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Late Breaker Track B

Phase I/II Study of Monoclonal Antibody VRC01 with Early Antiretroviral Therapy to Promote Clearance of HIV-1 infected Cells in Infants (IMPAACT 2008)

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AIDS 2022

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Conflicts of Interest

I have no relevant financial relationships with ineligible companies to disclose.

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Perinatal HIV-1 and Reservoirs

- 160,000 infants acquired HIV in 2021
- Latent viral reservoirs occur early in perinatal HIV-1
  - major barrier to ART-free remission
- Early ART initiation decreases viral reservoirs
- Broadly neutralizing antibodies are promising adjunctive therapies to reduce reservoirs
  - Directly targeting infected cells
  - Potential immune mechanisms

https://data.unicef.org/topic/hivaids/global-regional-trends/
Persaud D, et al. JAMA Pediatr, 2014; NEngl J Med, 2013. CROI 2022

VRC01

- VRC01 targets the CD4 binding site of gp120
- Adult Studies
  - Monotherapy delayed time to viral rebound off ART*
  - Prevented acquisition of sensitive virus (AMP Trial)#
- Pediatric Studies
  - Safe in infants exposed to HIV-1+
  - Dual bNAb treatment can maintain 24 weeks of viral suppression without ART 44% of children who received early ART (Tatelo Study)^
- **VRC01 combined with early ART** in infants may further reduce viral reservoirs

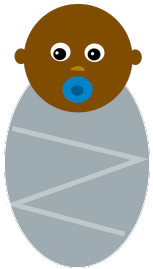
*Bar KJ. NEJM 2016; #Corey L. NEJM 2021; + Cunningham CK. JID 2020; ^Shapiro RL CROI 2022

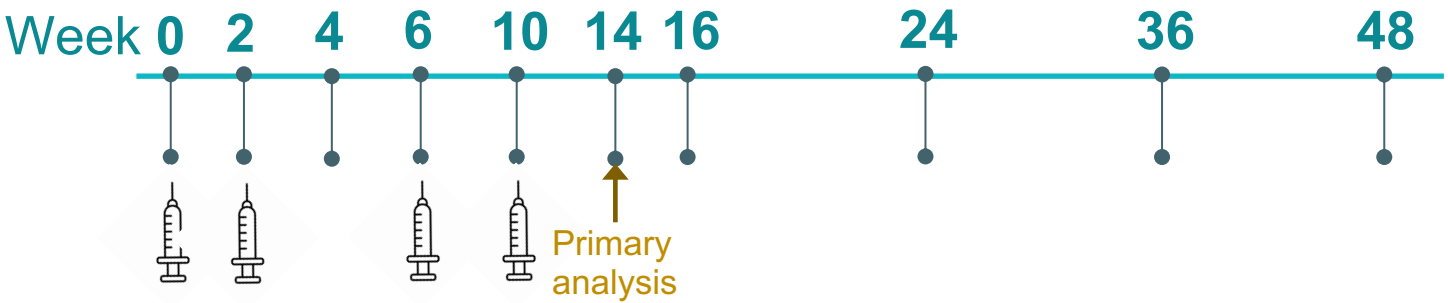
IMPAACT 2008 Objectives

- Evaluate safety of multi-dose VRC01 administered to infants living with HIV-1 with standard of care ART regimens

- Evaluate effect of VRC01 combined with early ART compared with ART only on HIV-1 DNA concentrations

Randomized Phase I/II Multisite, Open-label Study





Infants living with HIV-1:

