies, VRC07-523LS is to be stored in a freezer with a temperature range of -45^{0}C to -10^{0}C (-49^{0}F to 14^{0}F). Dispense one BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter item number 367294 for each syringe dispensed.

5.3 Thawing Instructions

Refer to the P1112 MOP for thawing instructions.

5.4 Study Product Preparation

Each dose of VRC01, VRC01LS, and VRC07-523LS must be ordered by prescription, and each prescription must include the infant's current weight. Upon receipt of each prescription, the site pharmacist prepares the 20 mg/kg dose or 40 mg/kg dose of VRC01 and 80mg or 100mg of VRC01LS or VRC07-523LS. Refer to the P1112 MOP for detailed instructions for preparation of VRC01, VRC01LS or VRC07-523LS.

5.5 Study Product Administration

VRC01, VRC01LS, and VRC07-523LS are administered subcutaneously, by slow push in the thigh using a BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter. After administration is completed, the sliding safety shield should be manually activated.

When administering VRC01, VRC01LS, or VRC07-523LS, the thigh where infant vaccines were administered within the preceding two weeks should be avoided, if possible, as should any site where the skin or tissue is irritated. For each subsequent dose

of VRC01, VRC01LS, or VRC07-523LS, alternate administration to the opposite thigh from the preceding dose, when feasible, and document whether the injection was given in the right or the left thigh on each occasion.

Refer to MOP Section 5.4 for more information on post-administration monitoring for injection site reactions.

5.6 Drug Supply, Distribution and Pharmacy

VRC01, VRC01LS, and VRC07-523LS are provided by the NIH VRC and available through the NIAID CRPMC. BD infusion 367294 BD Safety-Lok™ infusion set with a 25 G x 0.75-inch needle with 7 inches of tubing and a luer lock adapter is also available through the CRPMC. The site pharmacist can obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section titled *Study Product Management Responsibilities.*

The site pharmacists are required to maintain complete records of all study products received from the CRPMC and dispensed. All unused unopened vials of VRC01, VRC01LS, and VRC07-523LS must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are provided in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, in the section *Study Product Control*.

Partially used vials will not be administered to other participants or used for in vitro experimental studies. Any unused portion of entered vials, any BD infusions set, any used syringes and/or unused filled syringes should be disposed of in a biohazard bag and incinerated or autoclaved or as per approved local site policy. The site pharmacist at non-U.S. clinical research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.

6 PARTICIPANT MANAGEMENT

6.1 Toxicity Management

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, must be used and is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

Management of adverse experiences is done according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normals will be the institutional values. However, if a site does not have an age-specific normal range/value for a particular lab, the site should use the latest edition of the Harriet Lane Handbook for normal ranges/values and document this for

monitoring purposes. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2, or no further change expected.

This study involves a single or multiple dose(s) of VRC01, VRC01LS, or VRC07-523LS antibody. Safety data will be collected and reviewed by the study team on regular (twice a month) study conference calls.

Sites record and submit CRFs to the Data Management Center on all AEs from the time of the initial immunization as follows:

For Dose Groups 4 and 5 (both cohorts), all laboratory events required by the Schedules of Evaluations should be recorded on CRFs regardless of grade. See the CRF instructions for further details. For all other events:

- For Grade 1 reactogenicity AEs, and all Grade 2 AEs that study sites assess as possibly, probably or definitely related to the study product, and all AEs grade 3 or higher (regardless of their relationship to study product): CRFs should be submitted through the entire course of study.
- For all Grade 1 AEs (other than reactogenicity AEs), and Grade 2 AEs that sites assess as definitely not or probably not related to the study product: CRFs should only be submitted for these AEs occurring up to 30 days after the single immunization for Dose Groups 1 and 2 and Dose Groups 4 and 5 (Cohort 1) or 30 days after the final immunization for Dose Group 3 and Dose Groups 4 and 5 (Cohort 2). After that, sites will not be required to record/submit these AEs on CRFs. Note that sites should continue to report – beyond the time periods specified above – unresolved AEs that began during the reporting period.

The study Data Management Center report the data described above on a monthly basis for safety monitoring/review by the IMPAACT P1112 study team. All infants who receive an immunization will be followed for safety assessment for the full length of the study.

6.1.1 Toxicity Management Multiple Doses - Dose Groups 3, 4 (Cohort 2), and 5 (Cohort 2)

- After Grade 3 toxicities, subsequent doses should not be administered until after consultation with the protocol team AND improvement of the event to < Grade 3. After approval by the protocol team, subsequent doses may be administered. If the event recurs and is deemed related to study product, no further doses may be administered.
- After Grade 4 toxicities considered not related or probably not related, subsequent doses may be administered after improvement to < Grade 3 and consultation with the protocol team. If the event recurs, no further doses may be administered.
- After any Grade 4 toxicities considered possibly, probably, or definitely related to immunization, subsequent doses should not be administered.

Sites should evaluate all AEs to determine if the AE meets criteria for expedited AE reporting to DAIDS (Section 7).

6.2 Study Management Plan

Mothers may be consented prior to delivery or shortly after delivery of their infants, but enrollment of the mother-infant pair will not proceed until the infant eligibility criteria have been confirmed.

The Data Management Center will maintain a web page informing sites as to the availability of enrollment slots per dose group.

It is a study requirement that all enrolled infants receive the first immunization at less than 72 hours after birth (Dose Groups 1, 2, 4 [Cohort 1] and 5 [Cohort 1]) and by the end of Day 5 of life for Dose Group 3, 4 [Cohort 2] and 5 [Cohort 2]). If an infant is enrolled but there is a delay in administering the dose such that the infant is beyond the age cutoff, then the study immunization should not be administered and the infant should be withdrawn from the study. If an infant receives the dose after the designated age, it will be considered a protocol violation and the site must notify the team by email as soon as possible. These infants will still be followed for the length of the study (up to 48 weeks for Dose Groups 1 and 2 and 96 weeks for Dose Groups 3, 4 and 5).

If maternal sample #2 testing is negative and the infant has received any VRC01, VRC01LS, or VRC07-523LS immunizations, there will be no subsequent immunizations and the infant will be followed for safety as part of the study. If the infant has not received the VRC01, VRC01LS, or VRC07-523LS immunization, then the mother and infant will be removed from the study.

6.2.1 Dose Group Management

Dose Group 1

Under Version 1.0, Dose Group 1 closed to enrollment on 28 January 2016 after meeting full accrual.

Dose Group 2

On 2 February 2016, upon review of available date and documentation that all infants who had reached Day 28 (N=10) had passed the safety criteria, Dose Group 2 was opened to enrollment. On 2 November2016, Dose Group 2 was closed to enrollment after 14 mother-infant pairs had been enrolled.

Note. If 10 infants in Dose Groups 1 or 2 had completed Day 28 safety and PK assessments before all 13 had been enrolled in that dose group, the dose group could have been closed early (since assessments on 10 evaluable infants had been completed). However, as noted above, neither group closed early.

Dose Group 3

After the mini cohort of six infants in Dose Group 2 passed the Day 28 safety criteria, enrollment in Dose Group 3 began on 24 August 2016. On 1 February 2017, Dose Group 3 was closed to enrollment after 13 mother-infant pairs had been enrolled. After the first

infant enrolled into Dose Group 3 reaches the Week 24 milestone, the protocol team will review available safety data from adult and pediatric protocols of VRC01 (from P1112 database and safety reviews from other protocols); there will be no pause in either enrollment or administration of VRC01 during this review. Thereafter, all safety data will be reviewed every 6 months.

Dose Group 4

Upon release of Version 3.0, the protocol team reviewed available safety data from adult and pediatric protocols of VRC01 and VRC01LS (from P1112 database and safety reviews from other protocols) and Dose Group 3 accrual data. There was no safety signal, and the team determined that Dose Group 4, Cohort 1 could open to enrollment as soon as study documents were updated per protocol V3.0 and site approvals were obtained; see **Error! Reference source not found.**. This occurred on 21 June 2017. When the first six infants in Dose Group 4, Cohort 1 were immunized and completed 28 days of follow-up, the team reviewed all available safety data. This review of safety data revealed no signal, and enrollment into Dose Group 4, Cohort 2 was opened on 7 December 2017.

Dose Group 5

Upon release of Version 4.0, the protocol team will review available interim safety data from adult and pediatric protocols of VRC01, VRC01LS and VRC07-523LS (from P1112 database and safety reviews from other protocols). If there is no safety signal, the team will determine Dose Group 5, Cohort 1 may open to enrollment as soon as study documents are updated per protocol V4.0 and site approvals are obtained; see **Error! Reference source not found.**. When the first six infants in Dose Group 5, Cohort 1 have been immunized and completed 28 days of follow-up, the team will review interim safety and PK data. There will be no pause in Dose Group 5, Cohort 1 enrollment or immunization during this review. If review of safety and PK data reveals signal, the team will consult with the SMC. If review of safety and PK data reveals no signal, enrollment into Dose Group 5, Cohort 2 will be opened.

6.2.2 Study Pauses

Safety assessments are a continuous, real-time process. That is, the team reviews all AEs on conference calls twice a month while the study is enrolling. If study pause criteria as defined in Section 8.5.1 are met, enrollment and immunizations will be paused for SMC review. If the SMC decides that further enrollment and immunizations cannot be continued, the study will stop accrual but continue safety follow-up of all enrolled infants.

6.3 Criteria for Treatment Pause for Individual Participants

For Dose Groups 1 and 2, who received a single dose of VRC01, there were no criteria to pause the treatment for individual participants. For Dose Group 3 and Cohort 2 of Dose Groups 4 and 5, the decision to hold administration of subsequent doses may be at the discretion of the site clinician in consultation with the P1112 study team.

6.4 Criteria for Treatment Discontinuation

For Dose Groups 1 and 2, who received a single dose of VRC01, there were no criteria to discontinue the treatment for individual participants. For Dose Group 3 and Cohort 2 of Dose Groups 4 and 5, refer to Toxicity Management (Section 6.1.1) for criteria for treatment discontinuation. In addition, treatment discontinuation will occur if an infant is determined to be HIV-infected before he or she is 12 weeks old (see Section 6.6).

6.5 Criteria for Study Discontinuation

- Infant does not receive the first VRC01, VRC01LS, or VRC07-523LS immunization.
- The mother or legal guardian refuses infant follow-up evaluations.
- The investigator determines that further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The study may be discontinued by the NIH, Office of Human Research Protection (OHRP), U.S. Food, and Drug Administration (FDA), the IMPAACT Network, IRB/EC or local government regulatory agency.

6.6 If an Infant is Determined to be HIV-Infected

If an infant enrolled in P1112 has a positive HIV-1 NAT result at any time point, sites should notify the Protocol Team at impaact.teamP1112@fstrf.org as soon as possible. Infants in Dose Group 3 with a positive HIV-1 NAT will not continue to receive VRC01 and will continue to be followed as per APPENDIX ID: Schedule of Evaluations (Dose Group 3) per the columns "Observation Period: Every 12 weeks after BF Cessation, HIV Diagnosis, and/or at Weeks 84 and 96." Likewise, an infant identified as HIV-infected before he or she is 12 weeks old in Dose Groups 4 and 5 Cohort 2 would not receive a second dose of VRC01LS or VRC07-523LS and would continue to be followed per APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding) or APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding), respectively, per the column "Observation Following Dosing Period." In addition, an infant with a positive HIV-1 NAT result in any Dose Group will undergo additional testing to confirm the infection and to collect blood samples for viral quantification and evaluation. The additional evaluations are listed in APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]

7 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) Manual,

which is available on the Regulatory Support Center (RSC) website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

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

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, are used for this study.

The study agent for which expedited reporting is required are: VRC01, VRC01LS, and VRC07-523LS.

In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: immune complex disease.

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017, must be used with the exception of infant pain assessment. For pain assessment, a description of the pain grading to be used for IMPAACT P1112 may be found in the MOP. The DAIDS AE Grading Table is available on the RSC website at. https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

7.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is as per the EAE manual, i.e., from enrollment of a trial participant to the end of trial follow-up for that participant.

After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is an open label, multicenter, Phase 1 study to determine the safety and pharmacokinetic parameters of three subcutaneous, potent anti-HIV neutralizing monoclonal antibodies, VRC01, VRC01LS, and VRC07-523LS, in order to select a safe and PK-acceptable dose to be used in future efficacy clinical trials.

The study population is the newborns of HIV-1-infected women, who are ≥ 36 weeks gestation and are at increased risk for perinatal or post-natal HIV transmission (see Section 4.3.5 for definition of increased risk). The women do not receive study immunizations. After delivery, the mothers and their exposed neonates are checked for eligibility (see Section 4 for eligibility requirements for both mother and baby). If eligible, both the mothers and infants are enrolled. Only the infant is immunized with a subcutaneous injection(s) of VRC01, VRC01LS, or VRC07-523LS. Only the infants are assessed for safety and followed on the study.

The study will enroll 79 infants, with the aim of having approximately 62 evaluable infants: 10 of 13 (77%) each in Dose Groups 1-3 and 8 of 10 (80%) per cohort in Dose Groups 4 and 5. Evaluable infants must have received the required immunization(s) and have completed the required follow-up for the primary safety outcome measure for the relevant group (Day 28 evaluations for Dose Groups 1 and 2 and Cohort 1 in Dose Groups 4 and 5; Week 24 evaluations for Dose Group 3; and Week 16 evaluations for Cohort 2 in Dose Groups 4 and 5). .

Safety will be monitored in real time throughout the study. If none of the triggers listed in section 8.5.1 are met, the accrual and immunizations will proceed continuously, with no pause, until enrollment in the dose group has been completed. This will ensure that the study will remain open and all eligible infants will be enrolled and immunized in a timely manner.

If any safety triggers are met, subsequent enrollment and immunizations will be paused until the safety data are reviewed by the Study Monitoring Committee (SMC) (see Section 8.5.1) and they will advise the team on how to proceed.

Dose Groups 1-4 (Protocol Versions 1.0 - 3.0):

1) Initially, only Dose Group 1 was open to enrollment. Dose Group 1 accrued 13 women and their infants to provide at least 10 infants who received the immunization and completed study evaluations.

The infants received a single SC dose of 20 mg/kg of VRC01, as soon as possible after birth, and in all cases, less than 72 hours after birth.

Prior to opening Dose Group 2, the safety data through Day 28 after immunization for the first 10 infants immunized in Dose Group 1 were evaluated (see Section 8.5.1). After these infants had completed 28 days of follow up and had passed the safety criteria described in Section 8.5.1, AND after the enrollment in Dose Group 1 has been completed, AND the adult cohort using the dose of 40 mg/kg of VRC01 had been fully enrolled and all participants in it had completed day 28 evaluation, then

2) Dose Group 2 was opened and began accrual of a new set of 13 women and their infants, to provide at least 10 infants who received the immunization and study evaluations.

The infants in Dose Group 2 received a single SC dose of 40 mg/kg of VRC01, ideally as soon as possible after birth, but in all cases, less than 72 hours after birth.

Prior to opening Dose Group 3, the safety data through Day 28 after immunization for the first 6 infants immunized in Dose Group 2 were evaluated (see Section 8.5.1), After six Dose Group 2 infants completed 28 days of follow up and passed the safety criteria described in section 8.5.1, then

3) Dose Group 3 began accruing, concurrently with the remaining Dose Group 2 participants, a new set of 13 women and their infants, to provide at least 10 infants who received the immunizations and study evaluations.

The infants in Dose Group 3 received a SC dose of 40 mg/kg of VRC01, ideally as soon as possible after birth, but in all cases, not later than the 5th day of life, then doses of 20 mg/kg SC monthly for at least 24 weeks and no more than 72 weeks while breastfeeding.

Prior to opening Dose Group 4, all available safety data were evaluated (see Section 8.5.1).

4) Dose Group 4 accrued 21 women and their infants to two cohorts, to provide at least 8 infants in each cohort who will receive the immunizations and study evaluations. Enrollment into the two Dose Group 4 cohorts occurred sequentially (see **Error! Reference source not found.**, Section 3, and Section 6.2.1). An additional mother-infant pair was allowed to enroll because they had completed the screening when accrual limit was reached.

Infants in Dose Group 4 received a SC dose of VRC01LS as follows:

- Cohort 1 (non-breastfeeding): a single dose ideally as soon as possible after birth and within the first 72 hours of life.
- Cohort 2 (breastfeeding): a single dose ideally as soon as possible after birth, but in all cases, not later than the 5th day of life. A second dose of VRC01LS was administered at Week 12 if the infant has not achieved complete cessation of breastfeeding.

5) Dose Group 5 will accrue 20 women and their infants to two cohorts, to provide at least 8 infants in each cohort who will receive the immunizations and study evaluations. Enrollment into the two Dose Group 5 cohorts will occur sequentially (see **Error! Reference source not found.**, Section 3, and Section 6.2.1).

The infants in Dose Group 5 will receive a SC dose of VRC07-523LS as follows:

- Cohort 1 (non-breastfeeding): a single dose ideally as soon as possible after birth and within the first 72 hours of life.
- Cohort 2 (breastfeeding): a single dose ideally as soon as possible after birth, but in all cases, not later than the 5th day of life. A second dose of VRC07-523LS will be administered at Week 12 if the infant has not achieved complete cessation of breastfeeding.

Serious toxicity is not anticipated. However, safety will be monitored carefully, given that: a) study participants are newborns, b) they are born to women at increased risk for intrapartum HIV transmission and c) safety must be assessed before opening new cohorts.

8.2 Outcome Measures

All outcome measures apply to infants only.

8.2.1 Primary Outcome Measures
8.2.1.1 Safety
Through Day 28 for Dose Groups 1, 2, Cohort 1 in Dose Groups 4 and 5; Week 24 for Dose Group 3; and Week 16 for Cohort 2 in Dose Groups 4 and 5: • Death • Grade 3 or higher adverse events • Vaccine-related Grade 3 or higher adverse events • HIV infection
8.2.1.2 Pharmacologic
(See Section 9 for PK targets and parameters)
8.2.2 Secondary Outcome Measures
From the end of the observation period in the primary outcome measure through the end of follow-up: • Death • Grade 3 or higher adverse events • Vaccine-related Grade 3 or higher adverse events • HIV infection From vaccine administration to end of follow-up: • Development of anti-VRC01 antibodies (yes/no) • Development of anti-VRC01LS antibodies (yes/no) • Development of anti-VRC07-523LS antibodies (yes/no)

8.2.3 Other Outcome Measures

From vaccine administration to end of follow-up:

- The amount of VRC01/ VRC01LS/ VRC07-523LS in oral secretions.

