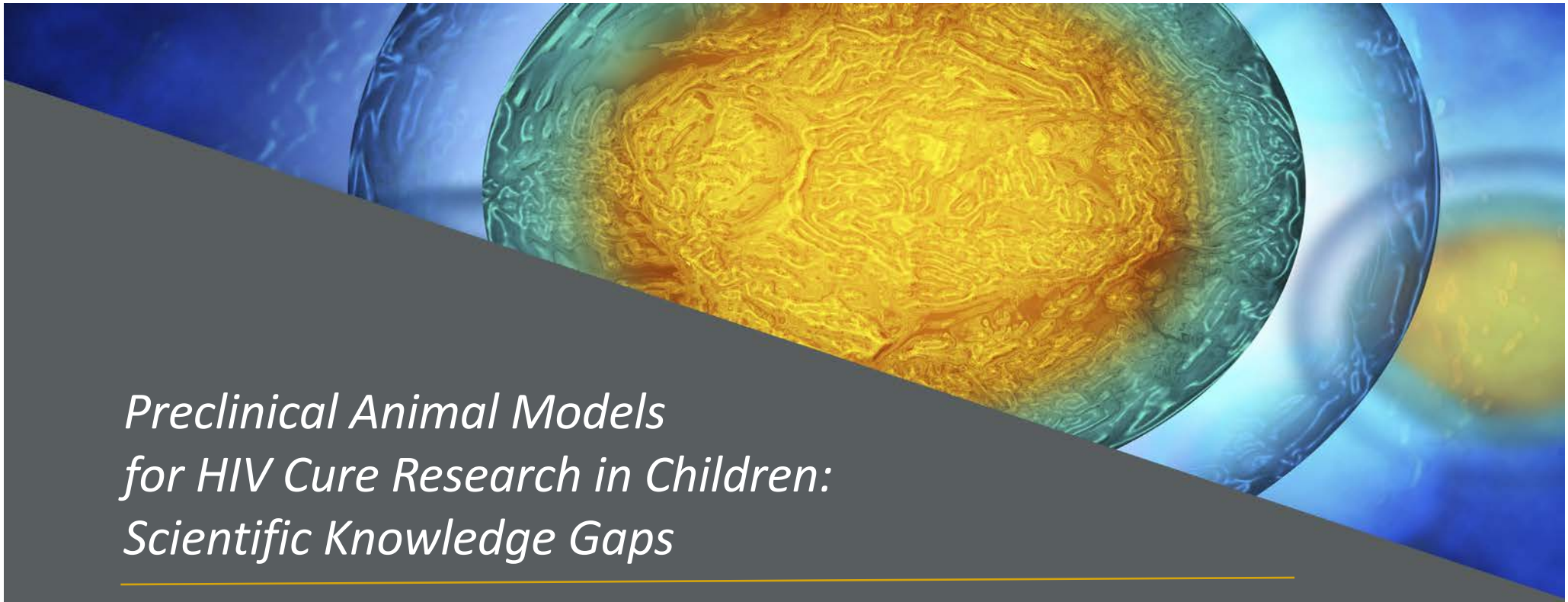


Preclinical Animal Models for HIV Cure Research in Children: Scientific Knowledge Gaps

NIAID Workshop, May 22-23, 2018

Nancy L. Haigwood, Oregon Health & Science University

OHSU

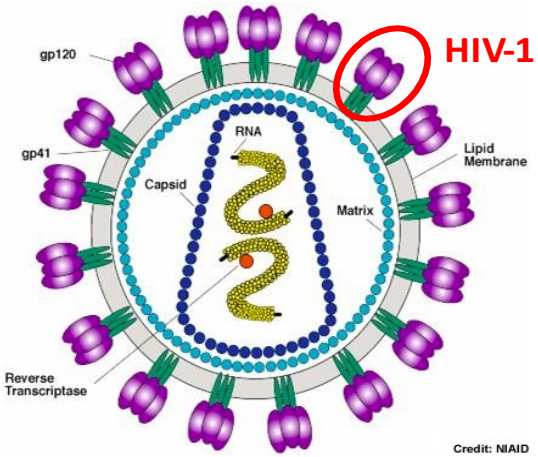
"Mississippi baby" case brought attention to the need to treat continuously after peripartum infection

Key Concepts in Cure Research for Babies and Children

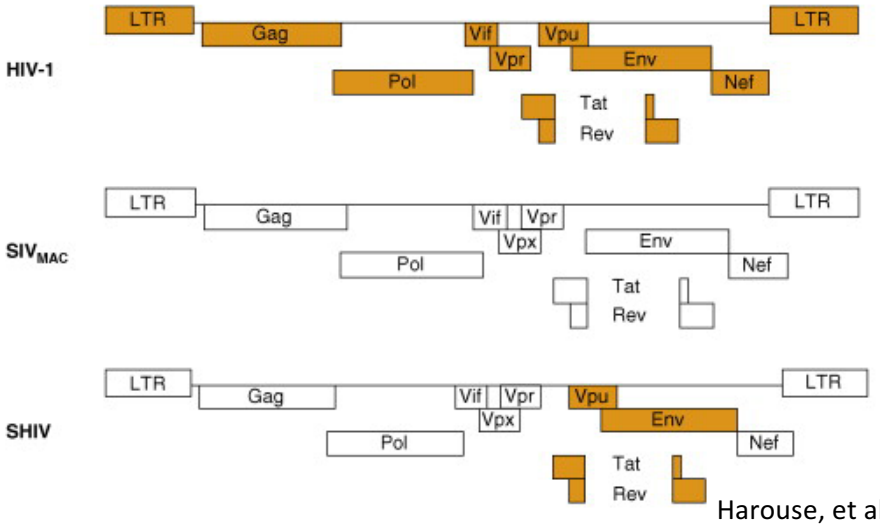
- To understand the earliest events in SIV/SHIV infection in models for pathogenesis in nonhuman primate *newborns and infants*
  - To define the kinetics and extent of viral penetrance *in vivo* following oral inoculation
  - To define the role of adaptive immunity in viral control
  - To explore the potential and timing for combination ART and antibody therapies to limit MTCT in newborns and children