- Age 72 hours to ≤ 84 days
- Started ART ≤14 days before study entry

VRC01

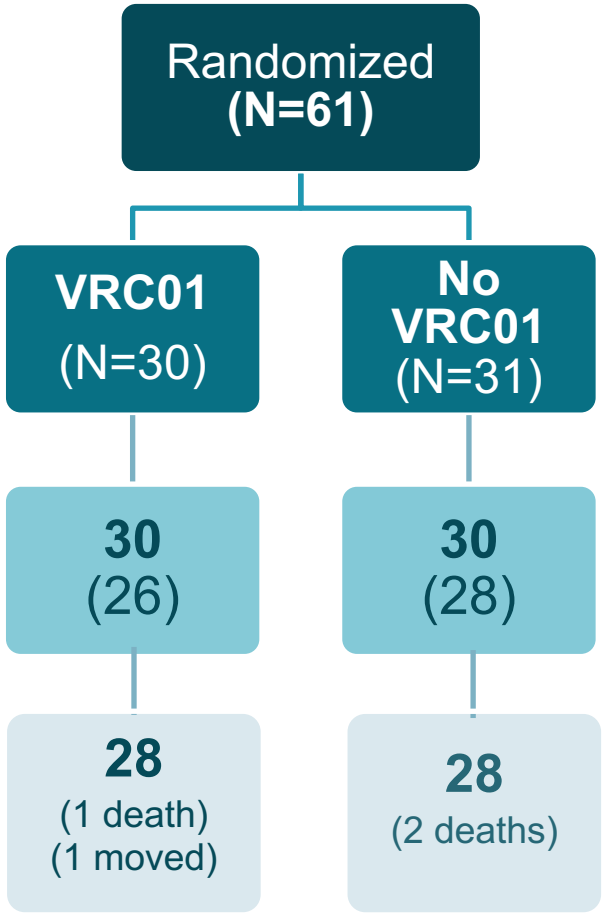
- ART per country standard of care regimen
- VRC01 40mg/kg subcutaneous doses at Weeks 0, 2, 6, 10

Randomized 1:1, Target n=34 per arm

No VRC01

- ART per country standard of care regimen

CONSORT Flow Diagram

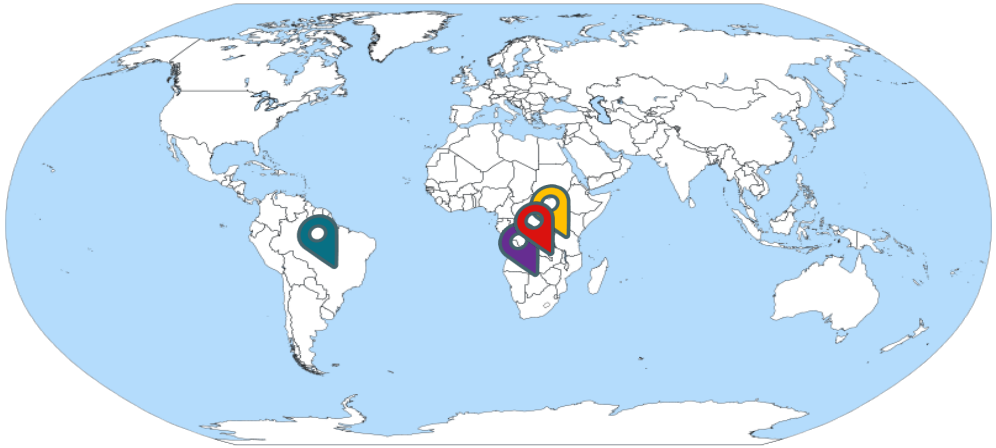


Completed Week 14
(Included in HIV-1 DNA analysis)
**VRC01 arm: received all 4 doses*

Completed Week 48

Enrollment

- Enrollment August 2018 – March 2020
- Closed at accrual of 61 of planned 68 due to COVID-19



	VRC01	No VRC01	Total
Botswana, N(%)	**0** (0%)	**7** (23%)	**7**
Brazil, N(%)	**3** (10%)	**3** (10%)	**6**
Malawi, N(%)	**25** (83%)	**17** (55%)	**42**
Zimbabwe, N(%)	**2** (7%)	**4** (13%)	**6**

Baseline Characteristics

	VRC01 (N=30)	**No VRC01** (N=31)
Female Sex N (%)	**14** (47%)	**21** (68%)
Black, Non Hispanic N (%)	**25** (83%)	**26** (84%)
Hispanic N (%)	**5** (17%)	**5** (16%)
Age (days)*	**72** (56, 82)	**73** (65, 82)
CD4 percent*	**23** (20, 31)	**30** (26, 36)
Entry Plasma HIV-1 RNA (log_{10} cp/mL)*	**4.1** (3.7, 5)	**4.4** (3.5, 5.7)
Last available Plasma HIV-1 RNA (log_{10} cp/mL)* before starting ART	**5.8** (5.2, 6.4) (N=15)	**5.9** (5.6, 6.3) (N=17)
% with Plasma HIV-1 RNA >100,000 cp/mL N (%)	**13** (87%)	**11** (65%)

*Median (Q1, Q3)