Measured in infants determined to be HIV-infected from vaccine administration to end of follow-up:

- The neutralization sensitivity of the infant and maternal virus
- The amount of HIV-1 provirus in PBMC and plasma HIV-1 RNA (measured in copies/mL)
- Serum neutralizing titer

8.3 Randomization and Stratification

There will be no randomization or stratification of participants.

8.4 Sample Size and Accrual

Both mothers and infants are enrolled in the study, but only infants receive the VRC01, VRC01LS, or VRC07-523LS immunization(s) and are followed on the study. The study will enroll 79 mother-infant pairs: 13 in each of Dose Groups 1-3 and 10 in each cohort in Dose Groups 4 and 5, with the aim of having 10 evaluable infants in each Dose Group 1-3 and 8 in each cohort in Dose Groups 4 and 5. Evaluable infants must have received the required study immunization(s) and have completed follow-up for the primary safety outcome measure (Day 28 evaluations for Dose Groups 1, 2 and Cohort 1 from Dose Groups 4 and 5; Week 24 evaluations for Dose Group 3; and Week 16 evaluations for Cohort 2 in Dose Groups 4 and 5). This assumes a maximum missing data rate of 23% in Dose Groups 1-3 and 20% in Dose Groups 4 and 5. Non-evaluability could be due to losses to follow-up, missed visits or problems with laboratory samples. Note that infants who do not receive the first immunization will be replaced.

Safety data will be assessed as described in Section 8.5.1. If any of the safety criteria are triggered, enrollment and further immunizations will be temporarily stopped until the SMC reviews the data and advises the protocol team on how to proceed. Section 8.5.1 discusses the error probabilities associated with the safety criteria and Section 8.6.1.2 discusses the precision that the sample size will provide for estimating AE rates and PK success rates. The sample size is based on target precision for the estimation of key safety and PK parameters. The calculations are located in Section 8.6.1.2 for ease of discussion.

We had anticipated that all participants in Dose Groups 1 and 2 would be enrolled within 2 years after Version 1.0 was opened to accrual. In fact, enrollment into both dose groups was more rapid than anticipated: taking less than 9 months to reach full accrual of each dose group. Likewise, Dose Group 3 reached full accrual within approximately 4 months. We had anticipated that Dose Group 4 would be fully enrolled within 1 year of that dose group being opened to accrual. However, this group also reached full accrual much faster than expected, within 6 months. It is anticipated that both cohorts in Dose Group 5 will be enrolled within 1 year after Version 4.0 opens to accrual.

8.5 Monitoring

The safety and tolerability of the VRC01, VRC01LS, and VRC07-523LS monoclonal antibodies are monitored by means of adverse events and toxicity reports presenting laboratory and clinical data collected throughout follow-up for the infants enrolled. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. The accrual and toxicity reports compiled by the Data Management Center are discussed by the protocol team, including the medical officers and the representatives of the VRC, on regularly scheduled conference calls. After the first infant enrolled into Dose Group 3 reached the Week 24 milestone, the team began reviews of available safety data of adult and pediatric protocols of VRC01 (from P1112 database and most recent safety reports available from the other protocols) every 6 months. These reviews will continue and include infants in Dose Groups 4 and 5 and data on VRC01LS and VRC07-523LS. There will be no pause in either enrollment or in administration of immunizations during these reviews.

The attribution of relationship of serious adverse events to study product is discussed on the team calls and the relationship determined by the study team, taking into account the site and the Medical Officer's assessment of the event. Interpretation of VRC01, VRC01LS, or VRC07-523LS relationship to adverse events is based on the type of event, the relationship of the event to the time of immunization, the known biology of the monoclonal antibody and the investigators' medical judgment. Gradation of relationship uses the following terminology: "not related," "probably not related," "possibly related," "probably related," or "definitely related."

In addition to regularly scheduled toxicity reviews by the protocol team, the study is monitored by an independent Study Monitoring Committee (SMC) according to IMPAACT Standard Operation Procedure (SOP) on Study Data and Safety Monitoring. The committee meets via conference call to review relevant data as described in the sections below.

8.5.1 Stopping Rules for Safety

Stopping rules have been and will be applied in order to protect the study participants from unnecessary exposure to the monoclonal antibody, should the safety profile prove unacceptable in this population. The evaluation of safety for the purpose of applying these guidelines will be based on data:

- through the first 28 days after immunization for Dose Groups 1, 2, and Cohort 1 of Dose Groups 4 and 5;
- on data through the first 8 weeks after the first immunization for Dose Group 3, which reflects the time point when this group would have received more immunizations than Dose Groups 1 and 2;
- on data through the first 28 days after the second immunization in Dose Groups 4 and 5, Cohort 2 (Week 16).

Due to the fact that infant hyperbilirubinemia is common in the first four to five weeks of life, especially during breastfeeding, and that Grade 3 neutropenia and anemia are common in infants on ARVs, these toxicities will not be counted in the safety evaluation algorithm presented below.

NOTE: If at any time during the study the triggers below are met, the study will be paused for evaluation, as described below and an SMC review performed within 7 days. The SMC will decide what additional data they would like to see and advise the study team on how to proceed.

To assess the early safety of the initial doses of VRC01, VRC01LS, and VRC07-523LS monoclonal antibodies, data from the first 6 infants immunized and followed through day 28 in Dose Groups 1, 2, and Cohort 1 of Dose Groups 4 and 5 will be examined. Similarly, the early safety of the multiple dose regimen of VRC01 monoclonal antibody in Dose Group 3 will be assessed based on data from the first 6 infants immunized and followed through Week 8. The early safety of the multiple-dose regimen of VRC01LS in Dose Group 4 (Cohort 2) and of VRC07-523LS in Dose Group 5 (Cohort 2) will be assessed based on data from the first 6 infants who have reached 28 days after the second dose (Week 16).

- If any of the infants dies or has a life-threatening adverse event or any Grade 4 event that is possibly, probably or definitely attributable to the VRC01, VRC01LS, or VRC07-523LS immunization, or
- If two or more of the six infants have a Grade ≥ 3 adverse event at least possibly related to the VRC01, VRC01LS, or VRC07-523LS immunization (excluding Grade 3 neutropenia and anemia, and hyperbilirubinemia), then future enrollment and immunizations will be stopped.

If these triggers are met, the team will confer with the SMC, which will judge whether enrollment and immunizations can be continued. Note: for deaths and grade 4 life-threatening events that are assessed by the protocol team as probably not related, immunizations will continue. However, an SMC review to determine if it is safe to continue immunizations must occur within 7 days of the team's awareness of the event.

If the ongoing monitoring process reveals that a dose group has already failed the safety criteria, then further enrollment and immunizations will be suspended, and an SMC review will be performed immediately (within seven days).

If the SMC decides that further enrollment and immunizations cannot be continued, the study will stop accrual but continue safety follow-up of all enrolled infants.

Subsequent to the initial safety evaluation of each dose group, if the toxicity among the additional infants who have been immunized while waiting for the first 6 to reach the evaluation time point would increase the rate of Grade ≥ 3 adverse events at least possibly related to the VRC01 VRC01LS, or VRC07-523LS immunization (excluding

Grade 3 neutropenia and anemia) to over 30%, then future enrollment and immunizations will be paused. For example, if only one of the first 6 infants enrolled had a Grade ≥ 3 adverse event at least possibly related to the VRC01, VRC01LS, or VRC07-523LS immunization, this is not enough to trigger the stopping rule. But if the next two infants each have a Grade ≥ 3 adverse event at least possibly related to the VRC01, VRC01LS, or VRC07-523LS immunization, this would represent a 37.5% (3/8) rate of such events, and because this is higher than 30%, the study will be paused for safety. The team will confer with the SMC, which will judge whether enrollment and immunizations can continue.

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

1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current VRC01, VRC01LS, or VRC07-523LS dose, the sample data may pass the safety guidelines;
2) In a group where the true rate of toxicity is low enough that further exposure to the current VRC01, VRC01LS, or VRC07-523LS dose 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 rates of "true toxicity" which could occur, if the study medication were used extensively among the participant population at the dose levels under question. The hypothetical situations presented in Table 6 range from conditions under which a given dosing regimen 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, we assume that a sample of six participants is drawn from the participant population and that the safety guidelines, summarized above, are followed.

Please note that the probabilities presented below would not apply if data from more than six infants were used.

Table 6: Probability of Meeting Safety Review Trigger Under Potential Rates of True Toxicity (N=6)

True Toxicity Rates		Probability of Meeting Safety Review Trigger
Grade ≥ 3 adverse events at least possibly related to the VRC01, VRC01LS, or VRC07-523LS immunization, excluding Grade 4 events probably or definitely attributable to the study immunizationVRC01 or VRC01LS immunization	Life-Threatening adverse event or Grade 4 events probably or definitely attributable to the VRC01, VRC01LS or VRC07-523LS immunization	
.50	.00	.89
.50	.05	.94
.50	.25	1.00
.25	.00	.47
.25	.05	.63
.25	.25	.83
.05	.00	.03
.05	.05	.29
.05	.25	.83
.00	.05	.26
.00	.25	.82

For example, Table 6 shows that there is a 94% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life-threatening toxicity is 50%. Assuming that a dosing regimen associated with this extent of severe toxicity would be unacceptable, the 6% chance of passing the safety criteria under these conditions would represent sampling error. Note that the true rate of Grade 3 events would have to be quite high to provide a strong probability of pausing the study at a dose where there is no life-threatening toxicity and no Grade 4 events at least probably attributable to VRC01, VRC01LS, or VRC07-523LS. 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 an experimental dose, which may be either toxic or subtherapeutic.

8.5.2 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. If less than one-third of eligible sites have registered after the protocol has been approved for 6 months, the team will re-assess the feasibility of the protocol and the reasons why sites have not registered and may amend the protocol accordingly. Once one third of eligible sites have registered, the team will assess accrual on a quarterly

basis. If the protocol has not accrued half its participants within 6 months of opening, the team will identify problems in accrual and possibly amend the protocol accordingly.

A full monitoring plan was developed before the study opened to accrual.

8.6 Analyses

8.6.1 Primary Analysis

8.6.1.1 Safety

Each participant's safety data will be summarized as: the worst grade of adverse event experienced during the time period of observation for primary objectives and the worst grade of adverse event judged to be at least possibly related to the immunization(s) during the same time interval. Descriptive analyses will consist of frequency distributions of these safety outcomes, broken down by dose group/Cohort. All available safety data will be used. All infants who receive an initial VRC01, VRC01LS, or VRC07-523LS immunization will be included in all analyses regardless of whether they receive ARV prophylaxis or are HIV-infected.

With the small sample size used in this study, there will be insufficient statistical power for a formal test of differences between dose groups with respect to safety. With insufficient power, a finding of no significant difference would not provide acceptable evidence of no adverse dose effect. Thus, estimates of Grade 3 or higher toxicity rates will be computed separately for each dose group and bounded by 90% confidence intervals (CI), reflecting the precision of the estimates. This will provide 95% assurance that the true rate of severe adverse events is not higher than the upper limits of the CI around the proportion of participants with grade 3 or higher events in the study sample. Because of the small sample sizes and the anticipated low toxicity rates, these intervals will be calculated using exact methods.

8.6.1.2 Precision of Estimates

The following table (Table 7) illustrates the confidence intervals for a range of hypothetical proportions of adverse events. This table shows that a sample finding of no grade 3 or higher adverse events in a total sample of 10 participants would provide 95% confidence that the probability in the population from which the sample was drawn is no greater than 26%.

Table 7: Exact 90% Confidence Intervals around Potential Proportions of Participants Exhibiting Grade 3 or Higher Adverse Events (N=8, 10 and 13)

Sample Toxicity Rates	90% Confidence Limits	
	Lower	Upper
0% (0/8)	0%	31%
12.5% (1/8)	0.6%	47%
25% (2/8)	5%	60%
37.5% (3/8)	11%	71%
50% (4/8)	19%	81%
0% (0/10)	0%	26%
10% (1/10)	0.5%	40%
20% (2/10)	4%	51%
30% (3/10)	9%	61%
40% (4/10)	15%	70%
0% (0/13)	0%	21%
7.7%(1/13)	0.4%	32%
15.4%(2/13)	3%	41%
23.1%(3/13)	7%	49%
30.8 (4/13)	11%	57%

The proportions of infants in each dose group with adequate PK levels (see Section 9 for definition) and other PK results will be presented in a separate PK report,
The table below (Table 8) presents exact 90% confidence intervals around various potential rates of PK success which might be observed in a total sample of 10 participants. This table shows that a sample finding of PK success in 6 of 10 participants would provide 95% confidence that the rate in the population from which the sample was drawn is no lower than 30%.

Table 8: Exact 90% Confidence Intervals around Potential Rates of PK Success (N=8, 10 and 13)

Sample Rates of PK Success	90% Confidence Limits	
	Lower	Upper
62.5% (5/8)	29%	89%
75% (6/8)	40%	95%
87.5% (7/8)	53%	99%
100% (8/8)	69%	100%
50% (5/10)	22%	78%
60% (6/10)	30%	85%
70% (7/10)	39%	91%
80% (8/10)	49%	96%
90% (9/10)	61%	99.5%
100% (10/10)	74%	100%
38.5% (5/13)	17%	65%
46.2% (6/13)	22%	71%
53.8% (7/13)	29%	78%
61.5% (8/13)	35%	83%
69.2% (9/13)	43%	89%
76.9% (10/13)	51%	93%
84.6% (11/13)	59%	97%
92.3% (12/13)	68%	99.6%
100% (13/13)	79%	100%

Should this occur, the number of infants in each dose group who become HIV-infected will be reported. The immunization is not expected to increase the rate of HIV infection. However, since these infants are born to women at increased risk of intrapartum HIV transmission, it is possible that a small percentage might become HIV-infected, and any infections will be brought to the attention of the SMC.

8.7 Secondary Analyses

Adverse events occurring after the initial review period and throughout the remainder of follow-up will be summarized in the same way as for the primary safety objective.

The number of infants in each dose group who develop anti-VRC01, VRC01LS, or VRC07-523LS antibodies will be summarized descriptively.

8.8 Exploratory Analyses

The VRC01, VRC01LS, and VRC07-523LS antibody levels in oral secretions will be summarized at each time point by calculating 95% CI around the mean or median, depending on whether the data are normally distributed.

Exploratory analyses will be performed in the infants who are determined to be HIV-infected. The neutralization sensitivity of the infant and maternal virus will be documented descriptively. In addition, the changes from baseline to subsequent time points in the amount of HIV provirus in PBMC and plasma HIV-1 RNA (measured in copies/mL) over time will be presented. HIV serum neutralization titer before and after the study immunization will be compared.

9 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

9.1.1 To determine pharmacokinetic profile of single dose, subcutaneous VRC01 in HIV-1-exposed infants (Dose Groups 1 and 2).

9.1.2 To determine pharmacokinetic profile of monthly subcutaneous VRC01 in HIV-1-exposed infants (Dose Group 3).

9.1.3 To determine pharmacokinetic profile of one or two subcutaneous doses of VRC01LS (Dose Group 4)

9.1.4 To determine pharmacokinetic profile of one or two subcutaneous doses of VRC07-523LS (Dose Group 5)

9.2 Primary and Secondary Data

Demographic data (gender, ethnicity, weight, length, birth weight, gestational age at birth), dose group, VRC01, VRC01LS, or VRC07-523LS dose date, time, dose amount, administration location and sample collection times will be obtained. Plasma VRC01 (Dose Groups 1-3), VRC01LS (Dose Group 4), or VRC07-523LS (Dose Group 5) concentrations will be measured:

- Dose Groups 1 and 2: before dosing and on days 1, 3, 7, 14 and 28; then at Weeks 8, 16, 24, 48, and at HIV confirmation visits will be measured.
- Dose Group 3: before dosing (on days 0 and 28 and weeks 16, 20, 24); for breastfeeding, HIV-exposed uninfected infants after Week 24: 36, 48, 60, 72, and early D/C visit.); on days 1 and 14; and during the observation period: at the first visit after complete cessation of breastfeeding or HIV diagnosis, every 12 weeks thereafter and then at Weeks 84 and 96.
- Dose Group 4, Cohort 1: before dosing (Day 0) on Day 1, 14 and 28, and Week 8, 12, 24, 36, 48, 60, 72, 84 and 96. Cohort 2 infants will have these same visits and for those in Cohort 2 who receive a second VRC01LS dose at Week 12 due to continuing

to breastfeed, the Week 12 sample will be collected prior to their second dose and additional samples will be collected at Weeks 14 and 16.

- Dose Group 5, Cohort 1: before dosing (Day 0) on Day 1, 3, 7, 14 and 28, and Week 8, 12, 24, 36, 48, 60, 72, 84 and 96. Cohort 2 infants will have these same visits and for those in Cohort 2, infants who receive a second VRC07-523LS dose at Week 12 due to continuing to breastfeed, the Week 12 sample will be collected prior to their second dose and additional samples will be collected at Weeks 14 and 16.

Assay Site: Plasma pharmacokinetic samples collected will be sent per the study-specific Laboratory Processing Chart (LPC) and will be assayed for serum/plasma concentration of VRC01, VRC01LS, or VRC07-523LS.

Methods to be used: All assay methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions. The assays will be performed using immune based method.

Reporting of Assay Data: At a minimum, assays will be conducted in batch after receipt of all samples through Week 8 for a particular participant in Dose Groups 1, 2, and 3 and through Week 12 for Dose Groups 4 and 5. Samples will be assayed within 60 days of the laboratory receiving the final Week 8 or Week 12 samples for Dose Groups 1-3 and 4-5, respectively. Samples received during the conduct of the study may be assayed prior to the final shipment. For Dose Group 5, Cohort 1, all samples collected to date will be assayed when the first six participants are enrolled. The designated lab will run the assays for VRC01, VRC01LS, and VRC07-523LS levels once per week as the trial begins and anti-drug antibody assays once per month. All PK samples will be registered in the Lab Data Management System (LDMS) database.

For the purposes of reporting initial PK results to clinicaltrials.gov, the $AUC_{0\text{-}\tau\alpha\upsilon}$ and concentration at the end of the first dose interval, $C_{\tau\alpha\upsilon}$, time will be provided. For Dose Groups 1-3 these are C_{28D} and $AUC_{0\text{-}28D}$ while for Dose Groups 4 and 5 they are C_{84D} and $AUC_{0\text{-}84D}$.