- Goal: determine whether/how much of the viral reservoir can be eliminated for 'functional cure' without continued ART

Nonhuman primate (NHP) models: SIV and SHIV infection of macaques: pathogenesis, adaptive responses, and tissue distribution



HIV and SIV Envelope proteins share receptor & coreceptor use, but are antigenically distinct



Harouse, et al. Science 1999

SHIV-SF162P3 as a model for assessing infant responsiveness

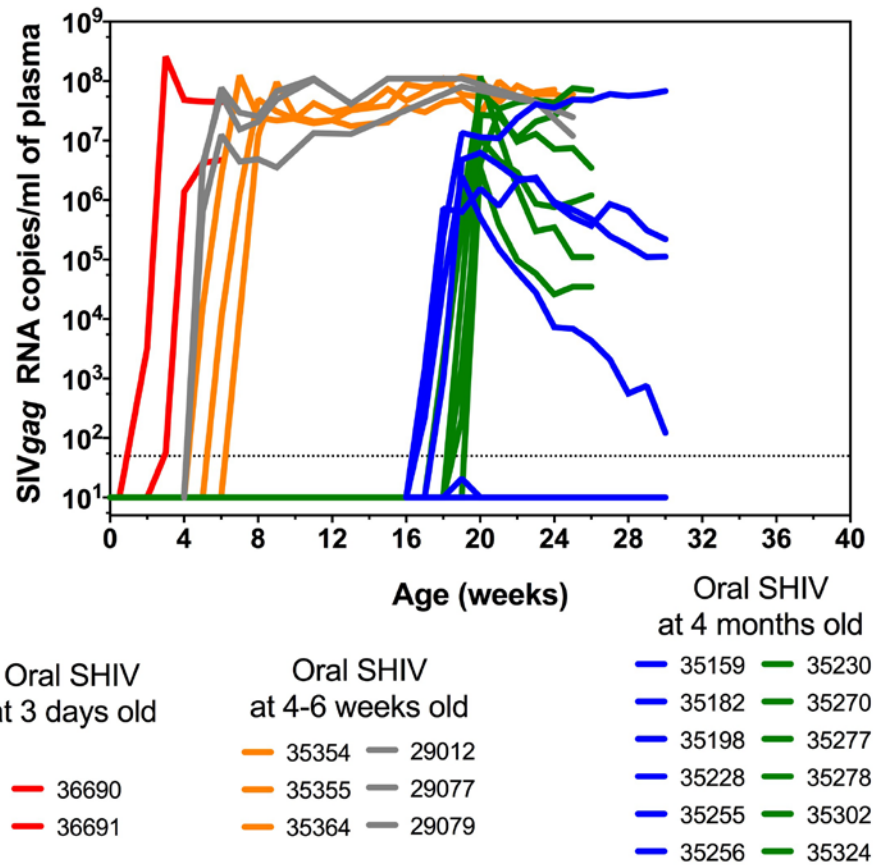
Infant rhesus macaques

- Born vaginally in natural setting and allowed to suckle up to 7 days (microbiome+)
- Oral high dose $SHIV_{SF162P3}$ exposure: 95% infection rate and rapid pathogenesis
- Pre-SHIV passive immunization (s.c.) with neutralizing IgG
  - Prevention of infection (high dose)
  - Modulation of infection & immunity
  - Prevention of disease (Ng, et al, 2010 *Nature Medicine*; Jaworski, et al., 2013 *J Virology)*

Ability to monitor immunity and to sample tissue reservoirs; responses to ART and antibody-based therapies; full suppression with daily injectable ART

[Tenofovir Disproxilfumarate (5.1 mg/kg); Emtricitabine (40 mg/kg); and Dolutegravir (2.5 mg/kg) given daily subcutaneously]

Age-dependent $SHIV_{SF162P3}$ pathogenesis in infants: model for rapid progression in HIV+ infants, high dose oral inoculation



Newborn infection:
High uncontrolled viremia
Death in 2-6 weeks

One-month-old infection:
Uncontrolled persistent viremia
No adaptive immunity
Loss of CD4 T cells
Death in 2-24 weeks

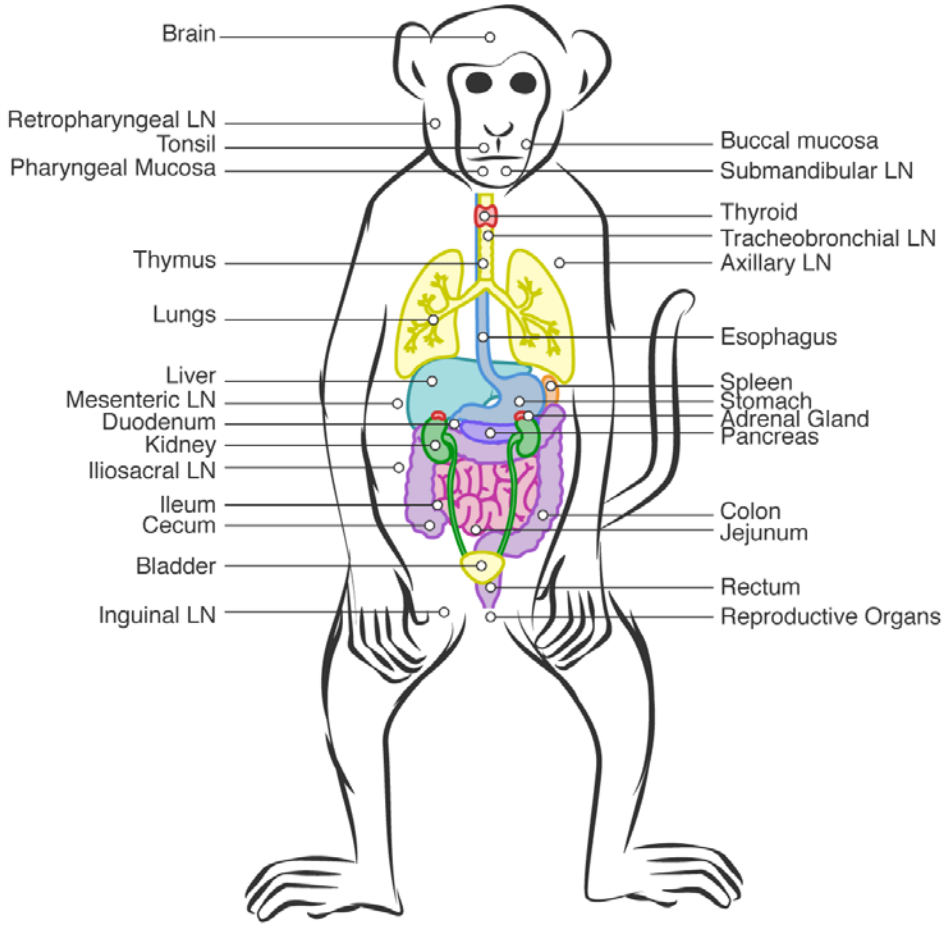
4-month-old infection:
SHIV viremia more variable
Adaptive immunity in most infants
Slowed loss of CD4 T cells
Extended time to before debilitating pathogenesis