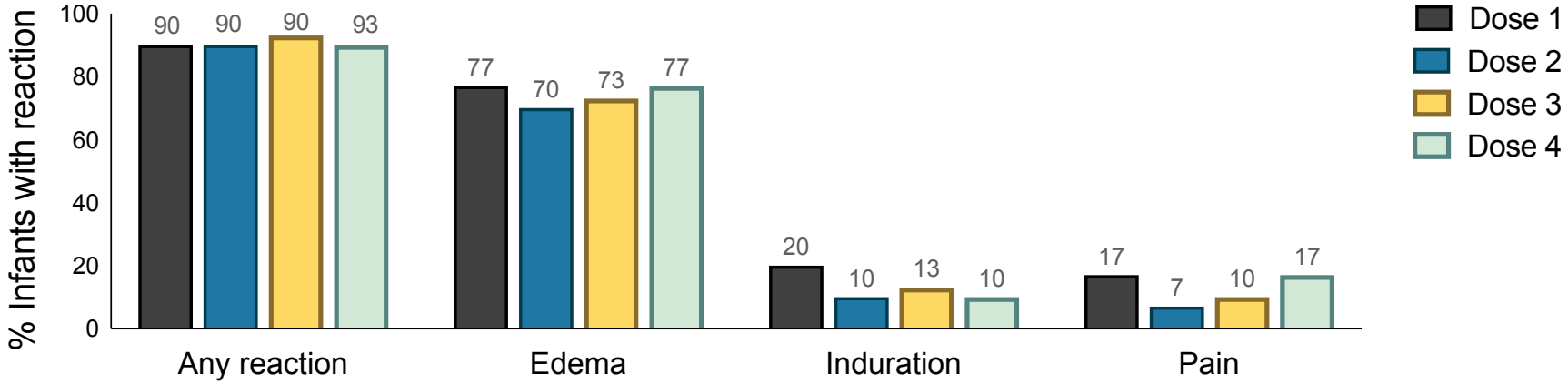
Baseline ART

	VRC01 (N=30)	No VRC01 (N=31)
Median days on ART prior to entry (Q1, Q3)	**8** (6, 11)	**6** (2, 10)
Initiated ART at entry, N (%)	1 (3%)	5 (16%)
Baseline ART, N (%)		
NVP regimen*	**16** (53%)	**9** (29%)
LPVr regimen*	14 (47%)	21 (71%)
ART Resistance, N (%)	10/23 (44%)	10/30 (33%)
NVP resistance	**10/13** (77%)	**8/9** (89%)
LPVr resistance	0/9 (0%)	0/18 (0%)
Resistant to both NRTIs*	0/22 (0%)	2/27 (7%)

*additional ARVs included 3TC and ZDV or ABC

Safety Outcomes by Week 14: Local reactions to VRC01

- Injection volume median (min, max) 2.2 to 2.4 (1.0, 3.2) mL
- All Grade ≤ 2 (mild to moderate)
- Most local reactions resolved within 1 day & no increase in local reactions with subsequent doses



Safety Outcomes by Week 14: Grade ≥3 adverse events

	VRC01 (N=30)	No VRC01 (N=30)	p-value*
Any adverse event Grade ≥3 (N, %)	**12** (40%)	**14** (47%)	0.79
Any anemia/neutropenia	**9** (30.0%)	**12** (40%)	0.59
Anemia (N)	**4** (13%)	**6** (20%)	
Neutropenia (N)	**6** (20%)	**7** (23%)	
Any other (N, %)	**6** (20%)	**5** (17%)	>0.99