9.3 Study Design, Modeling and Data Analysis

Pharmacokinetic blood samples will be collected as noted in Section 9.2 and Schedule of Evaluation Appendices: APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2), APPENDIX ID: Schedule of Evaluations (Dose Group 3), APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding) APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding), APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding) and APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding). The samples will be 1-2 mL whole blood to yield 0.4-1.0 mL plasma. Sample volume will be dependent on infant weight (See APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2)).

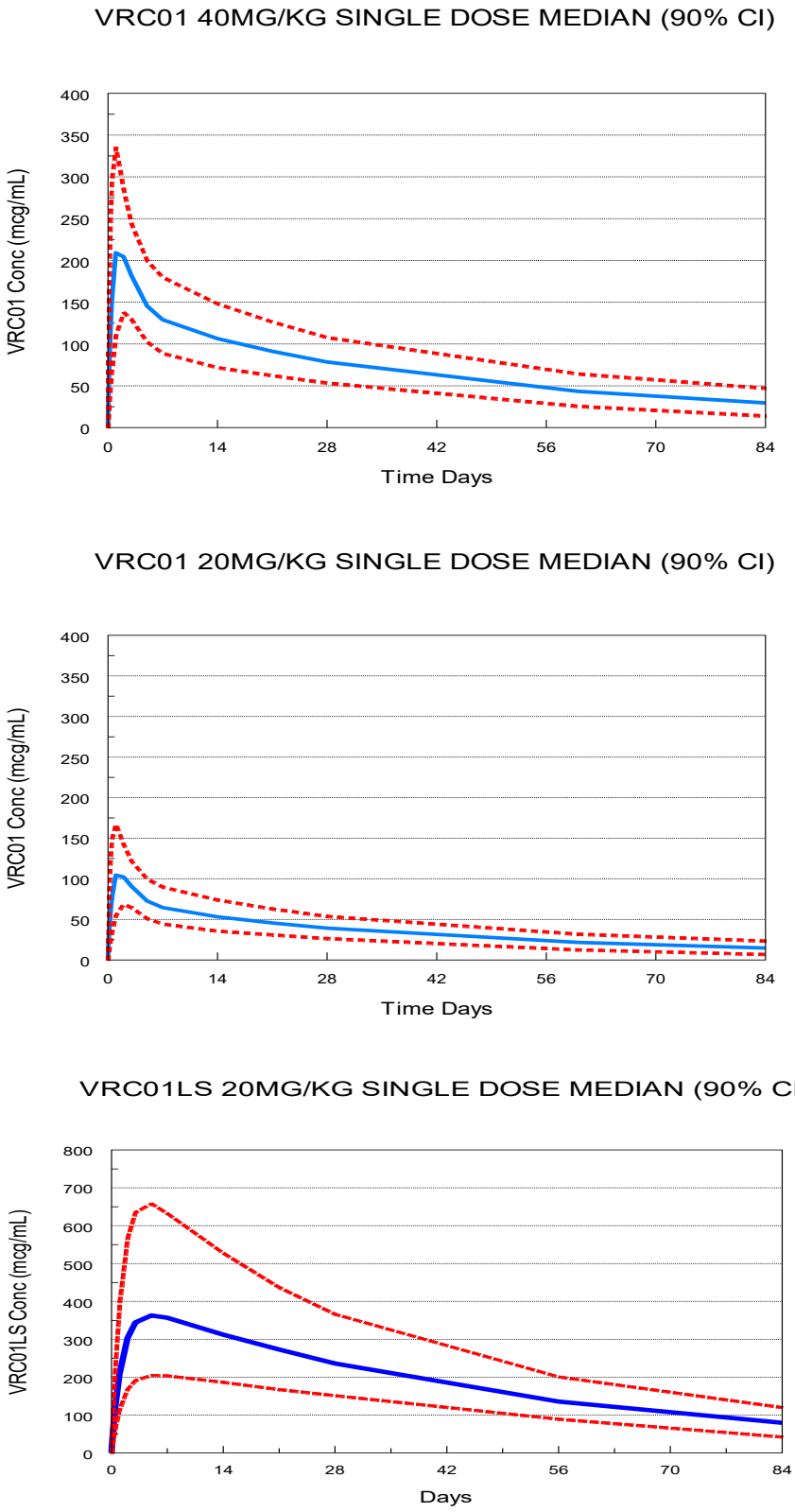
VRC01, VRC01LS, and VRC07-523LS concentrations will be presented by study day, dose group and dose number. The frequency of achieving Day 28 concentrations greater

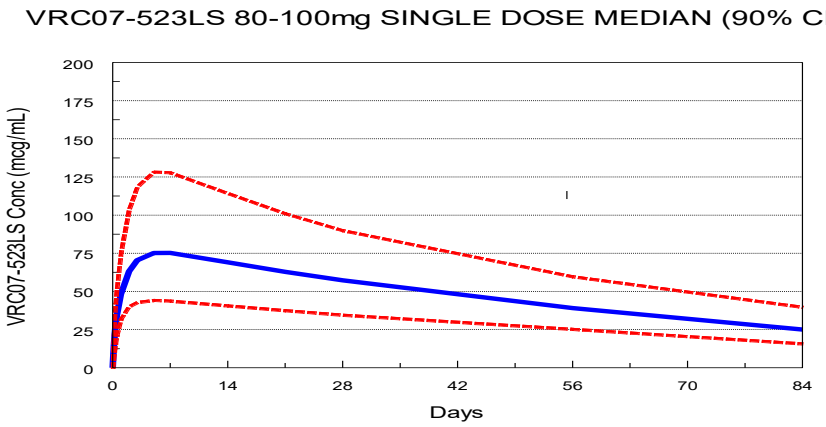
than 50 μg/mL will be calculated. For Dose Group 4, the frequency of maintaining VRC01LS concentrations >50 μg/mL at Week 12 will be determined; likewise, for Dose Group 5, the frequency of maintaining VRC07-523LS concentrations >15 μg/mL at Week 12 will be determined. The median, mean and standard deviation of concentrations will be calculated from evaluable samples by each dose level. Evaluable samples are defined as samples with volume and integrity to generate accurate concentration results and their associated accurate dosing and sample times data. It is expected that VRC01 pharmacokinetic parameters will have similar variability as those seen in infants with RSV monoclonal antibodies by Meissner et al [50]; CV=34% for apparent clearance (CL/F) and CV=33% for apparent volume (Vd/F). With 10 completed participants planned from each dose group, it is expected that the 95% CIs for primary PK parameters for each dose group will be encompass a range of less than $\pm$ 25% of the point estimate values.

While it is expected that the CL/F for VRC01LS will be substantially lower than for VRC01, we expect the overall variability (CV) for PK parameters to be similar. Thus, the proposed study will generate a similar confidence interval in the VRC01LS pharmacokinetic parameters. Recent findings from VRC605 found the CV for VRC07-523LS AUC to be < 25% for dosing groups receiving between 5-40 mg/kg and including following subcutaneous administration [62]. Based on these low variability values, the expected 95% CI will be tighter than those originally predicted for VRC01 based on RSV variability.

The observed VRC01, VRC01LS and VRC07-523LS concentrations will be compared to those seen in adults. Specifically, the geometric mean and 90% confidence interval for the Day 28 (VRC01) and Week 12 (VRC01LS and VRC07-523LS) concentrations will be generated. Based on RSV mAb pharmacokinetics in infants, it is expected that VRC01 Day 28 concentrations will fall within the range of 20-70 μg/mL for the 20mg/kg dose (Dose Group 1) and 65-115 μg/mL for the 40mg/kg dose (Dose Group 2). The predicted Week 12 VRC01LS and VRC07-523LS concentrations following 80-100mg SC are expected to be between 40-120 μg/mL and 15-40 μg/mL, respectively. These are lower than the predicted levels in adults at Week 12 in part due to a "diluting" effect from the large increase in body weight expected in the infants during the first 12 weeks of life. The predicted concentrations of VRC01 at 40 mg/kg and 20 mg/kg, VRC01LS at 20 mg/kg and VRC07-523LS at 80-100 mg are in Figure 7.

Figure 7: Predicted VRC01, VRC01LS, and VRC07-523LS Concentrations





Individual Participant Pharmacokinetic Analysis

A non-compartmental pharmacokinetic analysis will be performed using WinNonlin or a similar program on the VRC01, VRC01LS, and VRC07-523LS concentration data generated from each participant in Groups 1, 2, 4, and 5. Calculated pharmacokinetic parameters will include: area-under-the-curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), apparent clearance (CL/F), apparent volume of distribution (Vdz/F) and terminal elimination rate constant (λz) and the terminal half-life. C_{max} and T_{max} will be taken directly from the observed concentration-time data. The terminal slope, λz, will be determined from log- linear portion of the curve and the half-life ($T_{1/2}$) calculated as $0.693/\lambda z$. $AUC_{0\text{-last}}$ will be determined using the linear trapezoidal method. If the final samples have measurable VRC01, VRC01LS, or VRC07-523LS concentrations, the remaining AUC after the final concentration will be estimated as $C_{last}/\lambda z$. For the purposes of determining Vdz/F, it will be calculated as the ratio of (CL/F) / λz. Data will be summarized based by each dose group and overall for CL/F, Vdz/F and $T_{1/2}$. The potential for non-linearity pharmacokinetics between Dose Groups 1 and 2 will be determined by comparing the dose-adjusted ratios for C_{max} and AUC between study dose groups. Additional compartmental analysis will be performed as warranted by the data from Dose Groups 1, 2, 4, and 5. For Dose Group 3, no intensive PK data is being collected; thus, the individual participant specific pharmacokinetic analysis will be limited to estimation of potential accumulation or decline in pre-dose concentrations with repeated dosing. For these calculations, the Day 28 pre-dose VRC01 concentration will serve as the reference with the pre-dose concentrations collected at later weeks divided by the Day 28 pre-dose VRC01 concentration. Both raw and dose adjusted (to 20mg/kg) concentration ratios will be calculated.

Interim Pharmacokinetic Analyses

Incremental pharmacokinetic analyses will be performed as data from Dose Groups 1-3 through Week 8 and through Week 12 for Dose Groups 4-5 becomes available. VRC01, VRC01LS and VRC07-523LS concentration data generated will be summarized and made available to the study team. Given the long half-lives of VRC01LS and to a lesser

degree VRC07-523LS, a more limited pharmacokinetic analysis will be performed on preliminary data. The focus of the Dose Groups 4 and 5 analyses will be on the Week 12 VRC01LS and VRC07-523LS concentrations. The purpose of these incremental analyses is to ensure that results are within the range of the expected targets. If these interim results demonstrate significant inter-patient variability, the team will determine if protocol modifications are required.

Population Pharmacokinetic Analysis

Population pharmacokinetic analyses will be performed on the VRC01 pharmacokinetic data from P1112 Dose Groups 1-3 to determine compartmental PK parameters with the program NONMEM. Based on VRC01 PK studies in adults and prior pharmacokinetic studies of antibodies in infants, a two-compartment model will be used to characterize the P1112 VRC01 PK data. Both zero and first order absorption model will be assessed to determine the structural pharmacokinetic model. Additional drug absorption models will be evaluated if dictated by the data. The population analysis will generate estimates for initial and final apparent volumes of distribution (V1/F and V2/F), inter-compartmental clearance (Q/F), CL/F and absorption rate parameters either KA or the zero-order rate constant (R1). Given the small participant numbers, the population pharmacokinetic analysis will not include an exploratory covariate analysis to assess clinical factors as fixed effects associated with VRC01 pharmacokinetic parameters with the exception of dose level (20mg/kg vs 40mg/kg) and repeat dosing as fixed effects on F, KA/R1, CL and V1/V2.

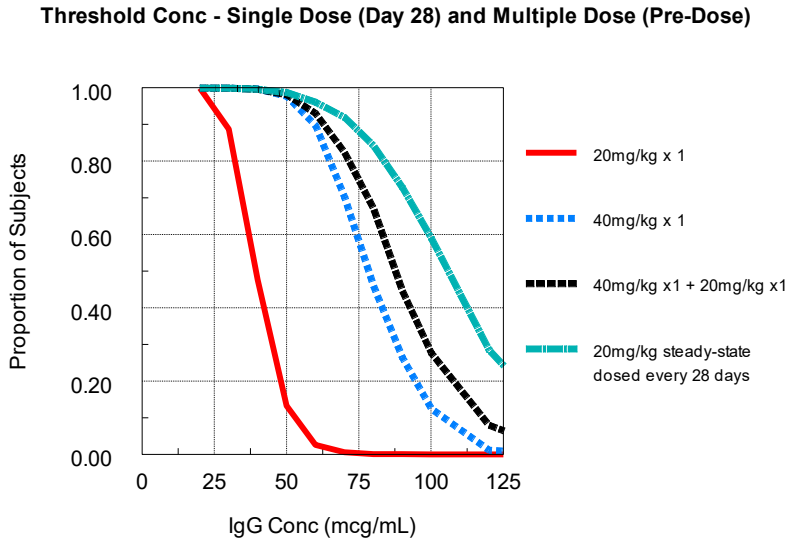
This population analysis will be used to quantify the unexplained between participant pharmacokinetic variability. Final model selection will be based on changes in the objective function and graphically by goodness of fit plots. The final population model parameters will be assessed using bootstrapping to generate 95% CIs for parameter estimates and by visual posterior predictive check. Post-hoc empiric Bayesian estimates of individual participant's pharmacokinetic parameters will be generated. The population parameters and their variability will be used as the input model to assess different dosing strategies. Each VRC01 dosing strategy and its ability to achieve and maintain of target VRC01 concentrations will be performed using the final population pharmacokinetic model and Monte Carlo simulations with at least 5000 replicates.

Similar population PK analyses will be performed on the VRC01LS and VRC07-523LS concentration data from Dose Groups 4 and 5. These analyses will likely need to be nested with pharmacokinetic data from adults since the relatively sparse sampling and small number of P1112 participants receiving VRC01LS and VRC07-523LS will limit parameter estimate precision. Monte Carlo simulations will be used to predict the expected VRC01LS and VRC07-523LS concentrations with the study dose and distribution of Week 12 concentrations.

9.4 Anticipated Outcomes

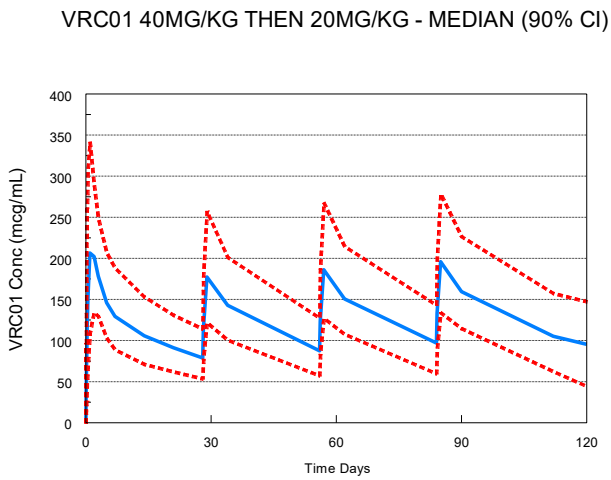
VRC01 exposure (Day 28 concentrations) will be consistently above 50 mcg/mL for 40mg/kg but a significant portion of participants receiving 20mg/kg will have Day 28 concentrations < 50 mcg/mL (Figure 8). In Group 3, there will be modest accumulation from Day 28 (pre-dose) concentration to later pre-dose concentrations following repeat monthly dosing of 20mg/kg. Accordingly, the ratio of pre-dose (repeat dosing)/pre-dose (Day 28) will likely be between 1 and 1.5. For Dose Group 4, it is expected that the vast majority of participants will maintain VRC01LS concentrations above 50 μg/mL for at least 12 weeks, while Dose Group 5 concentrations will maintain VRC07-523LS concentrations above 15 mg/mL for 12 weeks in most subjects.

Figure 8: Expected Day 28 VRC01 Concentrations



The individual participant non-compartmental and population pharmacokinetics of VRC01 will be determined and we expect there to be no relationships between VRC01 absorption (F or KA) and dose. For future protocols using repeated dosing, a dosing strategy of 40mg/kg initially then 20mg/kg every 4 weeks is expected to achieve therapeutic concentrations better than 20mg/kg every 4 weeks (Figure 9).

Figure 9: Expected VRC01 Concentrations



Monte Carlo simulations will help determine the optimal VRC01 VRC01LS, and VRC07-523LS dosing strategies to move forward into future infant trials.

10 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (APPENDIX IIA: IMPAACT P1112 Sample Informed Consent Template: Dose Group 5, Cohort 1 (Non-breastfeeding) and APPENDIX IIB: IMPAACT P1112 Sample Informed Consent Template: Dose Group 5, Cohort 2 (breastfeeding)), and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant (or parent or legal guardian).

> Note: in P1112 protocol V4.0, no changes were made to the sample informed consent templates for Dose Groups 1, 2, 3, and 4 (formerly Appendices IIA, IIB, IIC in previous versions of the protocol). These appendices are therefore not included in protocol V4.0; the sample informed consent templates for Dose Group 5 are instead included as Appendices IIA and IIB.

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will

include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by study staff, study monitors, the U.S. Food and Drug Administration (FDA) or other national Drug Regulatory Authority, the Office for Human Research Protections (OHRP), the NIH, the IMPAACT Network, the local IRB or Ethics Committee, or their designees, and other local, U.S., or international regulatory authorities.

10.3 Study Discontinuation

The study may be discontinued at any time by the NIH, Office of Human Research Protection (OHRP), the FDA, the IMPAACT Network, the IRB or EC, or other governmental agencies as part of their duties to ensure that research participants are protected.

11 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies.

12 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 Centers for Disease Control and Prevention.

All infectious specimens will be sent in accordance with the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.

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APPENDIX IA: Maternal Schedule of Evaluations (all dose groups)

	Screening[1]	Entry[2]
CLINICAL		
Consent	X	
History[3]	X	X
LABORATORY		
HIV diagnostic testing if not in medical record	5 ml	5 ml
PBMC and Plasma Store[4]		10 ml
Serum Store[4]		10 ml
Total Blood Volume Mother (mL)	0 – 5 ml	20 – 25 ml

Footnotes

1. Screening may be performed within 30 days prior to birth or may be performed after birth provided that the infant meets all inclusion/exclusion criteria. Screening and entry can be performed on the same date.
2. Entry visit occurs after the newborn is determined to be eligible for the study. Note that the Entry Visit is also the end of study for the maternal participant.
3. A complete history is required at Entry and includes date of birth; race; ethnicity; all quantitative HIV RNA tests, HIV genotypes, and CD4 T lymphocyte counts that are obtained during pregnancy and that are available to the site, all HIV-related diagnoses present during pregnancy, all antiretroviral medications received during pregnancy and delivery (doses not required), all diagnoses at labor and delivery.
4. Samples will be processed and shipped per the LPC for characterization of maternal virus and HIV antibodies. Left over serum, plasma, and PBMC will be stored per the LPC for future HIV-related studies (including possible genetic testing) overseen per the IMPAACT SOP. Maternal blood can be collected any time from Entry up until 14 days after Entry.

APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2)

	Screen[1]	Entry/ Day 0[2] 0 Hour	Day 1 24 hr[3] ± 6 hr	Day 3 72 hr[3] ± 24 hr	Day 7 168 hr[3] ±24 hr	Day 14[4] +3 days	Day 28[4] +3 days	Wk 8 ±1 wk	Wk 16[4] +2 wk	Wk 24 ±2 wks	Wk 48 ±2 wks	Early D/C post Day 14[5]	Q3 month f/u after Wk 48 if still HIV Ab+[21] ± 2 wks
History[6]	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam[7]	X	X	X	X	X	X	X	X	X	X	X	X	
DOSE VRC01[8]		X[8]											
LABORATORY EVALUATIONS													
Hematology[9]	1mL				1mL								
Chemistries[10,22]	1mL				1mL	1mL			1mL				
HIV-1 NAT testing[11]	1mL[12]					1mL	1mL		1mL	1mL			
HIV antibody test											1mL[21]		2mL[21]
Lymphocyte subsets (CD3/CD4/CD8)[13]	1mL				1mL								
VRC01 Plasma levels[14]		2mL	1mL	1mL	1mL	1-2mL[14]	2mL	1-2mL[14]	2mL	2mL	2mL	2mL	
PBMC storage[15]		X	X	X	X	X	X	X	X	X	X	X	
VRC01 serum[16,17]		0-1mL[17]				0-1 mL[17]	1 mL[17]	0-1 mL[17]	2 mL	2 mL	2 mL	2mL	
Anti-VRC01 Ab[18]		X						X		X	X		
Oral secretions[19]		X	X	X	X	X	X	X	X	X	X	X	
Total Blood Volume Infant (mL)	4mL	2-3mL	1mL	1mL	4mL	3-5mL	3-4mL	1-3mL	6mL	5mL	5mL	4mL	2mL
	NOTE: 18-24mL in 8-week period[20]												

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC01 is administered at less than 72 hours after birth.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC01 immunization is administered.
3. Hours (hr) after dose administration.
4. Window permits visit to be done only 3 days after (not before) Day 14 and 28, and only 2 weeks after Week 16 (not before) to assure the timing of HIV testing meets criteria for presumptive exclusion of infant HIV infection.
5. An Early Discontinuation visit should be scheduled if participant comes off study after Day 14 and prior to Week 48.
6. A complete history is required at birth and includes date of birth, Race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications, diagnoses, signs and symptoms, and vaccinations. Results of HIV-1 testing done outside of the study should be abstracted.
7. Complete physical exam including vitals, weight, length, and head circumference at Screening, Day 0, Day 28, and Weeks 8, 16, 24 and 48. Targeted physical exam including vitals and weight at Day 1, 3, 7, 14. Examination of VRC01 injection site should occur at all visits through Week 24.
8. The VRC01 immunization must be administered less than 72 hours after birth (see MOP for administration instructions).
   Dose Group 1: Single VRC01 20mg/kg subcutaneous injection less than 72 hours after birth.
   Dose Group 2: Single VRC01 40mg/kg subcutaneous injection less than 72 hours after birth.
   1. Infants should be monitored for a minimum of 4 hours after study treatment injection, with initial assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction.
   2. Infants will also be evaluated for local reactions and pain 1 hour (+/- 30 minutes) after the injection and results recorded on a study CRF.
9. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
10. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available).
11. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC01 might suppress HIV-1 RNA. For the screening NAT, see footnote 12. For U.S. sites, HIV-1 NAT testing must be run in a CLIA-approved laboratory. For non-U.S. sites, the HIV-1 NAT must be run at a VQA-certified laboratory. If the infant has a positive HIV-1 NAT at any time, confirmation and additional samples should be obtained as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]; infant follow up on study should also continue to be as per APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2). When possible APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2).
12. Blood for HIV-1 NAT drawn at Screening must be obtained prior to 48 hours of life AND prior to VRC01 administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to

48 hours of life and tested in a laboratory with CLIA approval (U.S. sites) or VQA approval (Non-U.S. sites), the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.

13. Lymphocyte subsets include CD3/CD4/CD8 counts and percentages. Results are not needed for study entry. Draw with CBC. Must be performed at CLIA-certified (or equivalent) laboratory.
14. Samples for VRC01 plasma levels to be obtained prior to VRC01 administration. For infants with birth weight <2.8kg use lower sample volume at Day 14 and Week 8. Plasma for VRC01 levels and anti-VRC01 levels processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
15. PBMC from the VRC01 plasma level sample will be isolated if site is capable of PBMC storage. PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. Samples for VRC01 serum to be obtained prior to VRC01 administration. Serum for VRC01 antibody levels and neutralization assays will be processed and batch shipped per the LPC. Leftover serum will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
17. For infants with birth weight <2.8kg: do not collect VRC01 serum samples at Entry, Day 14, Day 28, or Week 8.
18. Assay will be performed with plasma from VRC01 plasma level sample.
19. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC01 administration as baseline. Assay will be performed to detect VRC01 antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
20. For infants with birth weight <2.8kg lower sample volume will be collected. See also Footnotes 12 and 17. Volumes equate to $\leq$ 3ml/kg drawn within 24 hours and < 9.0 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.
21. HIV antibody testing will be performed at Week 48. If the infant remains antibody positive, he/she will remain on study for repeat antibody testing every 3 months until negative. U.S sites should perform testing according to CLIA requirements, including those sites utilizing CLIA-waived HIV rapid testing. For Non-U.S. sites, testing should be performed at the approved site-associated DAIDS-monitored laboratory.
22. Obtain additional ALT and AST measurement upon evidence of hepatic-related clinical adverse events (jaundice, enlargement of the liver).

Priority for blood samples at:

Screening and Entry	**Day 7**	**Subsequent visits**
1. HIV-1NAT	1. VRC01 Plasma levels	1. HIV-1 NAT
2. CBC, chemistry	2. CBC, chemistry	2. VRC01 Plasma levels
3. VRC01 plasma levels	3. Lymphocyte subsets	3. VRC01 Serum
4. Lymphocyte subsets		4. HIV Antibody
5. VRC01 serum		5. Chemistry

APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]

	1st Visit: Infected Infant (Confirmatory)[2]	2nd Visit: Infected Infant [3]	3rd Visit: Infected Infant[4]	Subsequent visits prior to initiation of ARVs[5] (q28d ±7d)	Follow up after initiation of ARVs[6]
History[7]	X	X	X	X	X
Physical exam	X	X	X	X	X
HIV-1 NAT testing[8]	1 mL[9]				
Quantitative HIV-1 RNA testing[10]	3 mL	3 mL	3 mL	3 mL	0 to 3 mL
mAb Plasma levels[11]	1 mL[11]	1 mL[11]	1 mL[11]		
Lymphocytes: CD3/CD4/CD8[16]	0 to 2 mL			0 to 2 mL [17]	0 to 2 mL[17]
PBMC storage	X[12]	X[12]	X[12]	1 mL	1 ml[13]
Stored plasma[14]	X	X	X	X	X
Total Blood Volume Infant (mL)	5-7 ml[15]	4 ml[15]	4 ml[15]	4 – 6 mL[15]	1 - 6 mL[15]

Footnotes

1. Visits for APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] should be scheduled to concur with visits for APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2), APPENDIX ID: Schedule of Evaluations (Dose Group 3), APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding), APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding), APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding), or APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding) whenever possible. The protocol team will review advance requests for deviations from the specified visit windows on a case-by-case basis.
2. The 1st Visit for an Infected Infant (Confirmatory visit) should be as soon as possible after site notification of the first positive result and not later than 14 days after the date of the blood draw of the first positive HIV-1 NAT test.
3. The 2nd Visit for an Infected Infant should be 28 days (± 7 days) after the date of the blood draw of the first positive HIV-1 NAT test.
4. The 3rd Visit for an Infected Infant Visit should be 56 days (± 10 days) after the date of the blood draw of the first positive HIV-1 NAT test.
5. Subsequent visits prior to initiation of ARVs should be every 28 days (± 7 days). Total duration of follow up after study entry should not exceed 48 weeks for Dose Groups 1 and 2 or 96 weeks for Dose Groups 3, 4, and 5.

6. After infant has been started on ARVs, history, physical exam, plasma HIV RNA and CD4 lymphocyte subsets will be abstracted from the medical records when obtained per standard of care. At standard of care clinical visits when blood will be obtained for clinical care, an additional sample for plasma and PBMC storage will be obtained for the study (see LPC). Total duration of follow up after study entry should not exceed 48 weeks for Dose Groups 1 and 2 or 96 weeks for Dose Groups 3, 4, and 5.
7. History should include ARV with start and stop dates, other medications, diagnoses, signs and symptoms, and vaccinations. Results of HIV-1 testing and lymphocyte subset testing done outside of the study should be abstracted.
8. Initial positive HIV-1 nucleic acid testing (NAT) should be confirmed with a repeat HIV-1 NAT. Assay must detect HIV DNA. For U.S. sites, HIV-1 NAT must be performed in a CLIA certified laboratory. For Non-U.S. sites, HIV-1 NAT must be performed at a VQA-certified laboratory. For infants with two positive HIV-1 NAT tests, no further HIV-1 tests detecting DNA are required for APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2), APPENDIX ID: Schedule of Evaluations (Dose Group 3), APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding), APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding), APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding), or APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding).
9. If the confirmatory HIV-1 NAT is not positive, consult with the team within 72 hours of receiving the result and continue to follow infant on APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] and APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2), APPENDIX ID: Schedule of Evaluations (Dose Group 3), APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding), APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding), APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding), or APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding).
10. Quantitative plasma HIV-1 RNA must be performed at a VQA-certified (for non-US) or CLIA –certified (or equivalent) (for US-based) laboratory. Each site should identify a single laboratory for all study specified HIV-1 RNA testing.
11. If the visit is concurrent with a visit for APPENDIX IB: Infant Schedule of Evaluations (Dose Groups 1 and 2), APPENDIX ID: Schedule of Evaluations (Dose Group 3), APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding), APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding), APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding)or APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding) that includes the mAb plasma level, do not obtain APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] mAb plasma levels. Samples will be processed and batch shipped per the LPC.
12. PBMC from the study product plasma level sample and HIV-1 RNA sample (if possible) will be collected. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for processing instructions.
13. At standard of care clinical visits when blood will be obtained, an additional sample for plasma and PBMC storage will be obtained for the study (see LPC). If there will be more than a three-month interval between blood samples for clinical care, then a study sample should be obtained at least every 3 months.
14. Leftover plasma remaining from study product plasma levels and quantitative HIV-1 RNA testing (if possible) and plasma from the PBMC storage sample will be stored per the LPC for future HIV-related studies per IMPAACT SOP.
15. Total study blood volume must be under a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period. Use the priority schema in APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] to further reduce blood volume if necessary for the infant weight.

16. Abstract from clinical chart if available. Obtain lymphocyte subsets if not done for clinical care within ± 2 weeks of 1st confirmatory visit. Draw with CBC if required for lymphocyte subset parameters. Must be performed at CLIA-certified (or equivalent) laboratory or at the approved site-associated DAIDS-monitored laboratory.
17. Abstract from clinical chart if available. If not, obtain every 12 weeks ± 4 weeks.

Priority for blood samples at:

1st Infected Infant Visit

1. HIV NAT
2. HIV-1 RNA
3. Study product Plasma levels
4. CBC, chemistry
5. Study product Serum storage
6. Lymphocyte subsets

2nd, 3rd, and Subsequent Infected Visits

1. HIV-1 RNA
2. Study product Plasma levels
3. CBC, chemistry
4. Study product Serum storage
5. Lymphocyte subsets

APPENDIX ID: Schedule of Evaluations (Dose Group 3)

	VRC01 DOSING PERIOD: BIRTH THROUGH WEEK 24 AND, THEREAFTER, THROUGH COMPLETE CESSATION OF BREASTFEEDING[7], DIAGNOSIS OF HIV INFECTION [7,11] OR WEEK 72 (WHICHEVER COMES FIRST)											OBSERVATION PERIOD: EVERY 12 WEEKS AFTER BF CESSATION[7], HIV DIAGNOSIS [7,11] AND/OR AT WEEKS 84 AND 96				
	Screen[1]	Entry/Day 0[2] 0 Hour	Day 1/24 hr[3] ± 6 hr	Day 14 +/-3 days	Day 28 +/-3 days	Wk 8 +1/-1 wks	Wk 12 +1/-1 wks	Wk 16 +1/-1 wks	Wk 20 +1/-1 wks	Wk 24 +1/-1 wks	Q 4 weeks until complete cessation of breastfeeding or Wk 72 +1/-1 wks	First visit after complete cessation of breastfeeding or HIV diagnosis +/- 1 wk	Every 12 wks after complete cessation of breastfeeding or HIV diagnosis +/-1wk	Wk 84 ±2 wks	Wk 96 ±2 wks	Early D/C of VRC 01 or of study[4]
History[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DOSE VRC01[7]		X			X	X	X	X	X	X	X					
LABORATORY EVALUATIONS																
Hematology[8]	1mL			1mL	1ml	1ml		1mL	1ml	1mL	1mL[9]	1mL	1mL			1mL
Chemistries[10]	1mL			1mL	1ml	1ml		1mL	1ml	1mL	1mL[9]	1mL	1mL			1mL
HIV-1 NAT testing[11]	1mL[12]			1mL	1mL			1mL		1mL	1mL[9]	1mL	1mL	1mL	1mL	1mL
HIV antibody test													2mL[13]	2mL[13]		
Lymphocyte: CD3/CD4/CD8[14]	1mL			1mL							1mL[9]	1mL				1mL
VRC01 Plasma levels[15]		2mL	1mL	0.5-2mL[15]	1-2mL	1-2mL[15]	.	2mL	2mL	2mL	2mL[9]	2mL	2mL	2mL	2mL	2mL
PBMC storage[16]		X	X	X	X	X		X		X	X	X	X	X	X	X
VRC01 serum[17]		0-1mL[17]		0-1 mL[17]	0-1 mL[17]	0-1 mL[17]		2mL		2mL	2mL[9]	2mL	2mL	2mL	2mL	2mL
Anti-VRC01 Ab[18]		X				X				X	X[9]	X	X	X	X	X
Oral secretions[19]		X	X	X	X	X		X		X	X[9]	X	X	X	X	X
Total Blood Volume Infant (mL)[20]	4mL	2-3mL	1mL	4.5-7mL	4-6mL	3-5mL	0mL	7mL	4mL	7mL	0-8mL	8mL	9mL	7mL	5mL	8mL
	NOTE: 18.5-26mL in 8-week period[20]															

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC01 is administered ideally within 24 hours to less than 72 hours after birth and not more than the 5th day of life.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC01 immunization is administered.
3. Hours (hr) after dose administration.
4. An Early Discontinuation visit should be scheduled if participant comes off study after receiving any doses of VRC01. This visit should also take place if a participant discontinues VRC01 but continues on study. Following the Early Discontinuation visit, that participant should follow the schedule of the Observation Period.
5. A complete history is required at birth and includes date of birth, race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications and vaccinations (including sites of injections), diagnoses, and signs and symptoms. Results of HIV-1 testing done outside of the study should be abstracted. Feeding history to determine breast milk exposure will be obtained at each visit until complete cessation of breastfeeding.
6. Complete physical exam including vitals, weight, length, and head circumference at all visits except Day 1 and 14. Targeted physical exam including vitals and weight at Day 1 and 14. Examination of VRC01 injection site should occur at all visits.
7. The initial VRC01 immunization, 40mg/kg subcutaneous injection, must be administered no later than the 5th day of life (see MOP for administration instructions). Subsequent immunizations of VRC01, 20mg/kg subcutaneous injections, will be administered monthly up to and including the Week 24 visit and, thereafter, until complete cessation of breastfeeding, HIV diagnosis or Week 72, whichever comes first. Complete cessation of breastfeeding is defined as having completely stopped all exposure to breast milk for $\geq$ 28 days. Administration of VRC01 should stop upon first positive HIV PCR test result.
    - Infants should be monitored for a minimum of 4 hours after initial study treatment injection, with assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction. Subsequent injections should be monitored for a minimum of 60 minutes (+30 minutes), with assessments at 15, 30 and 60 minutes post dose.
    - Infants will also be evaluated for local reactions and pain at 1 hour (+30 minutes) after every injection and results recorded on a study CRF.
    - Caregivers of participants will be provided with a diary card on which to note any reactions at the injection site. Study staff will contact caregivers between 3 to 5 days following the injection.
8. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
9. For breastfeeding, HIV-exposed uninfected infants after Week 24, hematology, chemistries, HIV-1 NAT, lymphocyte subsets, VRC01 plasma levels (including anti-VRC01) and VRC01 serum and oral secretions should be collected only at Weeks 36, 48, 60, 72, and early D/C visit.

10. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available). Obtain additional ALT and AST measurements upon evidence of hepatic-related clinical adverse events (jaundice, enlargement of the liver).
11. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC01 might suppress HIV-1 RNA. For the screening NAT, see footnote 12. HIV-1 NAT testing must be run in a VQA-approved laboratory. If the infant has a positive HIV-1 NAT at any time, confirmation and additional HIV testing should be performed as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]. With the exception of HIV testing, on study follow up of the HIV-infected infant continues as per APPENDIX ID: Schedule of Evaluations (Dose Group 3). When possible, APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with APPENDIX ID: Schedule of Evaluations (Dose Group 3).
12. Blood for HIV-1 NAT drawn at Screening must be obtained prior to 48 hours of life AND prior to VRC01 administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to 48 hours of life and tested in a laboratory with VQA approval, the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.
13. For HIV-exposed-uninfected infants that have achieved complete cessation of breastfeeding, HIV antibody testing will be performed every 12 weeks after complete cessation of breastfeeding and at Week 84. Testing should be performed at the approved site-associated DAIDS-monitored laboratory. If the infant remains antibody positive at either of those time points, notify the protocol team.
14. Lymphocyte subsets include CD3/CD4/CD8 counts and percentages. Results are not needed for study entry. Draw with CBC. Testing should be performed at the approved site-associated DAIDS-monitored laboratory.
15. Samples for VRC01 plasma levels should be obtained prior to VRC01 administration. For infants with birth weight <2.9kg use lower sample volume at Day 14 and Week 8. Plasma for VRC01 levels and anti-VRC01 levels will be processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. PBMC from the VRC01 plasma level sample will be isolated if site is capable of PBMC isolation and storage. PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
17. Samples for VRC01 serum should be obtained prior to VRC01 administration. For infants with birth weight <2.9kg: do not collect VRC01 serum samples at Entry, Day 14, Day 28, or Week 8. Serum for VRC01 antibody levels and neutralization assays will be processed and batch shipped per the LPC. Leftover serum will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
18. Anti-VRC01 Ab will be tested using plasma collected for VRC01 levels.
19. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC01 administration as baseline. Assay will be performed to detect VRC01 antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
20. For infants with birth weight <2.9kg lower sample volume will be collected. See also Footnotes 15 and 17. Volumes equate to $\leq$ 3ml/kg drawn within 24 hours and < 9.0 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.

Priority for blood samples: 1: HIV-1NAT; 2: CBC, chemistry; 3: VRC01 plasma levels; 4: VRC01 serum; 5: HIV-1 antibody; 6: Lymphocyte subsets

APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding)

	Screen[1]	Entry/Day 0[2] 0 Hour	Day 1/24 hr[3] ± 6 hr	Day 14 +/-3 days	Day 28 +/-3 days	Wk 8 +/-1 wks	Wk 12; +/-1 wk	Wk 24 +/- 1 wk	Wk 36 +/- 1 wk	Wks 48, 60, 72, 84 +/-2 wk	Wk 96: End of Study +/- 2 wk	Early Study D/C[4]
History[5]	X	X	X	X	X	X	X	X	X	X	X	X
PE[6]	X	X	X	X	X	X	X	X	X	X	X	X
VRC01LS[7]		X										
LABORATORY EVALUATIONS												
Hematology[8]	0-1mL			1mL	1mL		1mL	1mL				1mL
Chemistries[9]	1mL			1mL	1mL		1mL	1mL				1mL
HIV-1 NAT[10]	1mL[11]			1mL	1mL		1mL	1mL	1mL			1mL
HIV Ab test[12]										2mL	2mL	2mL
Lymphocyte: CD3/CD4/CD8[13]	1mL											1mL
VRC01LS Plasma levels[14]		2mL	1mL	1-2mL[14]	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
PBMC [15]		X	X	X	X	X	X	X	X	X	X	X
VRC01LS serum[16]		0-1mL		0-1mL[16]	0-1mL	0-1mL	2mL	2mL	2mL	2mL	2mL	2mL
Anti-VRC01LS Ab[17]		X				X	X	X	X	X	X	X
Oral secretions[18]		X	X	X	X	X	X	X	X	X	X	X
Total Blood Volume Infant (mL)[19]	3-4mL	2-3mL	1mL	4-6mL	5-6mL	2-3mL	7mL	7mL	5mL	6mL	6mL	10mL
	NOTE: 17-23mL from birth to 8 weeks[19]											

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC01LS is administered ideally within 24 hours to less than 72 hours after birth.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC01LS immunization is administered.
3. Hours (hr) after dose administration.
4. An Early Discontinuation visit should be scheduled if participant comes off study after receiving any doses of VRC01LS.
5. A complete history is required at birth and includes date of birth, race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications and vaccinations (including sites of injections), diagnoses, and signs and symptoms. Results of HIV-1 testing done outside of the study should be abstracted.
6. Complete physical exam including vitals (temperature, heart rate, respiratory rate, and, if possible, blood pressure), weight, length, and head circumference at all visits except Day 1 and 14. Targeted physical exam including vitals (as above) and weight at Days 1 and 14 visits. Examination of VRC01LS injection site should occur at all visits, for good clinical care, but data will only be recorded on CRFs through the Day 28 visit, with the exception that if there are still signs of a reaction present at those visits or any reaction noted at a later visit, data will be recorded at scheduled visits until resolved or until no further resolution is expected.
7. An initial VRC01LS immunization, 80 mg (if <4.5 kg) or 100 mg (if ≥ 4.5 kg) subcutaneous injection, must be administered less than 72 hours of life (see MOP for administration instructions).
   - Infants should be monitored for a minimum of 4 hours after the study treatment injection, with assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction.
   - Infants will also be evaluated for local reactions and pain at 1 hour (+30 minutes) after the injection and results recorded on a study CRF.
   - Caregivers of participants will be provided with a diary card on which to note any reactions at the injection site. Study staff will contact caregivers between 3 to 5 days following the injection.
8. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
9. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available). Obtain additional ALT and AST measurements upon evidence of hepatic-related clinical adverse events (jaundice, enlargement of the liver).
10. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC01LS might suppress HIV-1 RNA. For the NAT at Screening, see footnote 11. HIV-1 NAT testing must be run in a CLIA- or VQA-approved laboratory. If the infant has a positive HIV-1 NAT at screening at any time, confirmation and additional HIV testing should be performed as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]. Infants confirmed to be HIV-1-infected should be evaluated according to both APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding) and APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1], but without duplication of specific blood tests if the study visit dates are concurrent. When possible, APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with

APPENDIX IE: Schedule of Evaluations (Dose Group 4, Cohort 1: non-breastfeeding).

11. Blood for HIV-1 NAT drawn at Screening must be obtained prior to 48 hours of life AND prior to VRC01LS administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to 48 hours of life and tested in a laboratory with CLIA or VQA approval, the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.
12. HIV antibody testing should be performed at the approved site-associated DAIDS-monitored laboratory. If the infant remains antibody positive at or after 72 weeks, notify the protocol team. If HIV antibody is negative at Week 48 or later, subsequent HIV antibody testing is not required.
13. Lymphocyte subsets include CD3/CD4/CD8 counts and percentages. Results are not needed for study entry. Draw with CBC. Testing should be performed at the approved site-associated DAIDS-monitored or CLIA-approved laboratory.
14. Samples for VRC01LS plasma levels should be obtained prior to VRC01LS administration. For infants with birth weight <2.6kg use lower sample volume at Day 14. Plasma for VRC01LS levels and anti-VRC01LS levels will be processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
15. PBMC from the VRC01LS plasma level sample will be isolated if site is capable of PBMC isolation and storage (see LPC for qualifications). PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. Samples for VRC01LS serum should be obtained prior to VRC01LS administration. For infants with birth weight <2.6kg: do not collect VRC01LS serum samples at Entry, Day 14, Day 28, and Week 8. Serum for VRC01LS antibody levels and neutralization assays will be processed and batch shipped to central testing laboratory. Leftover serum may be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
17. Anti-VRC01LS Ab will be tested using plasma collected for VRC01LS levels.
18. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC01LS administration as baseline. Assay will be performed to detect VRC01LS antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
19. For infants with birth weight <2.6kg lower sample volume will be collected. See also Footnotes 14 and 16. Volumes equate to $\leq$ 3ml/kg drawn within 24 hours and < 9.0 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.

Priority for blood samples: 1: HIV-1NAT; 2: CBC, chemistry; 3: VRC01LS plasma levels; 4: VRC01LS serum; 5: HIV-1 antibody; 6: Lymphocyte subsets. At Day 28, Week 12, and 24 VRC01LS plasma levels are first priority.

APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding)

	VRC01LS DOSING PERIOD AFTER INITIAL DOSE: SCREENING TO WK 12							VRC01LS DOSING PERIOD AFTER 2ND DOSE: WK 14 AND 16		OBSERVATION FOLLOWING DOSING PERIOD(S)			
	Screen[1]	Entry/Day 0[2] 0 Hour	Day 1/24 hr[3] ± 6 hr	Day 14 +/-3 days	Day 28 +/-3 days	Wk 8 +/-1 wks	Wk 12; +/-1 wk	Wk 14 +/-3 days	Wk 16 +/-3 days	Wk 24 and 36 +/-1 wk	Wks 48, 60, 72, 84 +/-2 wk	Wk 96: End of Study +/- 2 wks	Early Study D/C[4]
History[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
PE[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
VRC01LS[7]		X					(X)						
LABORATORY EVALUATIONS													
Hematology[8]	0-1mL			1mL	1mL		1mL	1mL		1mL			1mL
Chemistries[9]	1mL			1mL	1mL		1mL	1mL		1mL			1mL
HIV-1 NAT[10]	1mL[11]			1mL	1mL		1mL			1mL	1mL	1mL	1mL
HIV Ab test[12]											2mL	2mL	2mL
Lymphocyte: CD3/CD4/CD8[13]	1mL												1mL
VRC01LS Plasma levels[14]		2mL	1mL	1-2mL[14]	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
PBMC [15]		X	X	X	X	X	X	X	X	X	X	X	X
VRC01LS serum[16]		0-1mL		0-1mL[16]	0-1mL	0-1mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Anti-VRC01LS Ab[17]		X				X	X			X	X	X	X
Oral secretions[18]		X	X	X	X	X	X	X	X	X	X	X	X
Total Blood Volume Infant (mL)[19]	3-4mL	2-3mL	1mL	4-6mL	5-6mL	2-3mL	7mL	6mL	4mL	7mL	7mL	7mL	10mL
	NOTE: 17 - 23mL from birth to 8 weeks[19]												

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC01LS is administered ideally within 24 hours to less than 72 hours after birth and not more than the 5th day of life.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC01LS immunization is administered.
3. Hours (hr) after dose administration.
4. An Early Discontinuation visit should be scheduled if participant comes off study after receiving any doses of VRC01LS.
5. A complete history is required at birth and includes date of birth, race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications and vaccinations (including sites of injections), diagnoses, and signs and symptoms. Results of HIV-1 testing done outside of the study should be abstracted. Feeding history to determine breast milk exposure will be obtained at each visit until complete cessation of breastfeeding.
6. Complete physical exam including vitals (temperature, heart rate, respiratory rate, and, if possible, blood pressure), weight, length, and head circumference at all visits except Day 1 and 14 and Week 14. Targeted physical exam including vitals (as above) and weight at Days 1 and 14 and Week 14 visits. Examination of VRC01LS injection site should occur at all visits for good clinical care, but data will only be recorded on CRFs through the Day 28 visit (for all participants) and the Week 16 visit (for Cohort 2 participants who received the second injection), with the exception that if there are still signs of a reaction present at those visits or any reaction noted at a later visit, data will be recorded at scheduled visits until resolved or until no further resolution is expected.
7. An initial VRC01LS immunization, 80 mg (if <4.5 kg) or 100 mg (if ≥ 4.5 kg) subcutaneous injection, must be administered no later than the 5th day of life (see MOP for administration instructions). A second immunization of VRC01LS, 100 mg subcutaneous injection, will be administered at Week 12 only if the infant has not had complete cessation of breastfeeding. Complete cessation of breastfeeding is defined as having completely stopped all exposure to breast milk for ≥ 28 days. There should be no administration of VRC01LS if the infant has had a positive HIV PCR test result.
    - Infants should be monitored for a minimum of 4 hours after initial study treatment injection, with assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction. The subsequent injection should be monitored for a minimum of 60 minutes (+ 30 minutes), with assessments at 15, 30 and 60 minutes post dose.
    - Infants will also be evaluated for local reactions and pain at 1 hour (+30 minutes) after each injection and results recorded on a study CRF.
    - Caregivers of participants will be provided with a diary card on which to note any reactions at the injection site. Study staff will contact caregivers between 3 to 5 days following the injection.
8. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
9. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available). Obtain additional ALT and AST measurements upon evidence of hepatic-related clinical adverse events (jaundice, enlargement of the liver).

10. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC01LS might suppress HIV-1 RNA. For NAT at Screening, see footnote 11. HIV-1 NAT testing must be run in a VQA-approved laboratory. If the infant has a positive HIV-1 NAT at any time, confirmation and additional HIV testing should be performed as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]. Infants confirmed to be HIV-1-infected should be evaluated according to both APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding) and APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1], but without duplication of specific blood tests if the study visit dates are concurrent. When possible, APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with APPENDIX IF: Schedule of Evaluations (Dose Group 4, Cohort 2: breastfeeding).
11. Blood for HIV-1 NAT drawn at Screening must be obtained prior to 48 hours of life AND prior to VRC01LS administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to 48 hours of life and tested in a laboratory with VQA approval, the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.
12. HIV antibody testing should be performed at the approved site-associated DAIDS-monitored laboratory. If the infant remains antibody positive at or after 72 weeks, notify the protocol team. If HIV antibody is negative at Week 48 or later, subsequent HIV antibody testing is not required.
13. Lymphocyte subsets include CD3/CD4/CD8 counts and percentages. Results are not needed for study entry. Draw with CBC. Testing should be performed at the approved site-associated DAIDS-monitored laboratory.
14. Samples for VRC01LS plasma levels should be obtained prior to VRC01 administration. For infants with birth weight <2.6kg use lower sample volume at Day 14. Plasma for VRC01LS levels and anti-VRC01LS levels will be processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
15. PBMC from the VRC01LS plasma level sample will be isolated if site is capable of PBMC isolation and storage (see LPC for qualifications). PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. Samples for VRC01LS serum should be obtained prior to VRC01LS administration. For infants with birth weight <2.6kg: do not collect VRC01LS serum samples at Entry, Day 14, Day 28, and Week 8. Serum for VRC01LS antibody levels and neutralization assays will be processed and batch shipped to central testing laboratory. Leftover serum may be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
17. Anti-VRC01LS Ab will be tested using plasma collected for VRC01LS levels.
18. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC01LS administration as baseline. Assay will be performed to detect VRC01LS antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
19. For infants with birth weight <2.6kg lower sample volume will be collected. See also Footnotes 14 and 16. Volumes equate to $\leq$ 3ml/kg drawn within 24 hours and < 9.0 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.

Priority for blood samples: 1: HIV-1NAT; 2: CBC, chemistry; 3: VRC01LS plasma levels; 4: VRC01LS serum; 5: HIV-1 antibody; 6: Lymphocyte subsets. At Day 28, Week 12, and 24 VRC01LS plasma levels are first priority.

APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding)

	Screen[1]	Entry/Day 0[2] 0 Hour	Day 1/24 hrs[3] ± 6 hrs	Day 3 ± 1 day	Day 7 +/-3 days	Day 14 +/-3 days	Day 28 +/-3 days	Wk 8 +/-1 wks	Wk 12; +/-1 wk	Wk 24 +/- 1 wk	Wk 36 +/- 1 wk	Wks 48, 60, 72, 84 +/-2 wk	Wk 96: End of Study +/- 2 wk	Early Study D/C[4]
History[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRC07-523LS[7]		X												
LABORATORY EVALUATIONS														
Hematology[8]	0-1mL						1mL		1mL	1mL				1mL
Chemistries[9]	1mL						1mL		1mL	1mL				1mL
HIV-1 NAT[10]	1mL[11]					1mL	1mL		1mL	1mL	1mL			1mL
HIV Ab test[12]												2mL	2mL	2mL
VRC07-523LS plasma levels[13]		2-3mL[13]	1mL	1mL	1mL	2mL	2mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
PBMC[14]		X	X			X	X	X	X	X	X	X	X	X
VRC07-523LS serum[15]		0-1mL[15]				0-1mL[15]	0-1mL[15]	0-1mL[15]	2mL	2mL	2mL	2mL	2mL	2mL
Anti-VRC07-523LS Ab[16]		X						X	X	X	X	X	X	X
Oral secretions[17]		X	X		X	X	X	X	X	X	X	X	X	X
Total blood volume infant (mL)[18]	2-3mL	2-4mL	1mL	1mL	1mL	3-4mL	5-6mL	3-4mL	8mL	8mL	6mL	7mL	7mL	10mL
	NOTE: 18-24mL from birth to 8 weeks[18]													

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC07-523LS is administered ideally within 24 hours to less than 72 hours after birth.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC07-523LS immunization is administered.
3. Hours (hr) after dose administration.
4. An Early Discontinuation visit should be scheduled if participant comes off study early after receiving VRC07-523LS.
5. A complete history is required at birth and includes date of birth, race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications and vaccinations (including sites of injections), diagnoses, and signs and symptoms. Results of HIV-1 testing done outside of the study should be abstracted.
6. Complete physical exam including vitals (temperature, heart rate, respiratory rate, and, if possible, blood pressure), weight, length, and head circumference at all visits except Day 1, 3, 7 and 14. Targeted physical exam including vitals (as above) and weight at Days 1, 3, 7 and 14 visits. Examination of VRC07-523LS injection site should occur at all visits. Data will only be recorded on CRFs through the Day 28 visit (for all participants), with the exception that if there are still signs of a reaction present at those visits or any reaction noted at a later visit, data will be recorded at scheduled visits until resolved or until no further resolution is expected.
7. The VRC07-523LS immunization, 80 mg (if <4.5 kg) or 100 mg (if ≥ 4.5 kg) subcutaneous injection, must be administered less than 72 hours of life (see MOP for administration instructions).
   - Infants should be monitored for a minimum of 4 hours after the study treatment injection, with assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction.
   - Infants will also be evaluated for local reactions and pain at 1 hour (+30 minutes) after the injection and results recorded on a study CRF.
   - Caregivers of participants will be provided with a diary card on which to note any reactions at the injection site. Study staff will review the diary card with the caregiver at the Day 3 and Day 7 visits.
8. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
9. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available). Obtain additional ALT and AST measurements upon evidence of hepatic-related clinical adverse events (jaundice, enlargement of the liver).
10. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC07-523LS might suppress HIV-1 RNA. For the NAT at Screening, see footnote 11. HIV-1 NAT testing must be run in a CLIA- or VQA-approved laboratory. If the infant has a positive HIV-1 NAT at screening at any time, confirmation and additional HIV testing should be performed as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]. Infants confirmed to be HIV-1-infected should be evaluated according to both APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding) and APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1], but without duplication of specific blood tests if the study visit dates are concurrent. When possible, APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with

APPENDIX IG: Schedule of Evaluations (Dose Group 5, Cohort 1: non-breastfeeding).