Infants and Newborns: Defining Gaps in Scientific Knowledge

- **Viral kinetics after oral inoculation in tissues and blood** – where and how much virus is found in tissues?
- **Evidence for antibody clearance of foci** – Importance for blocking, suppressing, or clearance of SHIVs in NHP models
- **Window of opportunity-** for post-exposure therapies to achieve clearance or durable suppression
- **Nanocapsule technology-** for bNAb delivery to improve half-life and tissue targeting

SHIV models—blood and tissue virus
How low is low enough?

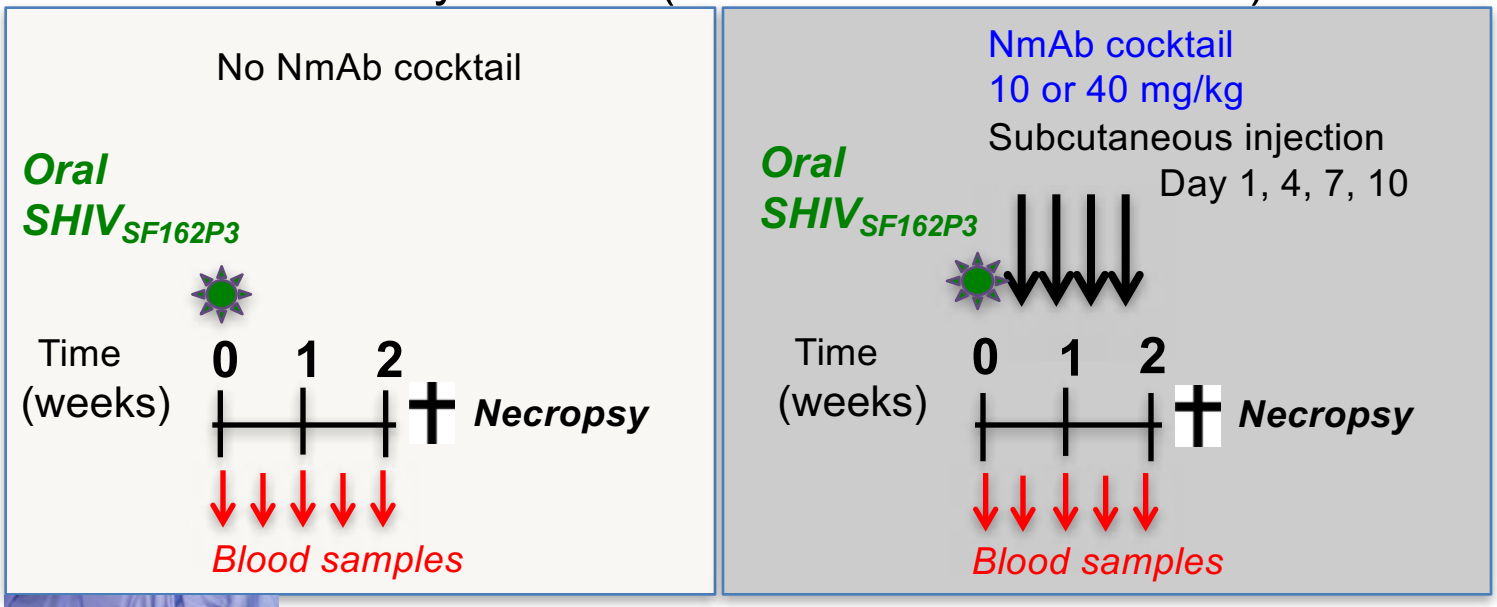
- **Where** is the virus in tissues and which cells are producing virus?
- **Is there evidence for functional cure?**



Hessell, et al., *Nature Med 2016*

Oral SHIV infection of newborns as a model for assessing the role of passive antibodies as post-exposure therapies in early infection

