IMPAACT 2008

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

A Study of the International Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by the NIAID and the NICHD

Study Product Provided by the NIAID Vaccine Research Center

Presented by Wm. Borkowsky, on behalf of the P2008 team

IMPAACT VRC01 2008 study

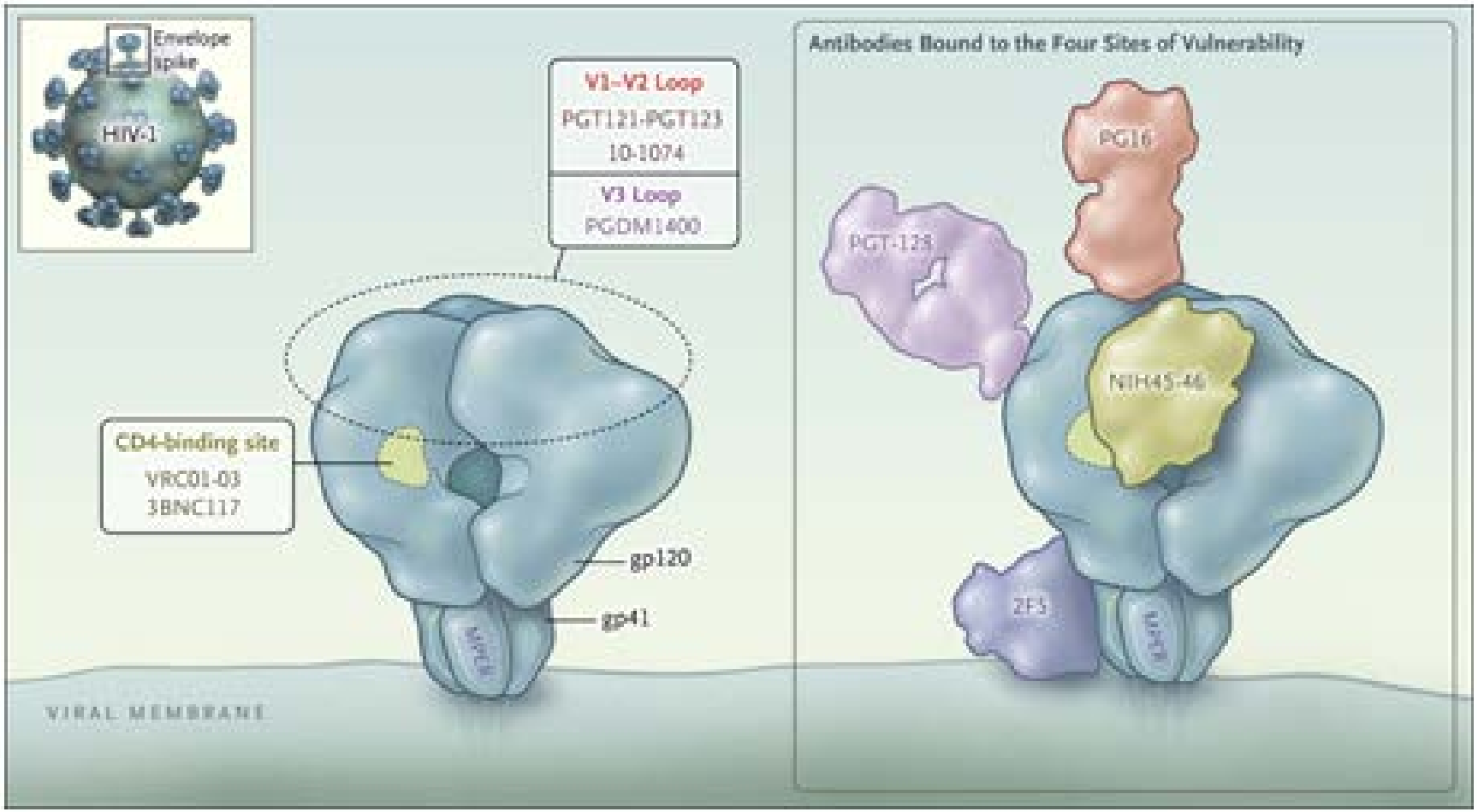
Phase I/II multisite randomized controlled study of mAb VRC01 with combination antiretroviral therapy to promote clearance of HIV-1-infected cells in infants

RATIONALE

- Addition to ART of an antibody with HIV neutralizing and ADCC activity may reduce the number of persistently infected cells by:
  - Rapid reduction of HIV-1 viremia during initial cART
  - Clearance of HIV infected cells

POPULATION

- HIV-1-infected infants ≤12 weeks of age within 14 days of start of first ART regimen