11. Blood for HIV-1 NAT drawn at Screening must be obtained prior to VRC07-523LS administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to study entry and tested in a laboratory with CLIA or VQA approval, the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.
12. HIV antibody testing should be performed at the approved site-associated DAIDS-monitored laboratory. If the infant remains antibody positive at or after 72 weeks, notify the protocol team. If HIV antibody is negative at Week 48 or later, subsequent HIV antibody testing is not required.
13. Samples for VRC07-523LS plasma levels should be obtained prior to VRC07-523LS administration. For infants with birth weight <2.6kg use lower sample volume at Entry. Plasma for VRC07-523LS levels and anti-VRC07-523LS levels will be processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
14. PBMC from the VRC07-523LS plasma level sample will be isolated if site is capable of PBMC isolation and storage (see LPC for qualifications). PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
15. Samples for VRC07-523LS serum should be obtained prior to VRC07-523LS administration. For infants with birth weight <2.6kg: do not collect VRC07-523LS serum samples at Entry, Day 14, Day 28, and Week 8. Serum for VRC07-523LS antibody levels and neutralization assays will be processed and batch shipped to central testing laboratory. Leftover serum may be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. Anti- VRC07-523LS Ab will be tested using plasma collected for VRC07-523LS levels.
17. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC07-523LS administration as baseline. Assay will be performed to detect VRC07-523LS antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
18. For infants with birth weight <2.6kg lower sample volume will be collected. See also Footnotes 13 and 15. Volumes equate to $\leq$ 3ml/kg drawn within 24 hours and $\leq$ 9.5 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.

Priority for blood samples: 1: HIV-1 NAT; 2: CBC, chemistry; 3: VRC07-523LS plasma levels; 4: VRC07-523LS serum; 5: HIV-1 antibody; At Day 28, Week 12, and 24, VRC07-523LS plasma levels are first priority.

APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding)

	VRC07-523LS DOSING PERIOD AFTER INITIAL DOSE: SCREENING TO WK 12									VRC07-523LS DOSING PERIOD AFTER 2ND DOSE: WK 14 AND 16		OBSERVATION FOLLOWING DOSING PERIOD(S)			
	Screen[1]	Entry/Day 0[2] 0 Hour	Day 1/24 hrs[3] ± 6 hrs	Day 3 ± 1 day	Day 7 +/-3 days	Day 14 +/-3 days	Day 28 +/-3 days	Wk 8 +/-1 wks	Wk 12; +/-1 wk	Wk 14 +/-3 days	Wk 16 +/-3 days	Wk 24 and 36 +/-1 wk	Wks 48, 60, 72, 84 +/-2 wk	Wk 96: End of Study +/- 2 wks	Early St.udy D/C[4]
History[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PE[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRC07-523LS[7]		X							(X)						
Hematology[8]	0-1mL						1mL		1mL	1mL		1mL			1mL
Chemistries[9]	1mL						1mL		1mL	1mL		1mL			1mL
HIV-1 NAT[10]	1mL[11]					1mL	1mL		1mL			1mL	1mL	1mL	1mL
HIV Ab test[12]													2mL	2mL	2mL
VRC07-523LS plasma levels[13]		2-3mL[13]	1mL	1mL	1mL	2mL	2mL	3mL	3mL	2mL	2mL	3mL	3mL	3mL	3mL
PBMC [14]		X	X			X	X	X	X	X	X	X	X	X	X
VRC07-523LS serum[15]		0-1mL[16]				0-1mL[16]	0-1mL[16]	0-1mL[16]	2mL	2mL	2mL	2mL	2mL	2mL	2mL
Anti- VRC07-523LS Ab[16]		X						X	X			X	X	X	X
Oral secretions[17]		X	X		X	X	X	X	X	X	X	X	X	X	X
Total blood volume infant (mL)[18]	2-3mL	2-4mL	1mL	1mL	1mL	3-4mL	5-6mL	3-4mL	8mL	6mL	4mL	8mL	8mL	8mL	10mL
	NOTE: 18-24 mL from birth to 8 weeks[18]														

Footnotes

1. Screening evaluations should be completed as soon as possible after birth. The laboratory testing needed for inclusion/exclusion (CBC, ALT) must be completed and eligibility confirmed in time so that the VRC07-523LS is administered ideally within 24 hours to less than 72 hours after birth and not more than the 5th day of life.
2. The Entry/Day 0 visit can take place on the same day as the Screening Visit. Blood for the Entry/Day 0 evaluations may be drawn with the screening blood or at the time of entry but must be drawn before the VRC07-523LS immunization is administered.
3. Hours (hr) after dose administration.
4. An Early Discontinuation visit should be scheduled if participant comes off study early after receiving any doses of VRC07-523LS.
5. A complete history is required at birth and includes date of birth, race, ethnicity, gender, maternal risk factor meeting the inclusion criteria, all diagnoses, all signs and symptoms, all antiretroviral medications (ARV) with start and stop dates and doses, all injected medications (i.e. vitamin K, Hepatitis B vaccine) including location of injection. At subsequent visits the history should include ARV doses with start and stop dates, other medications and vaccinations (including sites of injections), diagnoses, and signs and symptoms. Results of HIV-1 testing done outside of the study should be abstracted. Feeding history to determine breast milk exposure will be obtained at each visit until complete cessation of breastfeeding.
6. Complete physical exam including vitals (temperature, heart rate, respiratory rate, and, if possible, blood pressure), weight, length, and head circumference at all visits except Day 1, 3, 7 and 14 and Week 14. Targeted physical exam including vitals (as above) and weight at Days 1, 3, 7 and 14 and Week 14 visits. Examination of VRC07-523LS injection site should occur at all visits. Data will only be recorded on CRFs through the Day 28 visit (for all participants) and the Week 16 visit (for participants who received the second injection), with the exception that if there are still signs of a reaction present at those visits or any reaction noted at a later visit, data will be recorded at scheduled visits until resolved or until no further resolution is expected.
7. An initial VRC07-523LS immunization, 80 mg (if <4.5 kg) or 100 mg (if ≥ 4.5 kg) subcutaneous injection, must be administered no later than the 5th day of life (see MOP for administration instructions). A second immunization of VRC07-523LS, 100 mg subcutaneous injection, will be administered at Week 12 only if the infant has not had complete cessation of breastfeeding. Complete cessation of breastfeeding is defined as having completely stopped all exposure to breast milk for ≥ 28 days. There should be no administration of VRC07-523LS if the infant has had a positive HIV PCR test result.
    - Infants should be monitored for a minimum of 4 hours after initial study treatment injection, with assessments at 15, 30 and 60 minutes post dose. Clinic personnel must observe participant for any potential adverse reactions to the study immunization. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected adverse reaction. The subsequent injection should be monitored for a minimum of 60 minutes (+ 30 minutes), with assessments at 15, 30 and 60 minutes post dose.
    - Infants will also be evaluated for local reactions and pain at 1 hour (+30 minutes) after each injection and results recorded on a study CRF.
    - Caregivers of participants will be provided with a diary card on which to note any reactions at the injection site. After the initial injection, study staff will review the diary card with caregivers at the Day 3 and Day 7 visits. After the Week 12 injection (if administered), study staff will contact caregivers between 3 to 5 days following the injection to review the diary card.
8. Hematology should include CBC with differential and platelet count. (Not required at screening if collected clinically at birth and results are available).
9. Chemistries should include AST, ALT, total bilirubin, and creatinine. (Not required at screening if collected clinically at birth and ALT results are available). Obtain additional ALT and AST measurements upon evidence of hepatic-related clinical adverse events (jaundice, enlargement

of the liver).

10. HIV-1 NAT (nucleic acid testing) by a method that detects DNA is required for diagnostic testing since VRC07-523LS might suppress HIV-1 RNA. For NAT at Screening, see footnote 11. HIV-1 NAT testing must be run in a VQA-approved laboratory. If the infant has a positive HIV-1 NAT at any time, confirmation and additional HIV testing should be performed as per APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1]. Infants confirmed to be HIV-1-infected should be evaluated according to both APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding) and APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1], but without duplication of specific blood tests if the study visit dates are concurrent. When possible, APPENDIX IC: HIV-1 Infected Infant Schedule of Evaluations (all dose groups)[1] visits should be scheduled to coincide with APPENDIX IH: Schedule of Evaluations (Dose Group 5, Cohort 2: breastfeeding).
11. Blood for HIV-1 NAT drawn at Screening must be obtained prior to VRC07-523LS administration. It may be drawn with the Entry blood. Results may be pending at study entry. If an HIV-1 NAT (DNA or RNA or combined) was collected clinically prior to study entry and tested in a laboratory with VQA approval, the test does not need to be duplicated for the study; in this case, results will be abstracted for the study.
12. HIV antibody testing should be performed at the approved site-associated DAIDS-monitored laboratory. If the infant remains antibody positive at or after 72 weeks, notify the protocol team. If HIV antibody is negative at Week 48 or later, subsequent HIV antibody testing is not required.
13. Samples for VRC07-523LS plasma levels should be obtained prior to VRC07-523LS administration. For infants with birth weight <2.6kg use lower sample volume at Entry. Plasma for VRC07-523LS levels and anti-VRC07-523LS levels will be processed and batch shipped per the LPC. Leftover plasma will be stored per the LPC for future HIV-related studies overseen per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
14. PBMC from the VRC07-523LS plasma level sample will be isolated if site is capable of PBMC isolation and storage (see LPC for qualifications). PBMC will be used for HIV characterization if there are infants with HIV infection. Leftover PBMC will be stored per the LPC for future HIV-related studies (possibly including genetic testing) per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
15. Samples for VRC07-523LS serum should be obtained prior to VRC07-523LS administration. For infants with birth weight <2.6kg: do not collect VRC07-523LS serum samples at Entry, Day 14, Day 28, and Week 8. Serum for VRC07-523LS antibody levels and neutralization assays will be processed and batch shipped per the LPC. Leftover serum may be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
16. Anti- VRC07-523LS Ab will be tested using plasma collected for VRC07-523LS levels.
17. Oral fluid is collected with Weck-cel Sponge oral fluid collection device. Sample at Entry should be collected prior to VRC07-523LS administration as baseline. Assay will be performed to detect VRC07-523LS antibody level sample. Leftover oral fluid will be stored per the LPC for future HIV-related studies per IMPAACT SOP. See LPC for collection procedure, processing, storage, and shipping instructions.
18. For infants with birth weight <2.6kg lower sample volume will be collected. See also Footnotes 13 and 15. Volumes equate to ≤3ml/kg drawn within 24 hours and ≤ 9.5 ml/kg drawn over 8 weeks. These are below the NIH Clinical Center guidelines allowing a maximum of 5ml/kg within 24 hours and 9.5ml/kg drawn over an 8-week period.

Priority for blood samples: 1: HIV-1 NAT; 2: CBC, chemistry; 3: VRC07-523LS plasma levels; 4: VRC07-523LS serum; 5: HIV-1 antibody; At Day 28, Week 12, and 24 VRC07-523LS plasma levels are first priority.

APPENDIX IIA: IMPAACT P1112 Sample Informed Consent Template: Dose Group 5, Cohort 1 (Non-breastfeeding)

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT: DOSE GROUP 5, COHORT 1 (NON-BREASTFEEDING)

Protocol IMPAACT P1112

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1 Exposed Infants
Version 4.0, dated 06 November 2018

Short title for IMPAACT P1112: Immunization Study of VRC01/VRC01LS/VRC07-523LS in Infants

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV) and there is an increased risk that the infection may be passed onto your baby despite the fact that you may be taking antiretroviral medications (medications against HIV). You are being asked to allow your baby to receive an experimental immunization within the first 72 hours after he/she is born that may protect against HIV transmission. This study is sponsored by the National Institutes of Health (NIH) which has been developing the immunization for this study. The doctor in charge of this study is [insert name]. Before you decide whether you want your baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow you and your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The transfer of HIV to newborn babies from HIV-infected mothers can occur at the time of birth. You have been identified as a mother who may be at increased risk of passing the infection onto your baby. Your baby may be at increased risk of infection because you may not have been taking anti-HIV medications earlier in the pregnancy, or HIV can be measured in your blood, or you have had a prolonged rupture of membranes (greater than 12 hours) or the HIV virus that is in you is resistant to many of the anti-HIV medications available. This research is being done to help find a safe and effective

immunization that will give babies protection against HIV infection. Immunization is the process used to help strengthen the immune system against certain diseases.

The experimental study immunizations are monoclonal antibodies (mAb). Antibodies are one of the ways the human body fights infection. "Monoclonal" means that all the antibodies in the immunization are the same. This type of immunization is temporary because the antibodies will go away over time. There are three very similar immunizations being used in this study. The first two immunizations are called "VRC01" and "VRC01LS." The immunization your baby is being offered is called "VRC07-523LS." The formal name is "VRC-HIVMAB075-00-AB." In this consent document, and in scientific publications, this antibody is called "VRC07-523LS"

The VRC01, VRC01LS, and VRC07-523LS immunizations are human antibody that may be able to block HIV from infecting the baby. VRC01 was originally discovered in an HIV-infected person, but the immunization is <u>not</u> obtained by collecting it from a person. All of these immunizations are made using the same controlled, clean conditions used for making medications. They were developed by the National Institutes of Health (NIH).

The VRC01, VRC01LS, and VRC07-523LS have been shown to attach to and inactivate many HIV viruses in laboratory experiments. VRC01 has been tested in adults and babies to look at safety and to see what dose (how much) produces the desired blood levels of antibodies. VRC01LS and VRC07-523LS have been tested in the laboratory and in adults. VRC01LS has also been given to babies. We are using information from all of these studies to help us choose the correct dose of VRC07-523LS for babies.

In this study, babies will receive a single dose of the VRC07-523LS immunization and will be followed for safety and have blood collected to measure the levels of VRC07-523LS in the baby's blood. Another group of babies, who are breastfeeding, will receive either one or two doses of the VRC07-523LS.

WHAT DO I HAVE TO DO TO BE IN THE STUDY?

If you decide that you want to be in the study, we will check to make sure you are able to enroll in this study.

<u>Screening to see if you can be in the study</u>

- We will ask for your permission to review your medical records to see if you have been diagnosed with HIV according to the study criteria. If we do not find information about your HIV infection in your medical record, we will collect a 5 mL (1 teaspoon) sample of your blood to determine if you have HIV. We will also review the records for other illnesses that you may have had and that might have an impact on your baby's health.
- We will ask you questions about other studies you might have been in, and health conditions and treatments you might have received. If your baby is expected to receive any immunoglobulin products after birth, then you and your baby cannot participate.

- The review of your medical history and the interview with you may be done while you are still pregnant or shortly after you deliver your baby. If it is done while you are still pregnant you will also be asked some questions after your baby's birth.
- If you are able to be in the study, then we will check to make sure that your baby can be in the study.

Entry Visit or Day 0

- If we have not already done so, we will ask for your permission to review your medical records to see if you have been diagnosed with HIV according to the study criteria. We will also review the records for other illnesses you may have had and that might have an impact on your baby's health.
- We will ask you questions about other studies you might have been in, and health conditions and treatments you might have received.
- We will collect a 20 - 25 mL (1 and ½ tablespoon) sample of your blood. Some of this blood will be used to determine if you have HIV (if it is not clear in your medical record).. The rest of the blood will be stored for future use. The results of these tests will be used for research purposes only and will not be reported to you or your doctor.
- Please note that the screening and entry visit maybe combined on the same day.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

If you allow your baby to be in this study, your baby will receive a one-time dose of the VRC07-523LS immunization within the first 72 hours of his/her life. The dose of the immunization is based on your baby's weight. Depending on the dose of the immunization, the immunization will be given in either one or two injections into the skin of the upper leg(s). He/she will then be followed on the study for two years.

All babies who are enrolled and immunized on the study will be seen and evaluated several times throughout a two-year study period. If at any time during this period, the safety assessments show that the immunization maybe unsafe, no new babies will be immunized and the babies already on the study will continue to have follow-up evaluations until the end of the two-year period.

Study visits for your baby

Including the screening visit to check whether your baby is eligible for the study, there are 16 study visits. If your baby is found to be HIV-infected during the study, he/she will return for visits through Week 96; the number of visits will depend on the age of your baby at the time the HIV infection was discovered. If your baby was less than 2.6 kg at birth, we will collect less blood than if your baby was larger at birth. If this applies to your child, the study doctor or nurse will inform you.

[Sites that intend to conduct home visits should include detail throughout this section on the time study time points when home visits may be done in lieu of a clinic visit.]

Screening visit to see if your baby can be in the study

If you agree to allow your baby to be in this study, we will do some tests to make sure your baby is able to enter this study. This visit will last about 1-2 hours. At this visit, we will:

- Ask if you are willing for your baby to complete all scheduled study visits.
- Ask about your baby's medical history, which will include how your baby has been doing, if he/she has been sick, conditions he/she may have and any medicines he/she has been taking. This will also include your permission to review your baby's medical records to check for medical conditions and any treatment your baby may have received.
- Collect some demographic data such as race, ethnicity and gender.
- Do a physical examination that may include length, weight, head measurement and vital signs such as temperature, blood pressure, heart rate, and respiratory rate (how fast the baby breathes).
- Draw blood from either a vein (called a venipuncture) and/or from your baby's heel (called a heel stick). We will test your baby for HIV if this has not already been done as part of your baby's standard of care (the care your baby receives regardless of the study). In addition, routine blood tests will be done to tell us well your baby's liver and kidneys are working: again, these tests will only be performed for the study if they were not already collected for your baby's medical care. The total amount of blood drawn at this visit will be 2-3 mL (about half a teaspoon).
- In addition, study staff may contact your baby's doctor (if you have one) to inform the doctor about this study.

Entry Visit or Day 0

If your baby is able to be in the study, Day 0 is the day that he/she receives the VRC07-523LS immunization. Because the immunization must be given to the baby within 72 hours of his/her birth, the entry day or Day 0 may also be the same day as the screening day. This visit will last for a minimum of 4 hours.

- If the entry day is on a different day than the screening day, we will ask about any medical history since the screening visit and will also do a physical exam.
- In addition to the blood tests for screening, we will draw 2-3 mL (about a half teaspoon) of blood to measure a baseline of VRC07-523LS levels and anti-VRC07-523LS antibody levels to compare results at your baby's next visit. This will be drawn before your baby receives the VRC07-523LS injection. If the screening visit and entry (or Day 0) visit are done on the same day, then we may draw all the blood, a total of 6-7 mL (about 1½ teaspoon) all at the same time. Some of this blood may be stored for future use.
- We will also collect about 1 mL (¼ teaspoon) of saliva from your baby's mouth by placing a small pad (about the size of a thumbnail attached to stick) between the gum and cheek of your baby. After a minute or two we will remove the pad and put it in a container. The pad will be tested to measure the amount of VRC07-523LS in your baby's saliva.
- Depending on your baby's weight, your baby will be given one or two injections of VRC07-523LS in the skin of the upper leg. After your baby has received the

immunization, your baby will be observed for at least four hours so that we can check the immunization injection site and to make sure that he/she is well.
- You will be given a diary card to take with you. For a few days after this visit, you will be asked to note any reactions at the injection site(s) and other information about your baby's health on the diary card.