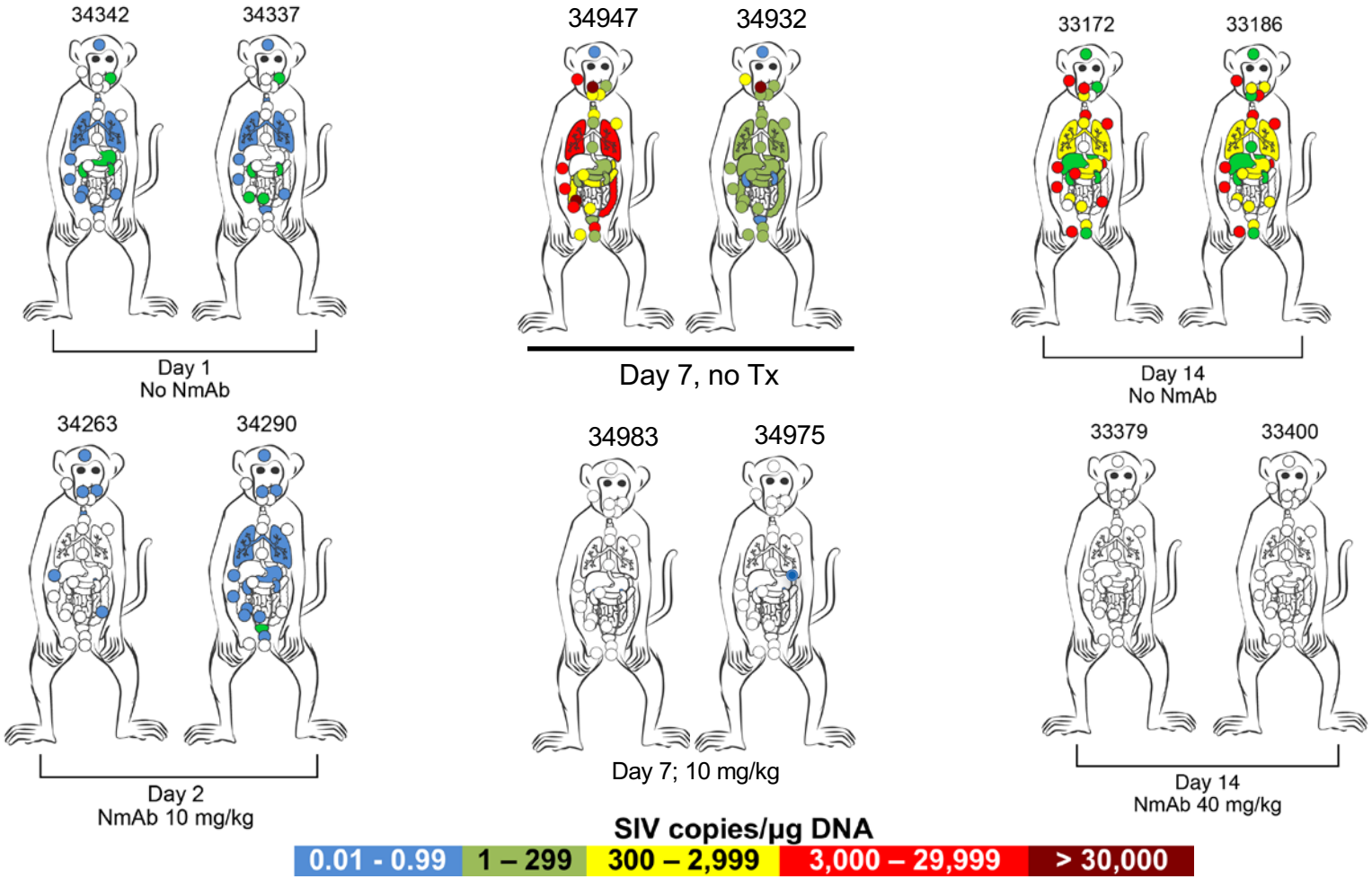
Antibody cocktail (PGT121 and VRC07-523)*



≤1-month-old infant rhesus macaques. No MHC class I *Mamu B*08, B*17*

*bNmAb production: J Mascola, XJ Chen – NIH/VRC

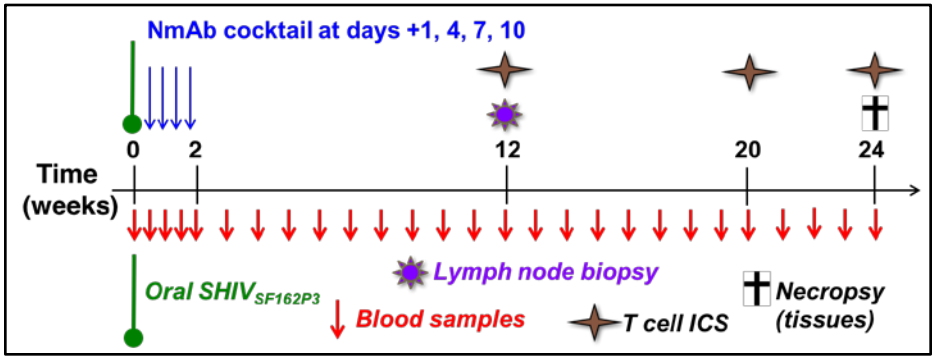
SHIV is quickly disrupted by antibody treatment (s.c.)



nature medicine

Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques

Ann J Hessell[1,2], J Pablo Jaworski[1], Erin Epson[1], Kenta Matsuda[3], Shilpi Pandey[1], Christoph Kahl[1], Jason Reed[2], William F Sutton[1], Katherine B Hammond[2], Tracy A Cheever[1], Philip T Barnette[1], Alfred W Legasse[1], Shannon Planer[1], Jeffrey J Stanton[1], Amarendra Pegu[4], Xuejun Chen[4], Keyun Wang[4], Don Siess[1], David Burke[1], Byung S Park[1], Michael K Axthelm[1,2], Anne Lewis[1], Vanessa M Hirsch[3], Barney S Graham[4], John R Mascola[4], Jonah B Sacha[1,2] & Nancy L Haigwood[1,2]