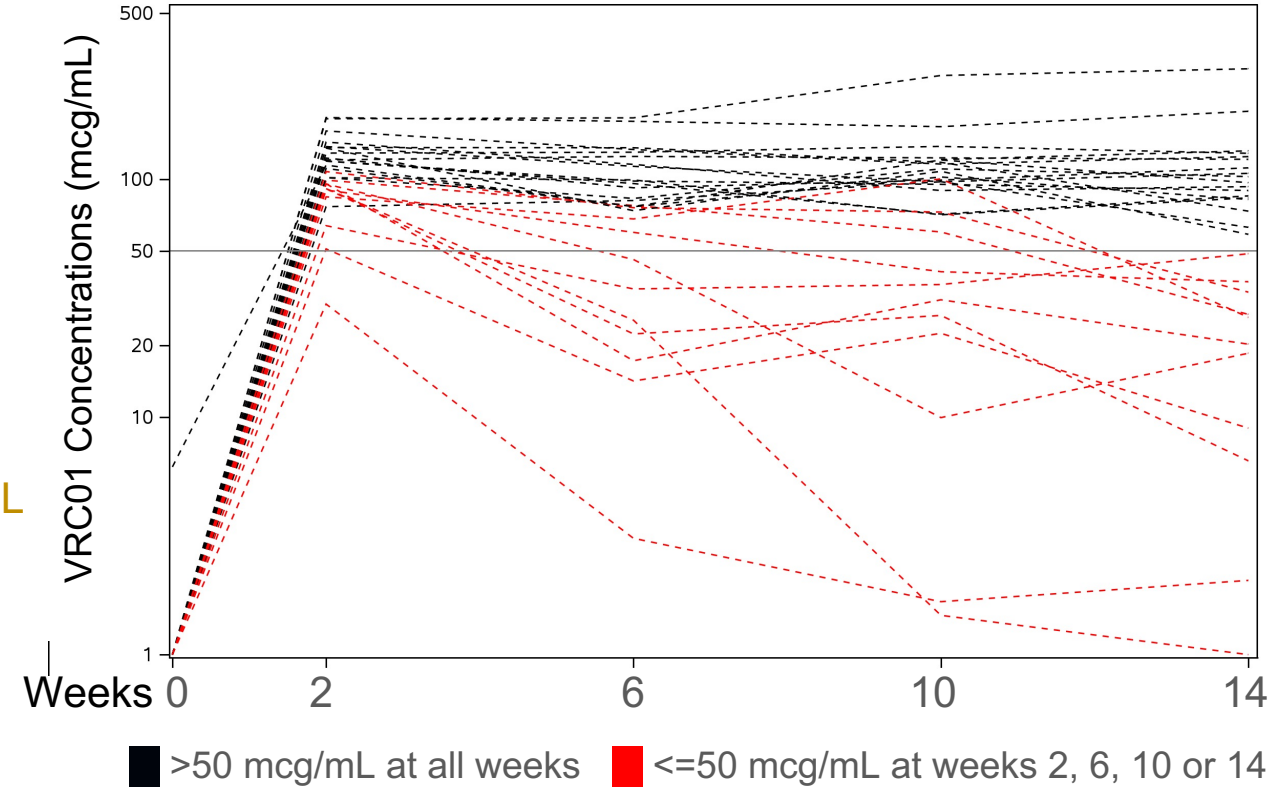
*Fisher's exact

VRC01 plasma concentrations

VRC01 pre-dose plasma concentration levels at Weeks 2, 6, 10 and 14

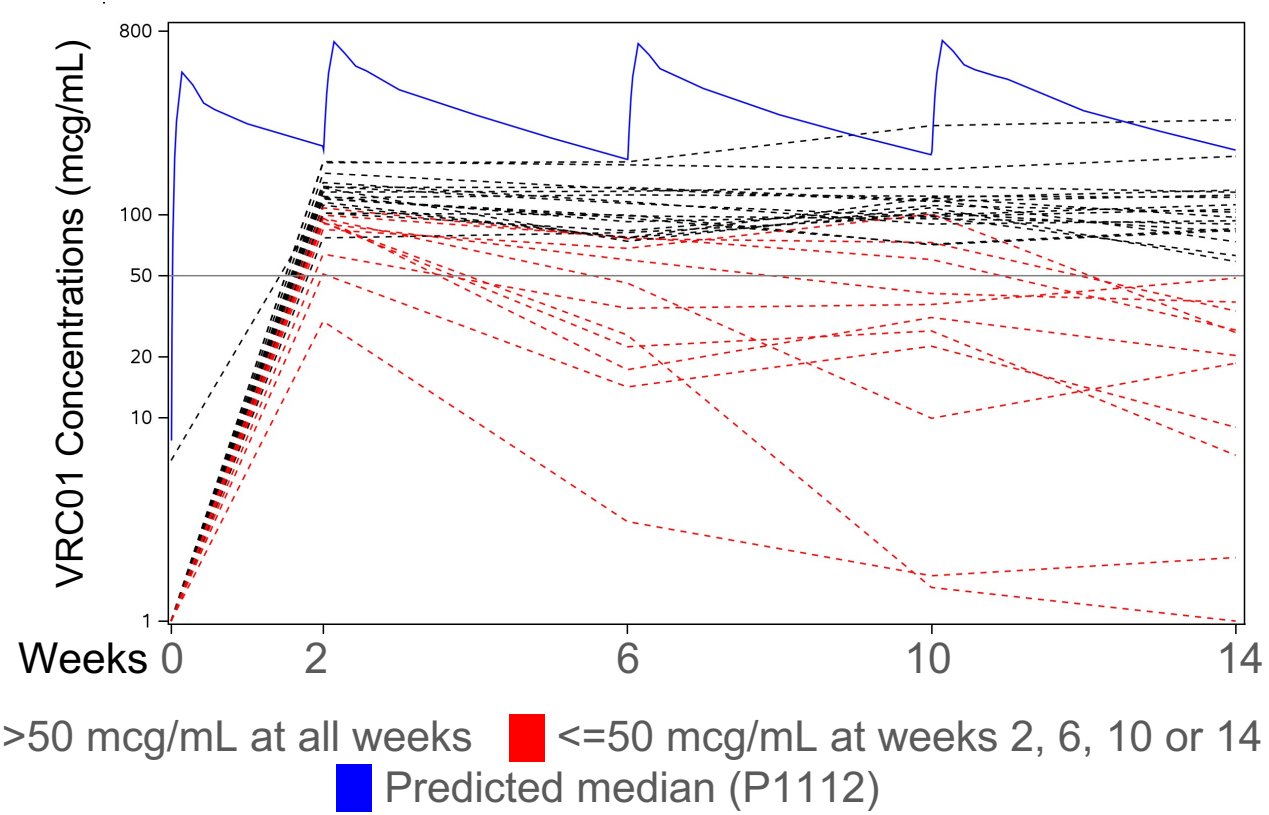
28 days after dose:

- Median levels: 83 mcg/mL
- 31% <50 mcg/mL



VRC01 plasma concentrations

- Median concentrations predicted from prior study of VRC01 administered to HEU*
- No anti-drug Abs detected



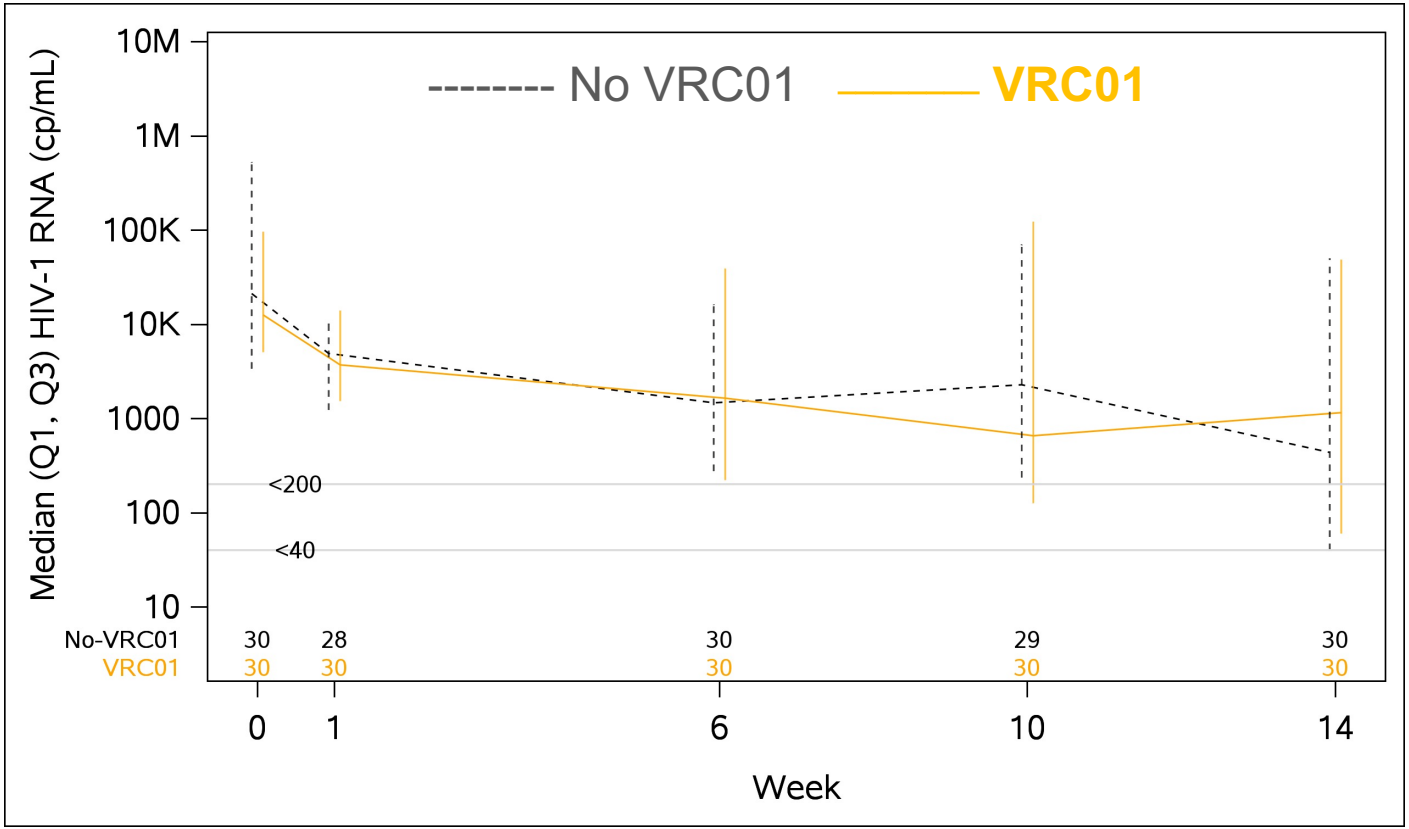
*Cunningham CK. JID 2020

VRC01 Resistance, Week 0

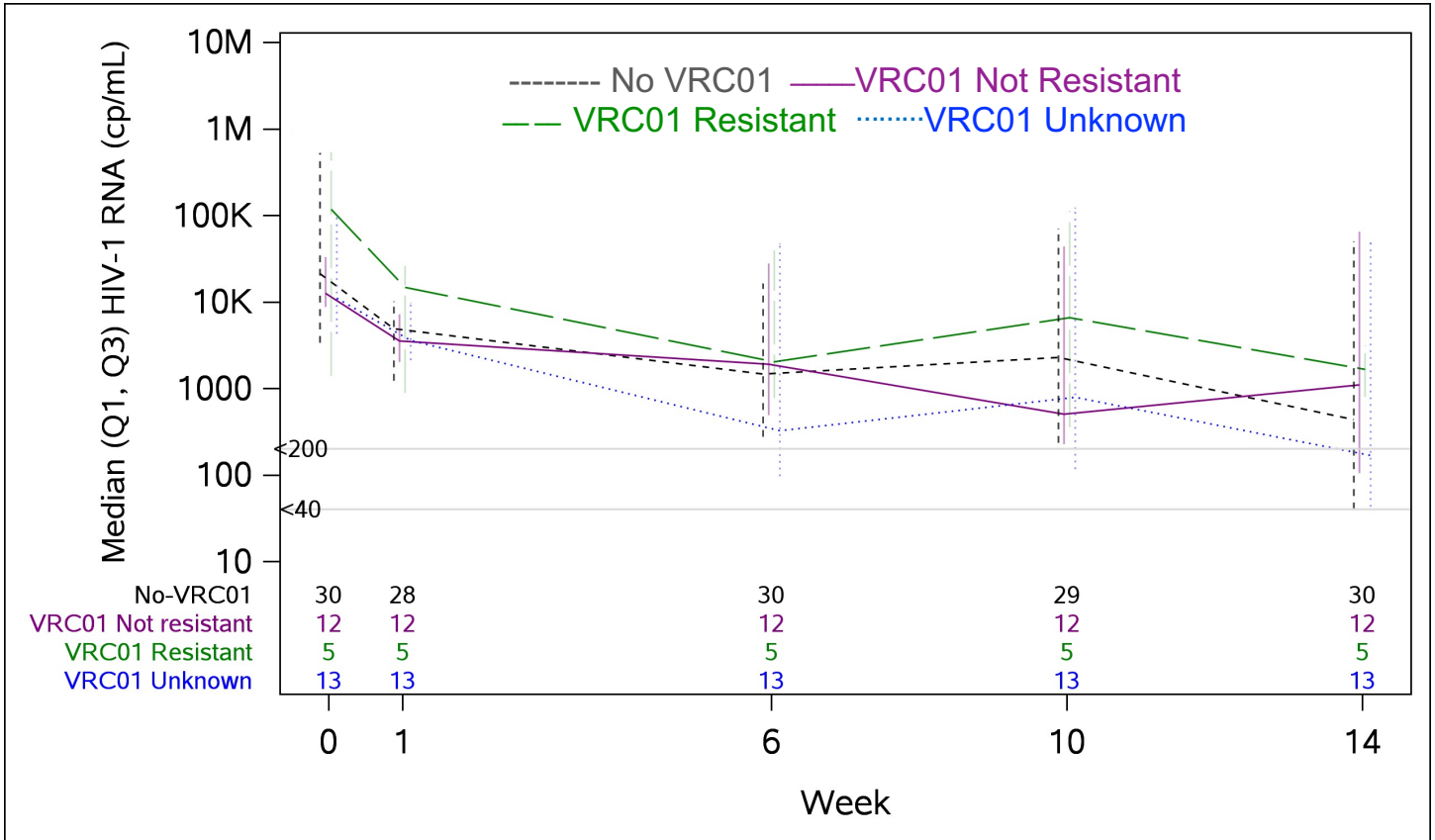
*1 sample not shipped due to insufficient volume