Day 1 visit

There will be a visit of about 1½ hours duration one day after your baby has received the immunization. At this visit, we will:
- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Day 3 visit

There will be a visit of about 1½ hours duration three days after your baby has received the immunization. At this visit, we will:
- Ask about your baby's medical history and review the diary card.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.

Day 7 visit

There will be a visit of about 1½ hours duration 7 days after your baby has received the immunization. At this visit, we will:
- Ask about your baby's medical history and review the diary card.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Day 14 and 28 and Week 8

There will be visits of about 1½ hours duration each at Day 14 and 28 and Week 8 after your baby has received the immunization. At these visits, we will:
- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 3 to 6 mL (about ½ teaspoon to slightly more than a teaspoon) of blood. Depending on the visit, we will measure the amount of VRC07-523LS in your baby's blood, measure your baby's response to the VRC07-523LS, test your baby for HIV, to tell us about your baby's blood cells and check how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Week 12, 24 and 36 visits

There will be visits of about 1½ hours duration at 12, 24 and 36 weeks after your baby has received the immunization. At these visits, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw up to 8 mL (about 1½ teaspoon) of blood to test your baby for HIV, and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood, and also (at Week 12 and Week 24) to tell us about your baby's blood cells and how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Week 48, 60, 72 and 84 visits

There will be visits of about 1½ hours duration 48, 60, 72 and 84 weeks after your baby has received the immunization. At these visits, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 7 mL (slightly more than a teaspoon) of blood to test your baby for HIV, and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Week 96 visit

There will be a visit of about 1½ hours duration 96 weeks after your baby has received the immunization. At this visit, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 7 mL (slightly more than a teaspoon) of blood for HIV testing and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Early Discontinuation visit

If your baby is not able to continue with the study after he/she has received the VRC07-523LS immunization, we will ask you to return for a final Early Discontinuation visit. This visit will take about 1 ½ hours. At this visit, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 10 mL (2 teaspoons) of blood to test your baby for HIV, and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood, to tell us about your baby's blood cells, and how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth

Testing for HIV

Your baby will be tested for HIV at different time intervals as part of his/her standard of care. *[Sites: please insert details about HIV testing as part of local standard of care and reporting requirements of a positive test.]*

***If your baby has a positive HIV test*:**

- It means that your baby may have HIV virus in his/her blood. It will be important that your baby return to the clinic as soon as possible for a test to confirm whether the baby is infected with HIV. About 5 mL (almost 1 teaspoon) of blood will be drawn to look for how much HIV is in your baby's blood and to measure your baby's T cells. We will ask about medical history since the last visit, do a physical examination and will draw an additional 1 mL (less than ¼ teaspoon) to look at the amount of VRC07-523LS in your baby's blood. If you consent, an additional 1 mL of blood will be drawn for storage.
- You and your baby will return about 2 weeks later when the results of the confirmatory test are available. These results will be shared with you and with your baby's healthcare provider. If your baby is confirmed to be HIV-infected, you will be asked to return at 2 weeks, 4 weeks, and monthly until your child's doctor begins ART for your child. Whenever possible, these will be scheduled to coincide with scheduled study visits. At each visit the following will be done:
    - History
    - Physical examination
    - Blood collection for HIV virus level
    - Blood collection for VRC07-523LS level
    - If you consent, an additional 1 mL of blood will be drawn for storage
- Once your baby is started on anti-HIV medications, your baby's study visits can be according to the standard of care. *[Sites to insert follow up for HIV-infected infants.]* Your baby will continue to return for study visits as regularly scheduled. At each of these visits, if your baby is having blood drawn as part of standard of care, and if you consent, an additional 1 mL (less than ¼ teaspoon) of blood will be drawn for storage.

Results of Tests

Throughout the study, you will be informed of the results of the HIV testing and routine blood tests when they become available. The results of the other blood tests and the results of the saliva testing will be used for research purposes only. These results will not be reported to you or your doctor.

Storage of Blood Samples

Some of your and your baby's blood and saliva will be stored (with protectors of identity) and used for future IMPAACT-approved, HIV-related research. Your baby can still participate in this study even if you decide that you do not want to have his/her blood stored for later testing.

Your/your baby's samples will be shipped to and stored at a special laboratory facility in the United States. Only approved researchers will have access to them. People who work at the facility will also have access to your/your child's samples to keep track of

them. These people won't have information that directly identifies you/your child. Your/your baby's samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your baby's samples will be reviewed by the United States National Institutes of Health (NIH). There is no time limit on how long your/your baby's samples will be stored.

The researchers do not plan to contact you or your baby's regular doctor with the results of studies done using your/your baby's stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your/your child's medical care. If the researchers decide that the result of a certain study provides important information for your/your baby's medical care, your/your baby's study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your/your baby's samples stored for future research studies. You/your baby can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your/your baby's samples at any time. If you withdraw your consent, these stored samples will be destroyed.

There are two types of testing that can be done with the specimens that are in storage. Please read the following statements carefully and then mark your initials and date in the appropriate space provided.

1. Testing for General HIV-related studies

Researchers would like to store your/your baby's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at what makes up you/your child's cells).

> Benefits: There are no direct benefits to you/your baby. You/Your baby will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.
>
> Risks: The specimens would be collected as part of you/your baby's study visits. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. Once in storage, there are few risks. You/your baby's name will not be available to the staff at the laboratory or to the scientists who may be doing any future test.

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, general HIV-related research studies.

_____ Yes _____ No _____ Date

I agree to allow my baby's blood and saliva samples to be stored for use in future IMPAACT-approved, general HIV-related research studies.

_____ Yes _____ No _____ Date

2. Testing for Special HIV-related studies

Researchers in this study would also like to store your/your baby's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person's genetic makeup (you/your baby's DNA or unique cell makeup) either protects them or puts them at greater risk. It may be that researchers use some of your/your baby's blood to make a "cell line." That means the blood cells can keep dividing and give an endless supply of you/your baby's DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you/your baby. You/your baby will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of you/your baby's study visits. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. Once in storage, there are few risks. Your/your baby's name will not be available to the laboratory staff or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on you/your baby's genetic makeup.

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, special HIV-related research studies.

_____ Yes _____ No _____ Date

I agree to allow my baby's blood and saliva samples to be stored for use in future IMPAACT-approved, special HIV-related research studies.

_____ Yes _____ No _____ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 39 mothers and their babies will be part of the VRC01 portion of this study. About 20 mothers and their babies will be part of the VRC01LS portion of this study. About 20 mothers and their babies will be part of the VRC07-523LS portion of this study.

HOW LONG WILL I/MY CHILD/BABY BE IN THIS STUDY?

You will only be in the study for as long as it takes to screen you and determine that you are eligible for the study (about one day) and have your blood collected. Your baby will be in this study for 96 weeks (about two years).

WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?

The study doctor may need to take you/your baby off the study early without your permission if:

- Your infant does not receive the VRC07-523LS immunization.
- You are unable to return for infant follow-up evaluations.
- The investigator determines that further participation would be detrimental to you or your baby's health or well-being.
- You are unable to comply with the study requirements so as to seriously interfere with the validity of the study results.
- The study may be discontinued by the NIH, Office of Human Research Protection (OHRP), U.S. Food and Drug Administration (FDA), the IMPAACT Network, an Institutional Research Board (IRB)/Ethics Committee (EC) or local government regulatory agency. An IRB or EC is a committee who watches over the safety and rights of research participants.

WHAT ARE THE RISKS OF THE STUDY?

This section describes the risks we know about. There may also be unknown risks, even serious ones which we do not know about. We will tell you if we learn anything new that may affect you/your baby's health and/or willingness to stay in the study.

Risks of routine medical procedures:
In this study, we will do some routine medical procedures including taking blood and collecting saliva. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. The saliva pad may be slightly uncomfortable for a few minutes while in the baby's mouth.

Risks from subcutaneous (SC) injections
It is possible that your baby may have some side effects from the VRC07-523LS injection. General risks of an injection method include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site and, rarely, local infection.

Risks of the VRC07-523LS
This study is the first time that VRC07-523LS is being given to babies, but to date, 26 adults have received VRC07-523LS and more than 40 infants have received the very similar VRC01 and VRC01LS immunizations.

There have been several studies of VRC01 in adults. So far, there have been no serious side effects seen in the adults who have received VRC01, VRC01LS or VRC07-523LS. There have been mild and brief local reactions such as redness, itching and swelling and mild pain in about 14% of the adults receiving an injection of VRC01. In those studies, about one half of the adults had one or more mild side effects such as a general feeling of discomfort, muscle aches, headache, nausea, rash and joint pain but most of these were mild.

In this study, nearly 40 babies have received VRC01 and 21 have received the VRC01LS. So far, there have been no serious side effects seen in the babies who have received VRC01 or VRC01LS. There has been some bruising, swelling and redness at the injection site, but these get better quickly. Most side effects tend to occur within the first 24 hours. Your baby will be observed for at least four hours after he/she has received the VRC07-523LS.

Side effects are expected to be rare but may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart or chest pain. These reactions may be related to how fast the antibody product is given. The immunization will be given to your baby slowly.

Monoclonal antibody products have a small risk of serious allergic reactions, including anaphylaxis. Anaphylaxis may include difficulty breathing, low blood pressure, hives or rash, swelling in the mouth and face. These reactions are life-threatening. Such reactions usually occur quickly after the injection. Therefore, your baby will be observed in clinic for at least four hours after receiving the VRC07-523LS. The clinics are prepared to treat allergic reactions.

Serum sickness is a delayed type of allergic reaction that may occur a week or two after a product is given. This reaction may include hives or rash, fever, big lymph nodes (glands in the neck and along the body), and pains in the joints. You will be contacted after the visit to make sure your baby is not having this type of reaction.

In adults who have received VRC01 and VRC01LS, allergic reactions have been seen but they have been rare and responded to treatment.

Some women will be offered enrollment while a confirmatory HIV test is pending. If this happens, there is a very small chance that your HIV infection will not be confirmed and that you are not HIV-infected. If so, your baby may have received VRC07-523LS even though he/she is not at risk of getting HIV.

In addition to the possible risks that are listed above, VRC07-523LS may have other side effects that are not yet known. It is also possible that the VRC07-523LS will have unknown effects on the course of your baby's HIV infection (if he/she becomes infected).

Risks of disclosure of your personal information
We will take several steps to protect you and your baby's personal information. Although the risk is very low, it is possible that you or your baby's personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you or your baby takes part in this study, it is possible that the immunization may prevent the transmission of HIV to the baby from the mother. However, the studies of VRC07-523LS have not looked at whether VRC07-523LS is good at preventing transmission of HIV. It is also possible that your baby may receive no benefit from being in this study. Information learned from this study may help others who are exposed to or infected with HIV.

WHAT OTHER CHOICES DOES MY BABY HAVE BESIDES THIS STUDY?

You and your baby do not have to participate in this study. You may choose to have standard of care**.** You and your baby will still receive care without being in the study. All babies will receive standard antiretroviral medications after their birth in order to decrease the likelihood that they may become HIV-infected whether on study or not.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health; this is enforceable only for United States sites. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your records include the U.S. Food and Drug Administration or other Drug Regulatory Authority *[international sites: insert as appropriate]*, Office of Human Research Protection (OHRP), the site IRB or EC *[insert name of site IRB or EC]*, the National Institutes of Health, the IMPAACT network, study staff, study monitors, and their designees, and other local, US, and international regulatory entities.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under certain circumstances such as child abuse.

As part of this study, you and your baby will be tested for HIV. We are required to report all positive HIV test results to *[add local Health Department/State Board of Health]*. The results will be kept confidential to the extent permissible under the law.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the study visits, examinations, blood tests or the immunization you will be given. You or your insurance will be responsible for costs that are considered standard of care that is the care you or your baby would receive whether or not you or your baby are on the study. *[Note to sites: This statement can be modified as needed for your site.]*

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. *[Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]*

WILL I RECEIVE ANY PAYMENT?

You will not be paid for your baby to be in this study. You may be paid back for the cost of transportation, meals and other personal expenses for this study. *[Sites – modify per local guidelines.]*

WHAT HAPPENS IF I AM/MY CHILD/BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or not to allow your baby to take part in this study. You may leave this study or take your baby out of the study at any time. You and your baby will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect you/your baby's health, welfare or willingness to stay in this study. If you want to know the final results of the study, let the study staff know.

[Site: if appropriate, include language here regarding the legal requirement to report positive HIV tests.]

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your/your child's/baby's rights as a research participant, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree take part in this study and you agree to allow your baby to be in this study, please sign your name below.

Mother's Name (print)	Mother's Signature, Date and Time
Study Staff Conducting Consent Discussion (print)	Study Staff Signature, Date and Time
Witness' Name (print) (As appropriate)	Witness's Signature, Date and Time
Father's Name (If father's consent is required)	Father's Signature, Date and Time (If father's consent is required)

APPENDIX IIB: IMPAACT P1112 Sample Informed Consent Template: Dose Group 5, Cohort 2 (breastfeeding)

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
Protocol IMPAACT P1112: Dose Group 5, Cohort 2 (breastfeeding)

Open-Label, Dose-Escalating, Phase I Study to Determine Safety and Pharmacokinetic Parameters of Subcutaneous (SC) VRC01, VRC01LS, and VRC07-523LS, Potent Anti-HIV Neutralizing Monoclonal Antibodies, in HIV-1 Exposed Infants
Version 4.0, dated 06 November 2018

Short title for IMPAACT P1112: Immunization Study of VRC01/VRC01LS/VRC07-523LS in Infants

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV) and you are breastfeeding. Even though you or your baby may be taking antiretroviral medications (medications against HIV), there is a chance your child could get HIV. You are being asked to allow your baby to receive a dose of an experimental immunization within the first 5 days after he/she is born and another dose at 12 weeks if you are still breastfeeding. This may protect against HIV transmission during the period that you are breastfeeding. This study is sponsored by the National Institutes of Health (NIH) which has been developing the immunization for this study. The doctor in charge of this study is [insert name]. Before you decide whether you want your baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to allow you and your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The transfer of HIV to newborn babies from HIV-infected mothers can occur at the time of birth and during breastfeeding. Your baby is at ongoing risk of HIV because you will be breastfeeding your baby. This research is being done to help find a safe and effective immunization that will give babies protection against HIV infection. Immunization is the process used to help strengthen the immune system against certain diseases.

The experimental study immunizations are monoclonal antibodies (mAb). Antibodies are one of the ways the human body fights infection. "Monoclonal" means that all the antibodies in the immunization are the same. This type of immunization is temporary because the antibodies will go away over time. There are three very similar immunizations being used in this study. The first two immunizations are called "VRC01" and "VRC01LS." The immunization your baby is being offered is called "VRC07-523LS." The formal name is "VRC-HIVMAB075-00-AB." In this consent document, and in scientific publications, this antibody is called "VRC07-523LS".

The VRC01, VRC01LS, and VRC07-523LS immunizations are human antibody that may be able to block HIV from infecting the baby. VRC01 was originally discovered in an HIV-infected person, but the immunization is not obtained by collecting it from a person. All of these immunizations are made using the same controlled, clean conditions used for making medications. They were developed by the National Institutes of Health (NIH).

The VRC01, VRC01LS, and VRC07-523LS have been shown to attach to and inactivate many HIV viruses in laboratory experiments. VRC01 has been tested in adults and babies to look at safety and to see what dose (how much) produces the desired blood levels of antibodies. VRC01LS and VRC07-523LS have been tested in the laboratory and in adults. VRC01LS has also been given to babies. We are using information from all of these studies to help us choose the correct dose of VRC07-523LS for babies.

In this study, babies will receive either one or two doses of the VRC07-523LS immunization and will be followed for safety and have blood collected to measure the levels of VRC07-523LS in the baby's blood. Another group of babies, who are not breastfeeding, will receive a single dose of the VRC07-523LS.

WHAT DO I HAVE TO DO TO BE IN THE STUDY?

If you decide that you want to be in the study, we will check to make sure you are able to enroll in this study.

Screening to see if you can be in the study

- We will ask for your permission to review your medical records to see if you have been diagnosed with HIV according to the study criteria. If we do not find information about your HIV infection in your medical record, we will collect a 5 mL (1 teaspoon) sample of your blood to determine if you have HIV. We will also review the records for other illnesses that you may have had and that might have an impact on your baby's health.
- We will ask you questions about other studies you might have been in, and health conditions and treatments you might have received. If your baby is expected to receive any immunoglobulin products after birth, then you and your baby cannot participate.
- The review of your medical history and the interview with you may be done while you are still pregnant or shortly after you deliver your baby. If it is done while you are still pregnant you will also be asked some questions after your baby's birth.

- If you are able to be in the study, then we will check to make sure that your baby can be in the study.

Entry Visit or Day 0

- If we have not already done so, we will ask for your permission to review your medical records to see if you have been diagnosed with HIV according to the study criteria. We will also review the records for other illnesses you may have had and that might have an impact on your baby's health.
- We will ask you questions about other studies you might have been in, and health conditions and treatments you might have received.
- We will collect a 20 mL (1 and ½ tablespoon) sample of your blood. Some of this blood will be used to determine if you have HIV (if it is not clear in your medical record), how much HIV is in your blood and how much it may have affected your immune system. The rest of the blood will be stored for future use. The results of these tests will be used for research purposes only and will not be reported to you or your doctor.
- Please note that the screening and entry visit maybe combined on the same day.

WHAT DOES MY BABY HAVE TO DO IF HE/SHE IS IN THIS STUDY?

If you allow your baby to be in this study, your baby will receive a dose of the VRC07-523LS immunization within the first 5 days of his/her life and then again at 12 weeks of life if you are still breastfeeding. The dose of the immunization is based on your baby's weight. Depending on the dose of the immunization, the immunization will be given in either one or two injections into the skin of the upper leg(s).

All babies who are enrolled and immunized on the study of VRC07-523LS will be seen and evaluated several times throughout a two-year study period. If at any time during this period, the safety assessments show that the immunization maybe unsafe, no new babies will be immunized and the babies already on the study will continue to have follow-up evaluations until the end of the two-year period.