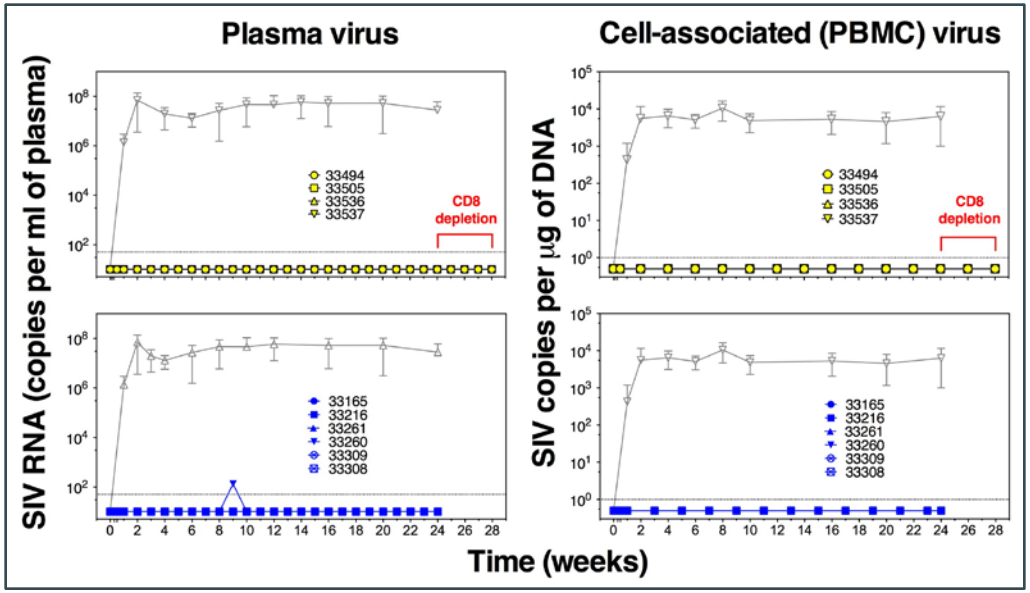
bNAb cocktail: PGT121 (V3 glycan); VRC07-523 (CD4bs)

No evidence of viral DNA in a panel of 33 lymphoid, mucosal and organ tissues,

CD8 depletion yielded no viral outgrowth

Antibody-mediated protection against SHIV challenge includes systemic clearance of distal virus

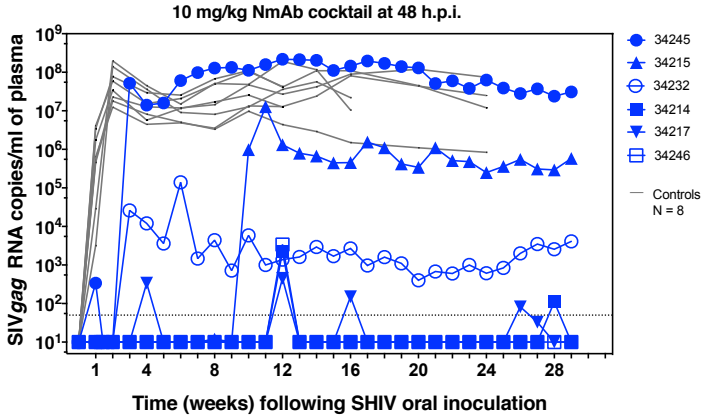
Jinyan Liu,[1] Khader Ghneim,[2] Devin Sok,[3] William J. Bosche,[4] Yuan Li,[4] Elizabeth Chipriano,[4] Brian Berkemeier,[4] Kelli Oswald,[4] Erica Borducchi,[1] Crystal Cabral,[1] Lauren Peter,[1] Amanda Brinkman,[1] Mayuri Shetty,[1] Jessica Jimenez,[1] Jade Mondesir,[1] Benjamin Lee,[1] Patricia Giglio,[1] Abishek Chandrashekar,[1] Peter Abbink,[1] Arnaud Colantonio,[5] Courtney Gittens,[6] Chantelle Baker,[6] Wendeline Wagner,[6] Mark G. Lewis,[6] Wenjun Li,[7] Rafick-Pierre Sekaly,[2*] Jeffrey D. Lifson,[3*] Dennis R. Burton,[3,8*] Dan H. Barouch[1,8*†]

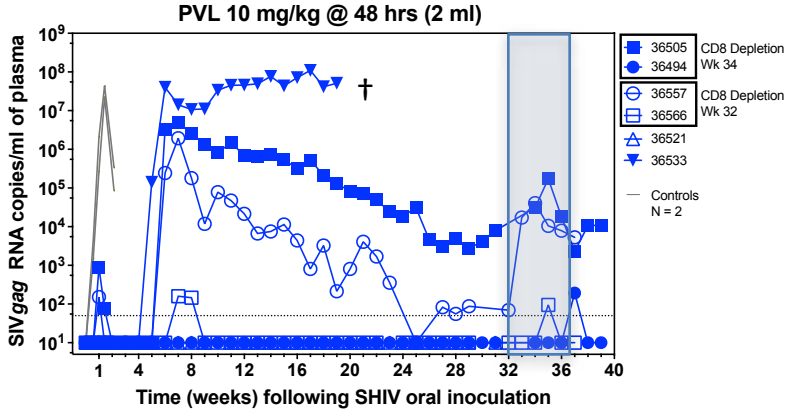


10 mg/kg
(5 mg/kg each)

40 mg/kg
(20 mg/kg each)

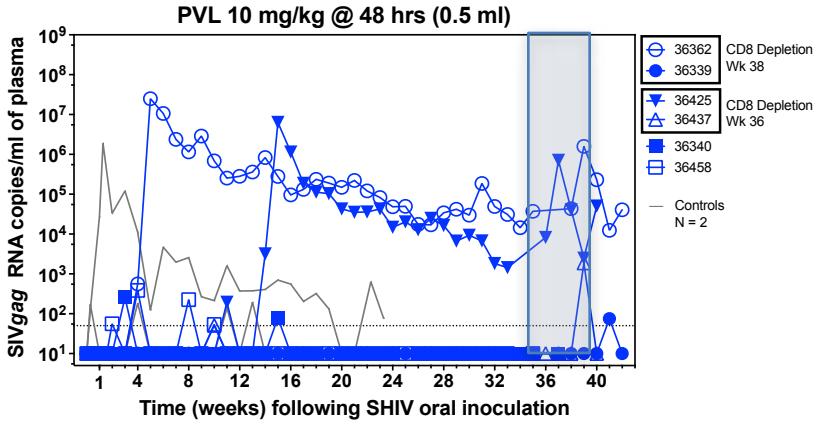
Viremia is delayed in infants treated with bNAbs at 48h post-challenge (n=18 treated, 10 controls)