**12 results unavailable due to assay failure in amplification, transformation, cell assay testing and/or insufficient sample

Median HIV-1 plasma RNA over 14 weeks



Median HIV-1 plasma RNA over 14 weeks by VRC01 resistance



HIV-1 DNA change (Week 14 minus Week 0)

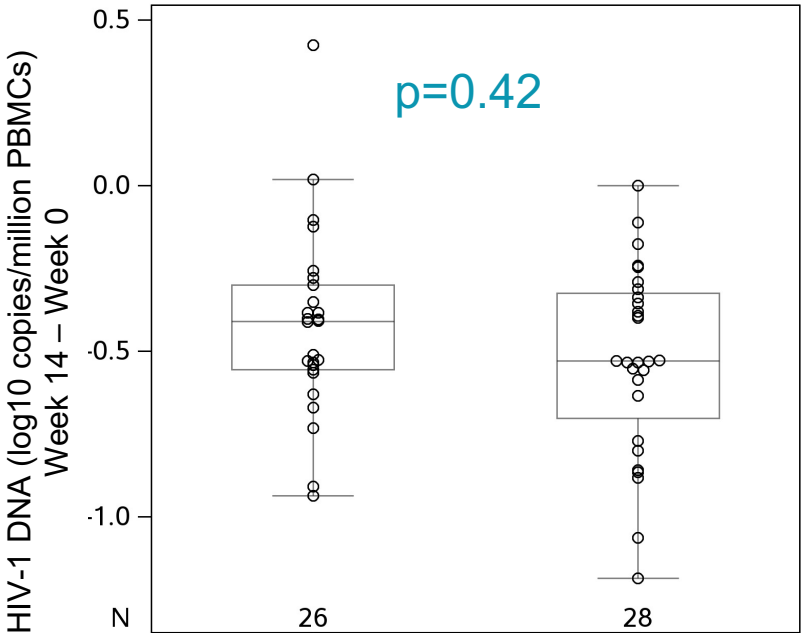
Analysis set

Both arms:

- Did not miss >3 consecutive days of ARVs
- HIV-1 DNA results available at Weeks 0 and 14

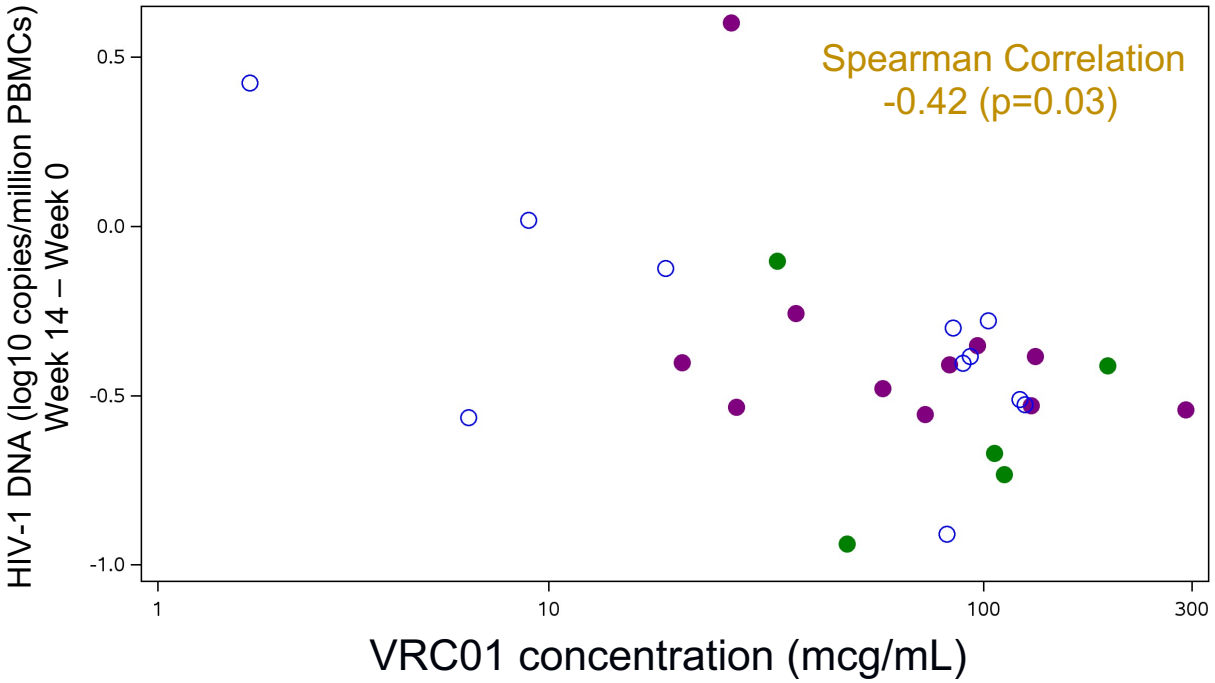
VRC01 arm only:

- Received all VRC01 doses



	VRC01	No VRC01
Median (Q1, Q3)	-0.41 (-0.94, -0.30)	-0.53 (-0.70, -0.33)

Change in HIV-1 DNA (Week 14 minus Week 0) versus VRC01 concentration at Week 14



Primary analysis VRC01 resistance definition: IC50

● <50 mcg/mL ● >= 50 mcg/mL o Unavailable

Limitations

- High baseline NNRTI resistance driven by NVP resistance
- More NVP in the VRC01 group may have influenced findings
- Relatively small sample size limits power for subset analyses
- HIV-1 DNA was determined by ddPCR (intact and defective virus) at Week 14
  - Assays planned at Weeks 24 and 48 and for intact provirus

Key Findings

- Multidose VRC01 subcutaneous administration of 40mg/kg dose was feasible and well tolerated by infants with no safety concerns
- HIV-1 RNA and DNA declines did not differ by treatment arm at Week 14
- Baseline VRC01 resistance, defined as IC50>50mcg/mL, was frequent
- VRC01 plasma levels were more variable and lower than predicted by VRC01 studies in infants exposed to HIV, but no anti-drug antibodies were detected
- Higher VRC01 plasma levels at Week 14 significantly correlated with larger declines in HIV-1 DNA to Week 14

Conclusions

- More potent ART regimens with combination bNAbs are likely needed to facilitate early clearance of infected cells in infants
- Infants are a special population and additional studies are needed to define how to optimally dose bNabs in viremic infants to attain efficacy.

https://www.unicef.org/sites/default/files/2018-07/UNICEF-Advocacy-Brochure.pdf

Acknowledgments

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Enrollment Sites: ● JHU Blantyre ● UNC Lilongwe ● Gaborone ● Molepolole ● ● Harare Fam Care ● Hosp dos Servidores ● Hosp Geral de Nova Iguacu

IMPAACT 2008 Team

- **Chair:** Elizabeth McFarland
- **Vice Chairs:** Alka Khaitan; William Borkowsky
- **Pharmacologist:** Edmund Capparelli
- **Virologist:** Deborah Persaud
- **Immunologist:** Sallie Permar
- **Statisticians:** Jane Lindsey; Camlin Tierney; Konstantia Angelidou
- **FHI 360 Clinical Research Managers:** Anne Coletti; Charlotte Perlowski
- **NIAID/DAIDS Med. Officers:** Dwight Yin; Hans M.L. Spiegel; Betsy Smith
- **NICHD Med. Officers:** Sai Majji; Jack Moye; Rohan Hazra
- **DAIDS Pharmacist:** Lynette Purdue
- **Investigator:** Mark Cotton
- **Collaborator**: Jintanat Ananworanich
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- **Lab Data Managers:** Kyle Whitson; Coleen Foley; Katelyn Hergott
- **IMPAACT Lab Specialist:** Diane Costello
- **Lab Technologist:** Paul Harding
- **Internatl. Community Advisory Board:** Maggie Peggy Malola; Dichaba Siane
- **Comm Prg:** Jonathon Lucas
- **Westat:** Kathryn Myers
- **NIH Vaccine Research Center (VRC):** Lucio Gama; Julie Ledgerwood

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