Study visits for your baby

The number of visits will depend on how long you breastfeed your baby and whether your baby receives one or two doses of the immunization. If you breastfeed only a short time (less than 2 months), your baby will have 15 visits. If you breastfeed for longer than 2 months, your baby will have 17 visits.

If your baby is found to be HIV-infected, he or she will return for visits through the end of the study. If your baby is found to be HIV-infected before he or she is 12 weeks old, your baby will not receive a second immunization.

If your baby was less than 2.6 kg at birth, we will collect less blood than if your baby was larger at birth. If this applies to your child, the study doctor or nurse will inform you.

[Sites that intend to conduct home visits should include detail throughout this section on the time study time points when home visits may be done in lieu of a clinic visit.]

Screening visit to see if your baby can be in the study

If you agree to allow your baby to be in this study, we will do some tests to make sure your baby is able to enter this study. This visit will last about 1-2 hours. At this visit, we will:

- Ask if you are willing for your baby to complete all scheduled study visits.
- Ask about your baby's medical history, which will include how your baby has been doing, if he/she has been sick, conditions he/she may have and any medicines he/she has been taking. This will also include your permission to review your baby's medical records to check for medical conditions and any treatment your baby may have received.
- Collect some demographic data such as race, ethnicity and gender.
- Do a physical examination that may include length, weight, head measurement and vital signs such as temperature, blood pressure, heart rate, and respiratory rate (how fast the baby breathes).
- Draw blood from either a vein (called a venipuncture) and/or from your baby's heel (called a heel stick). We will test your baby for HIV if this has not already been done as part of your baby's standard of care (the care your baby receives regardless of the study). In addition, routine blood tests will be done to tell us how well your baby's liver and kidneys are working: again, these tests will only be performed for the study if they were not already collected for your baby's medical care. The total amount of blood drawn at this visit will be 2-3 mL (about half a teaspoon).
- In addition, study staff may contact your baby's doctor (if you have one) to inform the doctor about this study.

Entry Visit or Day 0

If your baby is able to be in the study, Day 0 is the day that he/she receives the first dose of the VRC07-523LS immunization. Because the immunization must be given to the baby within the first 5 days of his/her birth, the entry day or Day 0 may also be the same day as the screening day. This visit will last for a minimum of 4 hours.

- If the entry day is on a different day than the screening day, we will ask about any medical history since the screening visit and will also do a physical exam.
- In addition to the blood tests for screening we will draw 2-4 mL (about a half teaspoon) of blood to measure a baseline of VRC07-523LS levels and anti-VRC07-523LS antibody levels to compare results at your baby's next visit. This will be drawn before your baby receives the VRC07-523LS injection. If the screening visit and entry (or Day 0) visit are done on the same day, then we may draw all the blood, a total of 4-7 mL (up to 1½ teaspoon) all at the same time. Some of this blood may be stored for future use.
- We will also collect about 1 mL (¼ teaspoon) of saliva from your baby's mouth by placing a small pad (about the size of a thumbnail attached to stick) between the gum and cheek of your baby. After a minute or two we will remove the pad and put it in a

container. The pad will be tested to measure the amount of VRC07-523LS in your baby's saliva.

- Depending on your baby's weight, **y**our baby will be given one or two injections of VRC07-523LS in the skin of the upper leg. After your baby has received the immunization, your baby will be observed for at least four hours so that we can check the immunization injection site(s) and to make sure that he/she is well.
- You will be given a diary card to take with you. For a few days after this visit, you will be asked to note any reactions at the injection site(s) and other information about your baby's health on the diary card.

Day 1 visit

There will be a visit of about 1½ hours duration 1 day after your baby has received the immunization. At this visit, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Day 3 visit

There will be a visit of about 1½ hours duration 3 days after your baby has received the immunization. At this visit, we will:

- Ask about your baby's medical history and review the diary card.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.

Day 7 visit

There will be a visit of about 1½ hours duration 7 days after your baby has received the immunization. At this visit, we will:

- Ask about your baby's medical history and review the diary card.
- Do a physical examination and check the immunization site(s).
- Draw 1 mL (¼ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Day 14 and 28 and Week 8

There will be visits of about 1½ hours duration each at Day 14 and 28 and Week 8 after your baby has received the immunization. At these visits, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 3 to 6 mL (about ½ teaspoon to slightly more than a teaspoon) of blood. Depending on the visit, we will measure the amount of VRC07-523LS in your baby's blood, measure your baby's response to the VRC07-523LS, test your baby for HIV,

to tell us about your baby's blood cells and check how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Week 12

There will be a visit 12 weeks after your baby has received the immunization. If your baby has not been at your breast at all during the prior 28 days, this visit will be of about 1½ hours. If your baby has been at your breast, even once, in the past 28 days, your baby will receive another immunization at this visit. If your baby receives an immunization, this visit will last at least 2 hours.

At this visit, we will:
- Ask about your baby's medical history.
- Do a physical examination and check the immunization sites.
- Draw 8 mL (about 1½ teaspoon) of blood to measure the amount of VRC07-523LS in your baby's blood, measure your baby's response to the VRC07-523LS, test your baby for HIV, tell us about your baby's blood cells, and check how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.
- If your baby receives an immunization at this visit, he/she will be observed for at least one hour so that we can check the immunization injection site(s) and to make sure that he/she is well. We will then phone you between 3 and 5 days after the immunization to make sure all is still well.

Week 14 and Week 16 (if your baby receives a second immunization)

If your baby receives a second immunization at Week 12, there will be visits 2 weeks and 4 weeks after that second immunization. These visits will take approximately 1 ½ hours. At this visit we will:
- Ask about your baby's medical history.
- Do a physical examination and check the immunization sites.
- Draw 4-6 mL (about 1 teaspoon) of blood to measure VRC07-523LS levels. Two weeks after the second immunization, we will draw 2 more mL of blood to tell us about your baby's blood cells and how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth.

Weeks 24, 36, 48, 60, 72, and 84

Once your baby has been in the study 24 weeks, we will ask you and your baby to return to the clinic every 12 weeks (3 months). These visits will last about 1 ½ hours. At these visits we will:
- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw about 8 mL (about 1½ teaspoons) of blood to test your baby for HIV, to measure VRC07-523LS levels and your baby's response to VRC07-523LS and also to tell us about your baby's blood cells and how well your baby's liver and kidneys are working (at Weeks 24 and 36). Some of this blood may be stored for future use.

- Collect a small amount of saliva from your baby's mouth.

Week 96 visit

There will be a visit of about 1½ hours duration 96 weeks after your baby started the study. At this visit, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 8 mL (about 1½ teaspoons) of blood for HIV testing and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth

Early Discontinuation visit

If your baby is not able to continue with the study after receiving the VRC07-523LS immunization, we will ask you to return for a final Early Discontinuation visit. This visit will take about 1½ hours. At this visit, we will:

- Ask about your baby's medical history.
- Do a physical examination and check the immunization site(s).
- Draw 10 mL (2 teaspoons) of blood to of blood to test your baby for HIV, and to measure the baby's response to the VRC07-523LS as well as the amount of VRC07-523LS in your baby's blood, to tell us about your baby's blood cells, and how well your baby's liver and kidneys are working. Some of this blood may be stored for future use.
- Collect a small amount of saliva from your baby's mouth

Visits if your baby is found to be HIV-infected

As noted in the visit details, your baby will be tested for HIV at most study visits. *[Sites: please insert details about HIV testing as part of local standard of care and reporting requirements of a positive test.]*

***If your baby has a positive HIV test*:**

- It means that your baby may have HIV virus in his/her blood. If requested, it will be It will be important that your baby return to the clinic as soon as possible for a test to confirm whether the baby is infected with HIV. About 5 mL (almost 1 teaspoon) of blood will be drawn to look for how much HIV is in your baby's blood and to measure your baby's T cells. If this visit is not a regular study visit day, we will ask about medical history since the last visit, do a physical examination and will draw an additional 1 mL (less than ¼ teaspoon) to look at the amount of VRC07-523LS in your baby's blood. If you consent, an additional 1 mL of blood will be drawn for storage.
- You and your baby will return about 2 weeks later when the results of the confirmatory test are available. These results will be shared with you and with your baby's healthcare provider. If your baby is confirmed to be HIV-infected, you will be asked to return at 2 weeks, 4 weeks, and monthly until your child's doctor begins

ART for your child. Whenever possible, these will be scheduled to coincide with scheduled study visits. At each visit the following will be done:

- History
- Physical examination
- Blood collection for HIV virus level
- Blood collection for VRC07-523LS level
- If you consent, an additional 1 mL of blood will be drawn for storage

- Once your baby is started on anti-HIV medications, your baby's study visits can be according to the standard of care. *[Sites to insert follow up for HIV-infected infants.]* Your baby will continue to return for study visits as regularly scheduled. At each of these visits, if your baby is having blood drawn as part of standard of care, and if you consent, an additional 1 mL (less than ¼ teaspoon) of blood will be drawn for storage.

Results of Tests

Throughout the study, you will be informed of the results of the HIV testing and routine blood tests when they become available. The results of the other blood tests and the results of the saliva testing will be used for research purposes only. These results will not be reported to you or your doctor.

Storage of Blood Samples

Some of your and your baby's blood and saliva will be stored (with protectors of identity) and used for future IMPAACT-approved, HIV-related research. Your baby can still participate in this study even if you decide that you do not want to have his/her blood stored for later testing.

Your/your baby's samples will be shipped to and stored at a special laboratory facility in the United States. Only approved researchers will have access to them. People who work at the facility will also have access to your/your child's samples to keep track of them. These people won't have information that directly identifies you/your child. Your/your baby's samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your baby's samples will be reviewed by the United States National Institutes of Health (NIH). There is no time limit on how long your/your baby's samples will be stored.

The researchers do not plan to contact you or your baby's regular doctor with the results of studies done using your/your baby's stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your/your child's medical care. If the researchers decide that the result of a certain study provides important information for your/your baby's medical care, your/your baby's study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your/your baby's samples stored for future research studies. You/your baby can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your/your baby's samples at any time. If you withdraw your consent, these stored samples will be destroyed.

There are two types of testing that can be done with the specimens that are in storage. Please read the following statements carefully and then mark your initials and date in the appropriate space provided.

1. Testing for General HIV-related studies

Researchers would like to store your/your baby's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at what makes up you/your child's cells).

Benefits: There are no direct benefits to you/your baby. You/your baby will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of you/your baby's study visits. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. Once in storage, there are few risks. You/your baby's name will not be available to the staff at the laboratory or to the scientists who may be doing any future test.

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, general HIV-related research studies.

_____ Yes _____ No _____ Date

I agree to allow my baby's blood and saliva samples to be stored for use in future IMPAACT-approved, general HIV-related research studies.

_____ Yes _____ No _____ Date

2. Testing for Special HIV-related studies

Researchers in this study would also like to store your/your baby's specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person's genetic makeup (you/your baby's DNA or unique cell makeup) either protects them or puts them at greater risk. It may be that researchers use some of your/your baby's blood to make a "cell line." That means the blood cells can keep dividing and give an endless supply of you/your baby's DNA for tests to be done in the future. This kind of information will be

particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you/your baby. You/your baby will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of you/your baby's study visits. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. Once in storage, there are few risks. Your/your baby's name will not be available to the laboratory staff or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on you/your baby's genetic makeup.

I agree to allow my blood samples to be stored for use in future IMPAACT-approved, special HIV-related research studies.

_____ Yes _____ No _____ Date

I agree to allow my baby's blood and saliva samples to be stored for use in future IMPAACT-approved, special HIV-related research studies.

_____ Yes _____ No _____ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 39 mothers and their babies will be part of the VRC01 portion of this study. About 20 mothers and their babies will be part of the VRC01LS portion of this study. About 20 mothers and their babies will be part of the VRC07-523LS portion of this study.

HOW LONG WILL I/MY CHILD/BABY BE IN THIS STUDY?

You will only be in the study for as long as it takes to screen you and determine that you are eligible for the study (about one day) and have your blood collected. Your baby will be in this study for at 96 weeks (about two years).

WHY WOULD THE DOCTOR TAKE MY BABY OFF THIS STUDY EARLY?

The study doctor may need to take you/your baby off the study early without your permission if:

- Your infant does not receive the VRC07-523LS immunization.
- You are unable to return for infant follow-up evaluations.
- The investigator determines that further participation would be detrimental to you or your baby's health or well-being.

- You are unable to comply with the study requirements so as to seriously interfere with the validity of the study results.
- The study may be discontinued by the NIH, Office of Human Research Protection (OHRP), U.S. Food and Drug Administration (FDA), the IMPAACT Network, an Institutional Research Board (IRB) /Ethics Committee (EC) or local government regulatory agency. An IRB or EC is a committee who watches over the safety and rights of research participants.

WHAT ARE THE RISKS OF THE STUDY?

This section describes the risks we know about. There may also be unknown risks, even serious ones which we do not know about. We will tell you if we learn anything new that may affect you/your baby's health and/or willingness to stay in the study.

Risks of routine medical procedures:
In this study, we will do some routine medical procedures including taking blood and collecting saliva. Blood collection can cause bruising, pain and infrequently fainting or lightheadedness. The saliva pad may be slightly uncomfortable for a few minutes while in the baby's mouth.

Risks from subcutaneous (SC) injections
It is possible that your baby may have some side effects from the VRC07-523LS injection. General risks of an injection method include stinging, discomfort, pain, soreness, redness, bruising, swelling or a tiny cut at the needle insertion site and, rarely, local infection.

Risks of the VRC07-523LS
This study is the first time that VRC07-523LS is being given to babies, but to date, 26 adults have received VRC07-523LS and more than 40 infants have received the very similar VRC01 and VRC01LS immunization.

There have been several studies of VRC01 in adults. So far there have been no serious side effects seen in the adults who have received VRC01, VRC01LS, or VRC07-523LS. There have been mild and brief local reactions such as redness, itching and swelling and mild pain in about 14% of the adults receiving an injection of VRC01. In those studies, about one half of the adults had one or more mild side effects such as a general feeling of discomfort, muscle aches, headache, nausea, rash and joint pain but most of these were mild.

In this study, nearly40 babies have received VRC01 and 21 have received the VRC01LS. So far, there have been no serious side effects seen in the babies who have received VRC01 or VRC01LS. There has been some bruising, swelling and redness at the injection site, but these get better quickly. Most side effects tend to occur within the first 24 hours. Your baby will be observed for at least four hours after he/she has received the first dose of VRC07-523LS. If your baby receives a second dose of VRC07-523LSat Week 12, he/she will be observed for at least one hour after that dose.

Side effects are expected to be rare but may include fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heart or chest pain. These reactions may be related to how fast the antibody product is given. The immunization will be given to your baby slowly.

Monoclonal antibody products have a small risk of serious allergic reactions, including anaphylaxis. Anaphylaxis may include difficulty breathing, low blood pressure, hives or rash, swelling in the mouth and face. These reactions are life-threatening. Such reactions usually occur quickly after the injection. Therefore, your baby will be observed in clinic for at least four hours after the first dose and at least one hour after the second dose (if received). The clinics are prepared to treat allergic reactions.

Serum sickness is a delayed type of allergic reaction that may occur a week or two after a product is given. This reaction may include hives or rash, fever, big lymph nodes (glands in the neck and along the body), and pains in the joints. You will be contacted after the visit to make sure your baby is not having this type of reaction.

In adults who have received VRC01 and VRC01LS, allergic reactions have been seen but they have been rare and responded to treatment.

Some women will be offered enrollment while a confirmatory HIV test is pending. If this happens, there is a very small chance that your HIV infection will not be confirmed and that you are not HIV-infected. If so, your baby may have received VRC07-523LS even though he/she is not at risk of getting HIV.

In addition to the possible risks that are listed above, VRC07-523LS may have other side effects that are not yet known. It is also possible that the VRC07-523LS will have unknown effects on the course of your baby's HIV infection (if he/she becomes infected).

Risks of disclosure of your personal information
We will take several steps to protect you and your baby's personal information. Although the risk is very low, it is possible that you or your baby's personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you or your baby takes part in this study, it is possible that the immunization may prevent the transmission of HIV to the baby from the mother. However, the studies of VRC07-523LS have not looked at whether VRC07-523LS is good at preventing transmission of HIV. It is also possible that your baby may receive no benefit from being in this study. Information learned from this study may help others who are exposed to or infected with HIV.

WHAT OTHER CHOICES DOES MY BABY HAVE BESIDES THIS STUDY?

You and your baby do not have to participate in this study. You may choose to have standard of care**.** You and your baby will still receive care without being in the study. All babies will receive standard antiretroviral medications after their birth in order to decrease the likelihood that they may become HIV-infected whether on study or not.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health; this is enforceable only for United States sites. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your records include the U.S. Food and Drug Administration or other Drug Regulatory Authority *[international sites: insert as appropriate]*, Office of Human Research Protection (OHRP), the site IRB or EC *[insert name of site IRB or EC]*, the National Institutes of Health, the IMPAACT network, study staff, study monitors, and their designees, and other local, US, and international regulatory entities.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under certain circumstances such as child abuse.

As part of this study, you and your baby will be tested for HIV. We are required to report all positive HIV test results to *[add local Health Department/State Board of Health]*. The results will be kept confidential to the extent permissible under the law.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the study visits, examinations, blood tests or the immunization you will be given. You or your insurance will be responsible for costs that are considered standard of care that is the care you or your baby would receive whether or not you or your baby are on the study. *[Note to sites: This statement can be modified as needed for your site.]*

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. *[Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]*

WILL I RECEIVE ANY PAYMENT?

You will not be paid for your baby to be in this study. You may be paid back for the cost of transportation, meals and other personal expenses for this study. *[Sites – modify per local guidelines.]*

WHAT HAPPENS IF I AM/MY CHILD/BABY IS INJURED?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or not to allow your baby to take part in this study. You may leave this study or take your baby out of the study at any time. You and your baby will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect you/your baby's health, welfare or willingness to stay in this study. If you want to know the final results of the study, let the study staff know.

[Site: if appropriate, include language here regarding the legal requirement to report positive HIV tests.]

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff

- telephone number of above

For questions about your/your child's/baby's rights as a research participant, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree take part in this study and you agree to allow your baby to be in this study, please sign your name below.

Mother's Name (print)	Mother's Signature, Date and Time
Study Staff Conducting Consent Discussion (print)	Study Staff Signature, Date and Time
Witness' Name (print) (As appropriate)	Witness's Signature, Date and Time
Father's Name (If father's consent is required)	Father's Signature, Date and Time (If father's consent is required)