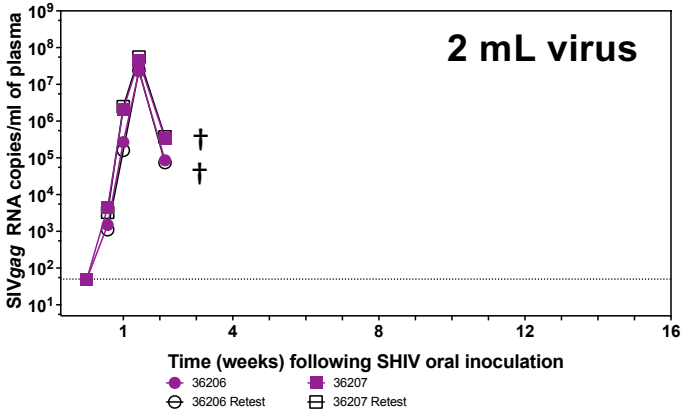
- Only animals with moderate viremia—but not tight controllers or rapid progressors—develop antibody and T cell responses to SHIV

- Transient rebound after CD8 depletion in moderately viremic animals, but not in tight controllers

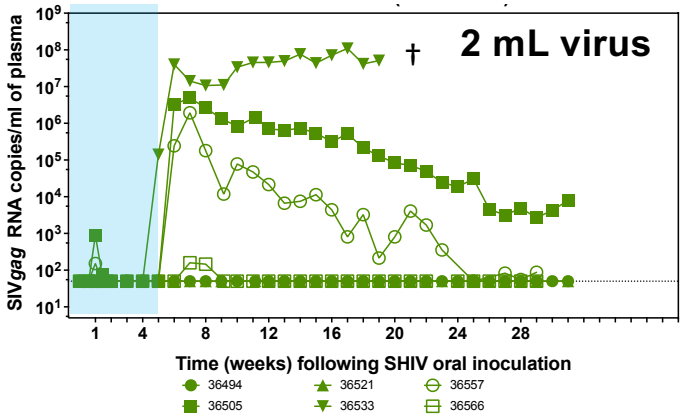


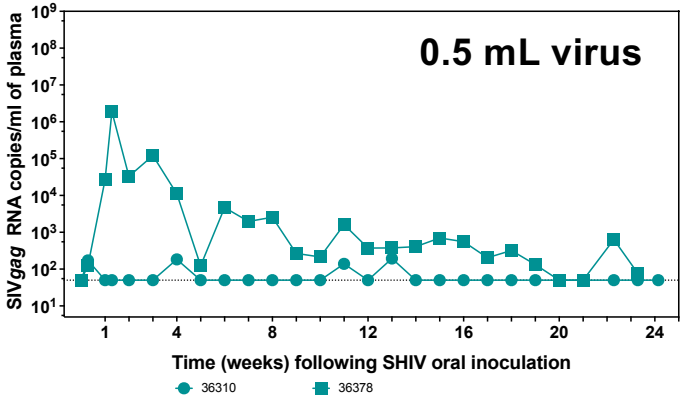
Dose-dependence in delayed viremia/control in infants treated with bNAbs at 48h post-challenge