Envelope spike
HIV-1
V1–V2 Loop
PGT121-PGT123
10-1074
V3 Loop
PGDM1400
CD4-binding site
VRC01-03
3BNC117
gp120
gp41
VIRAL MEMBRANE
Antibodies Bound to the Four Sites of Vulnerability
PG16
PGT-123
NIH45-46
2F5

VRC01 bNAb

- Fully humanized
- Neutralizes 91% of tier 2 virus at 50ug/mL, a level achievable with proposed dosing (Wu et al. Science 2010)
- Neutralization of infant founder virus (Nakamura et al, AIDS 2013; Fouda et al, Retrovirology 2013)
- IgG1—associated immune functions mediated by Fc receptor such as ADCC
- No evidence of auto- or poly-reactivity with human tissue (absent ANA, anticardiolipin, or anti-PTT);38 types of tissue for adults and 21 for neonates
- VRC01 has been tested extensively in adults
- VRC01 has been studied in exposed infants enrolling (P1112)

RATIONALE FOR MONOCLONAL PASSIVE IMMUNOTHERAPY

- Antibodies differ from small-molecule drugs in having naturally long half-lives of 2 to 3 weeks.
- Immune opsonization may enhance target-cell clearance
- They may activate dendritic cells by opsonized immune complexes, leading to enhanced antigen processing and presentation to T cells. Activated T cells can kill target cells directly or act as helper cells for antibody responses.
- In phase 1 clinical trials, bNAbs enhanced clearance of HIV-1, infected cells, or both and boosted host humoral immunity to HIV-1.

Studies of VRC01 in people at risk of HIV

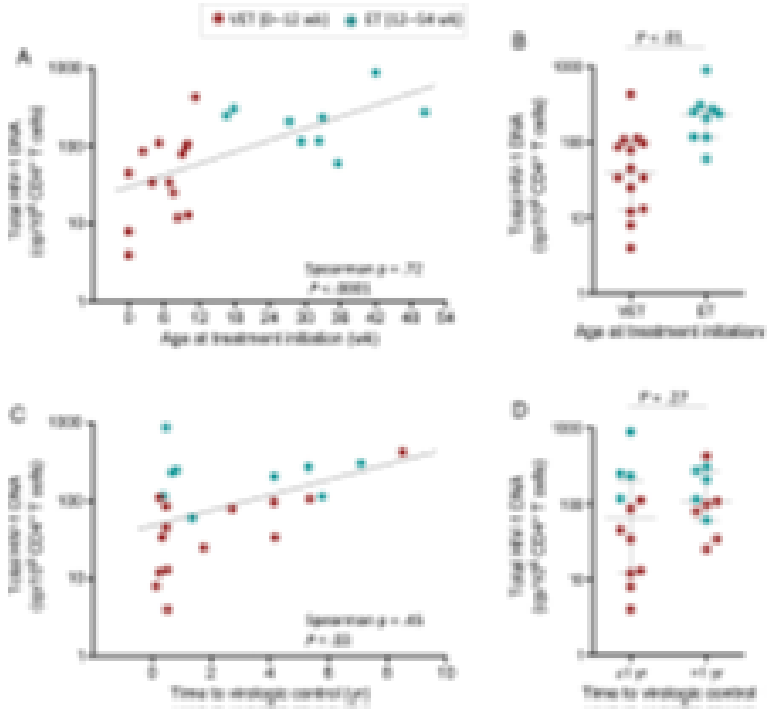
Study	Study Design	Participant Population
VRC 602 (Completed)	Phase I, open label, dose escalation of VRC01	Healthy adults
VRC 606 (Enrolling)	Phase I, open label, dose escalation of VRC01 and VRC01LS	Healthy adults
IMPAACT P1112 (Ongoing)	Phase I, open label, dose escalation of VRC01	Newborn infants of mothers with HIV
HVTN 104 (Completed)	Phase 1, multicenter randomized trial	Adults at risk of HIV
HVTN 116 (Open to accrual)	Phase I, multicenter, randomized, open-label VRC01 and VRC01LS	Adults at risk of HIV
HVTN 703 / HPTN 081 (Recruiting)	Phase 2b, multicenter randomized trial, double-blind, placebo controlled VRC01	sub-Saharan African women at risk of HIV
HVTN 704 / HPTN 085 (Recruiting)	Phase 2b, multicenter randomized trial, double-blind, placebo controlled VRC01/VRC01LS	Men and transgender persons who have sex with men at risk of HIV

Studies of VRC01 in people with HIV

Study	Study Design	Participant Population
VRC 601 (Completed)	Phase I, open label, dose escalation of VRC01	Adults with HIV (NIH)
A5342 (Completed)	Phase 1, multicenter randomized trial, double-blind, placebo controlled VRC01	Adults with HIV (multicenter USA)
A5340 (Participants off study and primary analysis completed)	Phase 1, open label VRC01	Adults with HIV (Penn/Alabama)
15-I-01040 (Completed)	Phase I/II, open label VRC01	Adults with HIV
RV397 (completed)	Phase II single center randomized placebo controlled trial of VRC01	Adults with HIV, acutely treated (Thai SEARCH))
RV398 (Near Completion)	Phase I multicenter randomized placebo controlled trial of VRC01	Adults with acute HIV infection (Thai/Kenya/Uganda)

DIFFERENCES BETWEEN ADULT AND PEDIATRIC OUTCOMES

- YOUNG INFANTS MAY HAVE LOWER HIV DNA
- YOUNG INFANTS PROBABLY HAVE LIMITED QUASISPECIES REDUCING THE LIKELIHOOD OF VRC001 RESISTANT ISOLATES



IMPAACT 2008 Team

Protocol Chair: Elizabeth (Betsy) McFarland
Protocol Co-Chair: William Borkowsky

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Charlotte Perlowski

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Sallie Permar (protocol immunologist)
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Jenna Kearly

Laboratory Data Manager: Katelyn Hergott

Laboratory Specialist: Diane Costello

Laboratory Technologist: Paul Harding

Protocol Pharmacist: Lynette Purdue

Statisticians: Jane Lindsey
Camlin Tierney

Hypothesis

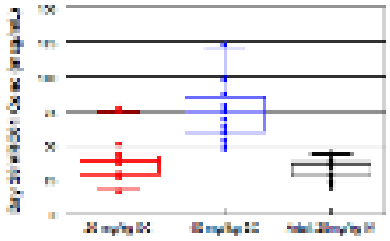
- A regimen of four 40 mg/kg doses of VRC01 will be safe and well tolerated among HIV-1-infected infants initiating cART
- HIV-1-infected infants who receive a regimen of four doses of VRC01 in addition to ART will experience a greater decrease in the concentration of HIV-1 DNA in PBMCs compared to infants who do not receive VRC01 as marker of clearance of HIV-1-infected cells

CROI 2017

SAFETY & PHARMACOKINETICS OF THE MONOCLONAL ANTIBODY, VRC01, IN HIVEXPOSED NEWBORNS Abstract Number: 446

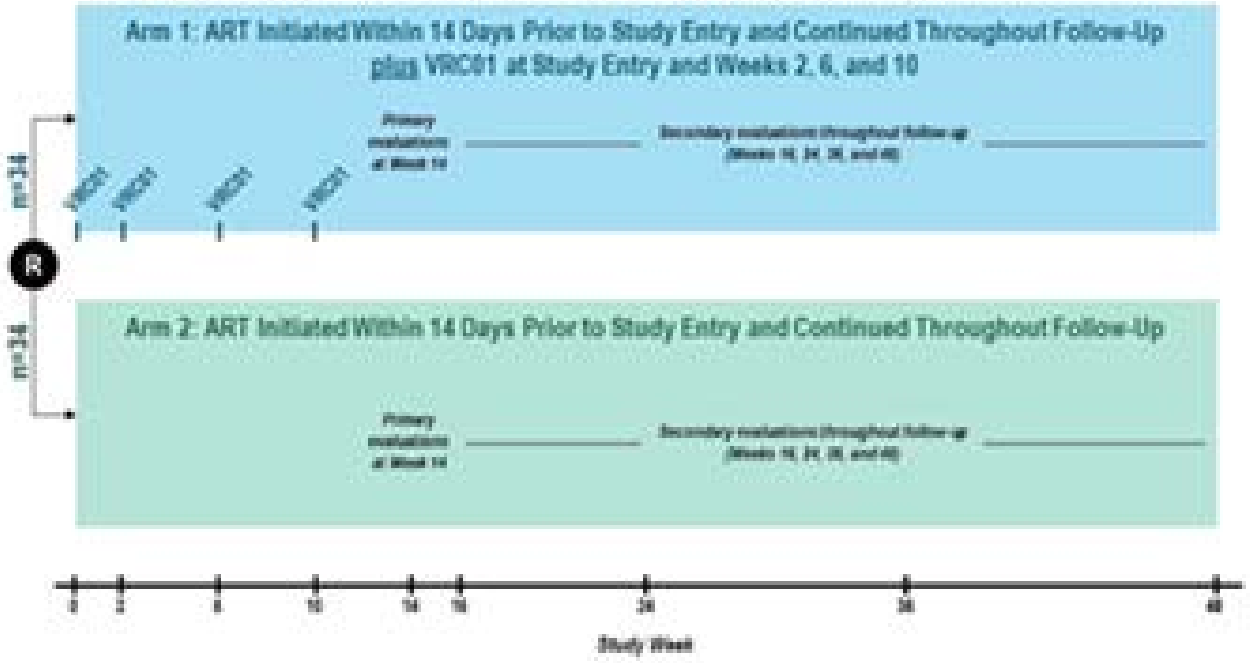
Coleen K Cunningham, Elizabeth J McFarland, Edmund V Capparelli, Petronella Muresan, Charlotte Perlowski, Megan Valentine, Elizabeth Smith, John R Mascola, Barney S Graham, for the IMPAACT P1112 Team