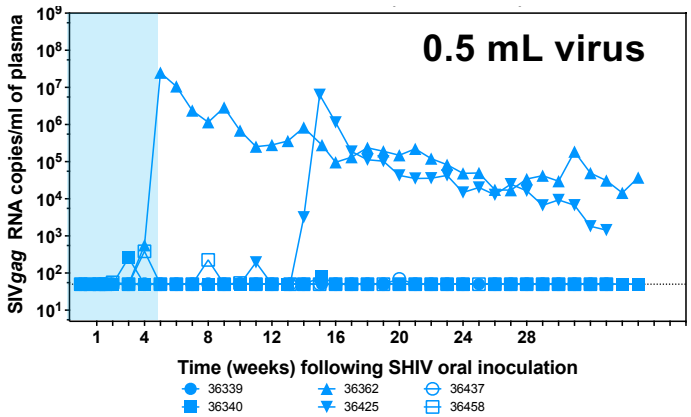
SHIV-only controls



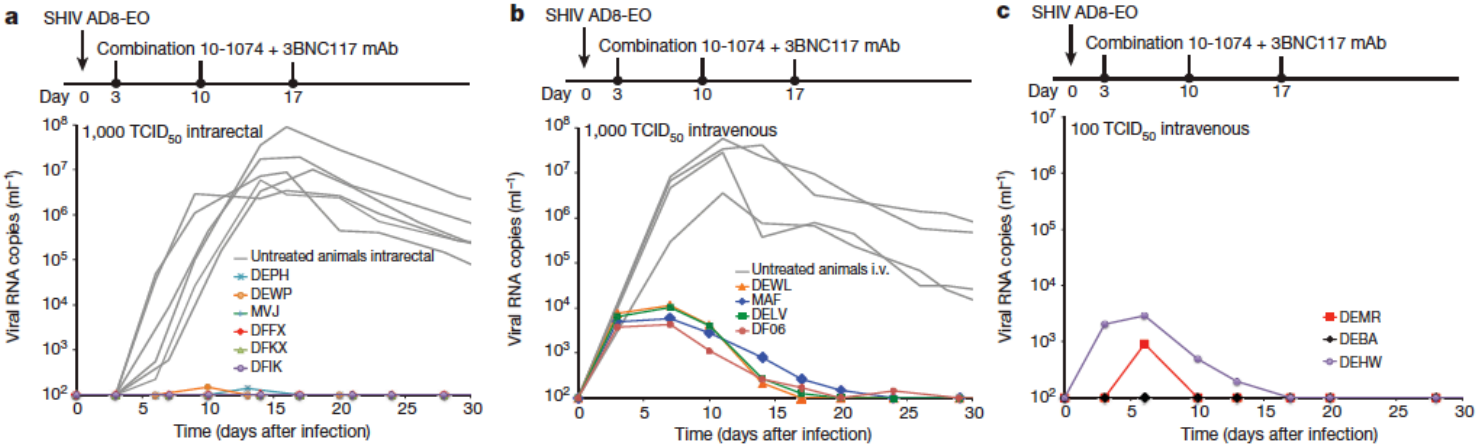
48h bNAb treatment







Degree of control of SHIV-AD8-EO viremia after delayed treatment (3 days) is route and dose-dependent in older macaques



Nishimura, Martin et al., 2017 *Nature*

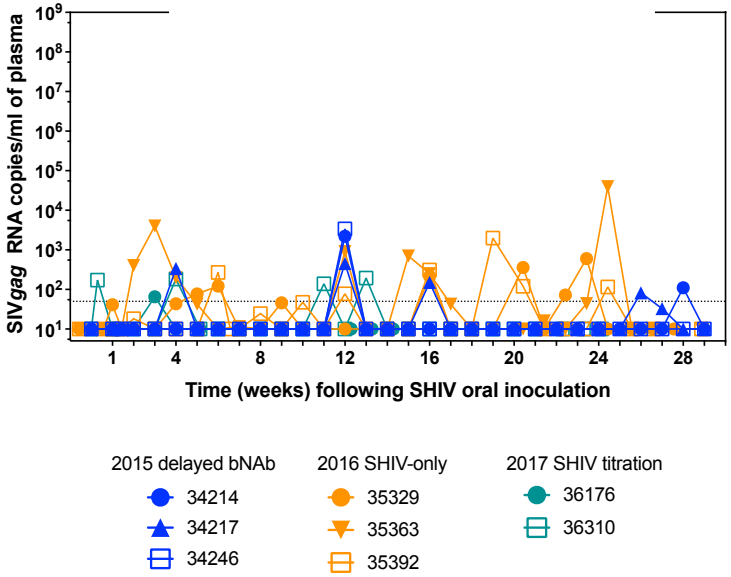
- bNAb cocktail: 10-1074 and 3BNC117
- Viral rebound after antibody decay
- Control seen in ~50% of animals without further treatment
- Rebound virus controlled by CD8+ T cells

Time- and dose-dependence of bNAb effectiveness in early Tx

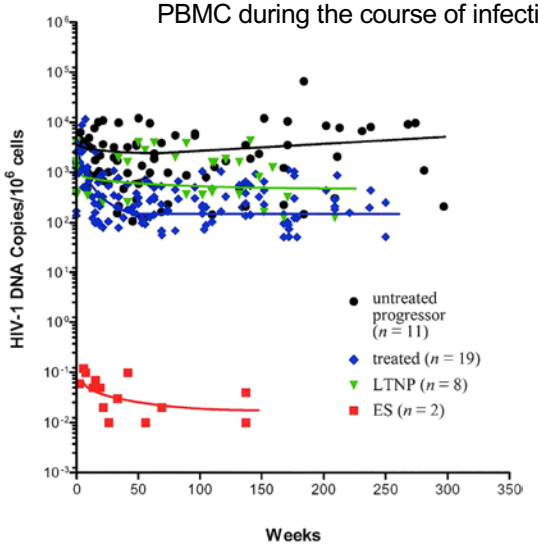
- **Day 0** —100% effective in blocking infection
- **Day 1** —100% effective in clearance and preventing reservoir, no rebound; 12/12 no virus
- **Day 1 "half" dose** —tight control in 5/6 with no rebound
- **Day 2 —**partial control in 8/18 and tight control in 8/18, rebound observed in 1/18
- **Day 3** —dose dependent, partial control and rebound with development of controlling T cells (Nishimura, Martin study)
- **Day 10** --control as effective as ART but all rebounded (Bolton e*t al.* J Virol 2015. HIV-1 monoclonal antibodies suppress acute SHIV viremia and limit seeding of cell-associated viral reservoirs)
- **Established infection** –control is transient

Conclusion: full clearance may require rapid <48h application of treatment(s)

Low transient plasma viremia in SHIV titration—and in HIV/SIV infection—due to lower "seeding" of infectious centers



Representative patterns of variation in the level of cell-associated HIV-1 DNA in PBMC during the course of infection.