VRC01 was well tolerated with no attributable serious systemic reactions. Local reactions were common, occurring in six (46%) and nine (75%) infants in the low and high dose groups, respectively. None of the local reactions were serious and 100% and 90% in the 20 and 40 mg dose groups, respectively, resolved within four hours of injection



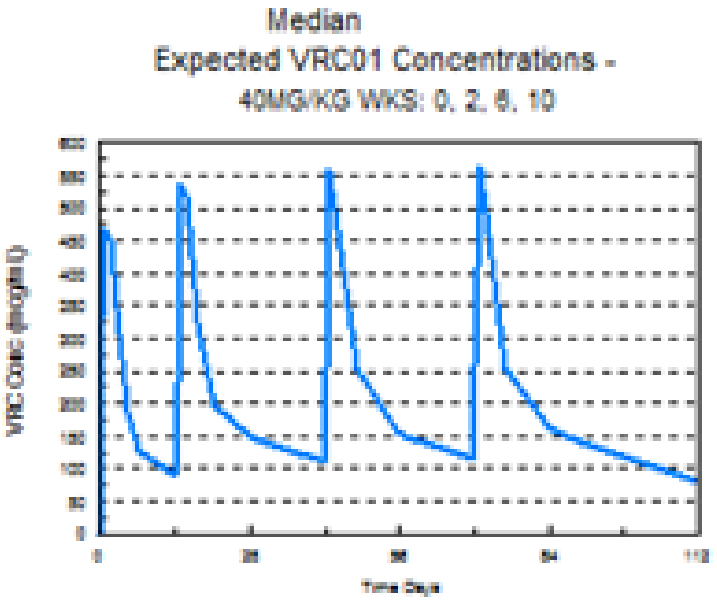
Schema

- Phase I/II multisiterandomized study
- Sample size: 68 participants (34 per arm)
- VRC01 40 mg/kg: weeks 0, 2, 6 and 10
- Study visits: weeks 0, 2, 6, 10, 14, 16, 24, 36, 48



Dosing strategy

- VRC01 40mg/kg/dose
- Wk 0, 2, 6, 10
- Trough levels above 50mcg/ml though 14 weeks
- Covers through median time to suppressed VL in study of early ART



Primary and secondary objectives

1. Safety

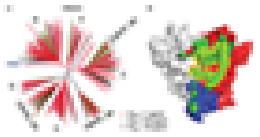
- Safety of VRC01 administered with ART through Week 14

1. Antiviral activity

- Effect of VRC01 on HIV-1 DNA concentrations in PBMCs at Week 14

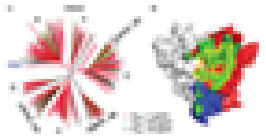
2. PK of VRC01

- VRC01 trough concentrations at Weeks 2, 6, 10 and 14, 16



Other objectives

- Longer-term safety of VRC01 administered with ART (W48)
- Development of anti-VRC01 antibodies (W14, 24, 48)
- Time to achieve plasma HIV-1 RNA < 40 copies/mL (W48)
- Effect of VRC01 on key biomarkers of HIV persistence in PBMCs (W24, 48)
  - HIV-1 DNA concentration
  - HIV-1 RNA concentrations (multiply-spliced and unspliced)
  - Total inducible HIV-1 RNA concentration
- Effect of VRC01 on HIV-1 specific ADCC and virus neutralization against infant viral isolates (W14, 24, 48)



Current Status

- First Protocol Initiation Review by SMC Oct 2016
- Version 1.0 to FDA, comments received Nov 18, 2016
- Version 2.0 to FDA and sites – May 29, 2017
- Hands-on training on subcutaneous infusions – June 2017
- Webinar training for US sites - Oct 2017
- Regional training for non-US – Jan/Feb 2018
- International training (Johannesburg) – April 2018
- Protocol officially open- May 8, 2018
- First enrollments are expected by May-June 2018