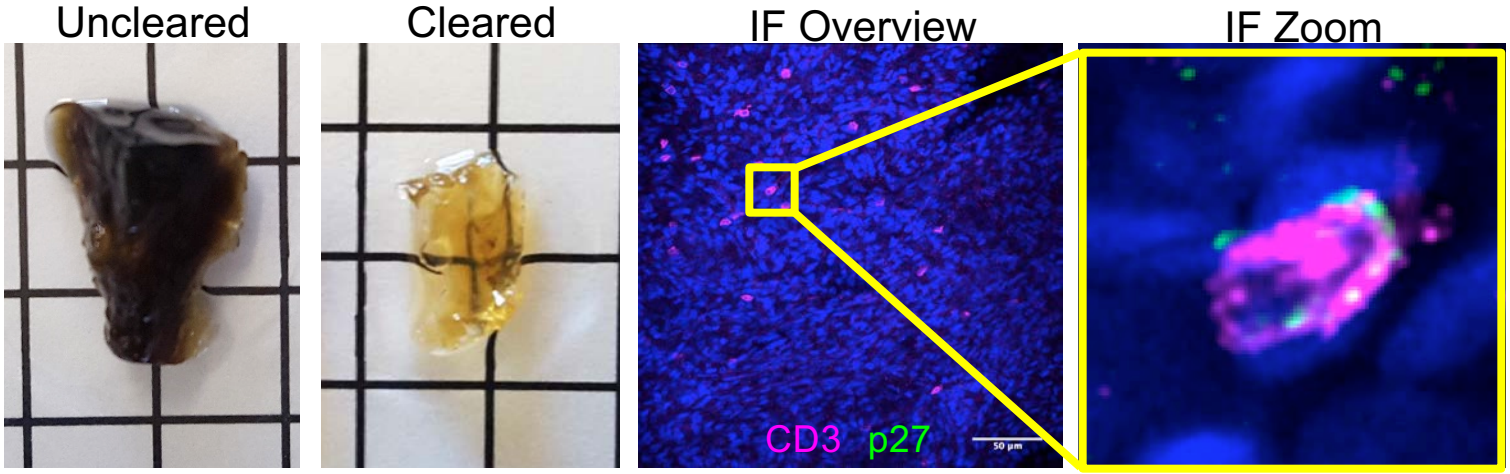


Tuofu Zhu et al. J. Virol. 2003;77:6108-6116

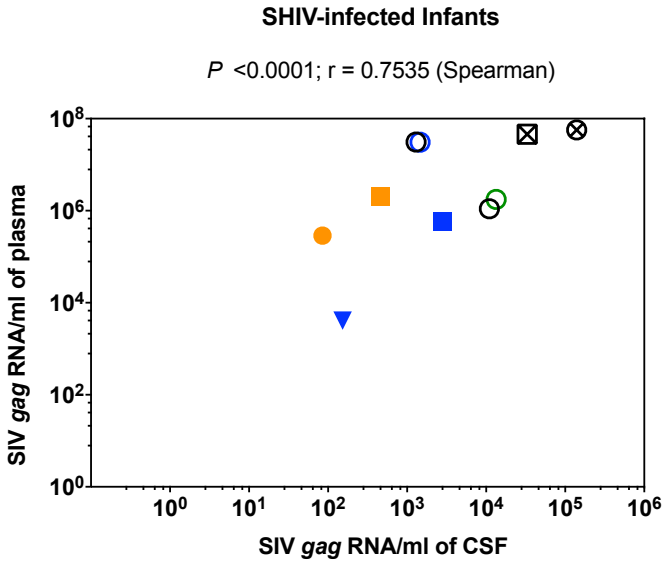
- Observed in infant macaques, SHIV titration; SIV-vaccinated macaques; HIV-1 exposed/seronegatives
- No adaptive responses; CD8 depletion did not result in rebound
- Low level viral DNA was detected in few tissues of 4/8 at necropsy
- **Are these low transient viral blips replication-competent virus? If so, in which tissue(s) are infected? QVOA assay in progress suggests they are below detection**

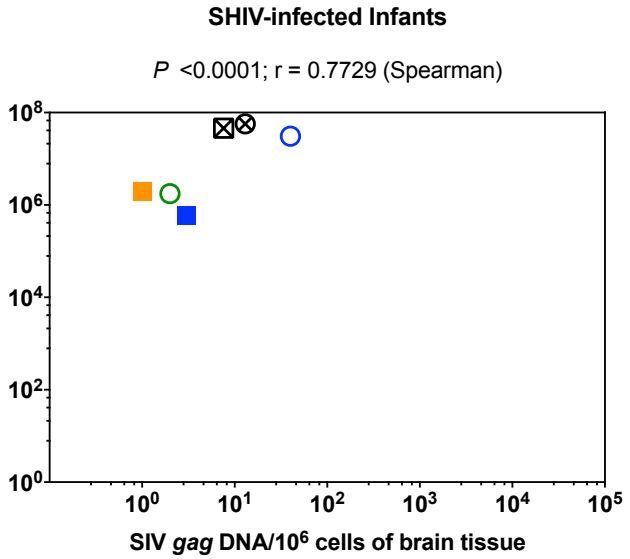
SHIV is expressed in tissue-resident splenic CD3⁺ cells

C. Kieffer and P. Bjorkman, Caltech



Correlation of CSF, brain, and plasma virus in infant rhesus macaques





34215 29wpi
34232 29wpi
34245 29wpi
34338 24wpi

NmAb 10 mg/kg day 2, 4, 7, 10

NmAb 5 mg/kg day 1, 4, 7, 10

34932 1wpi
34947 1wpi

No NmAb

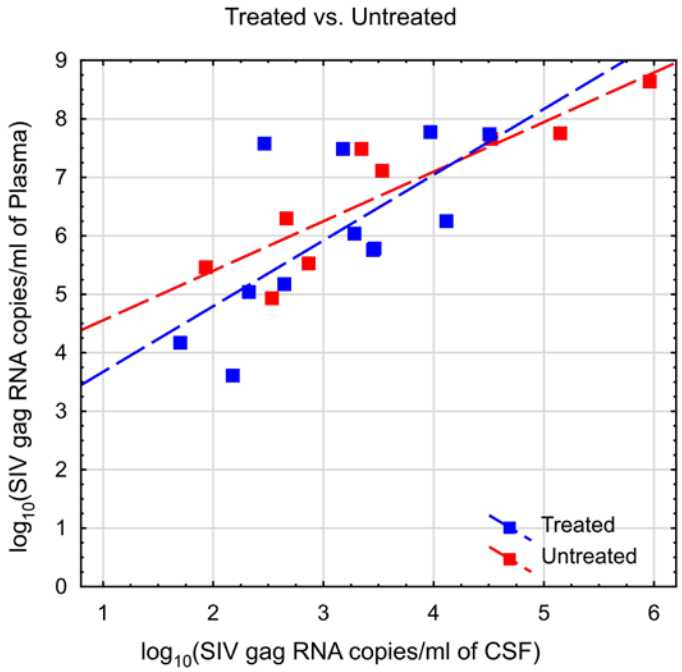
33172 2wpi
33186 2wpi

No NmAb

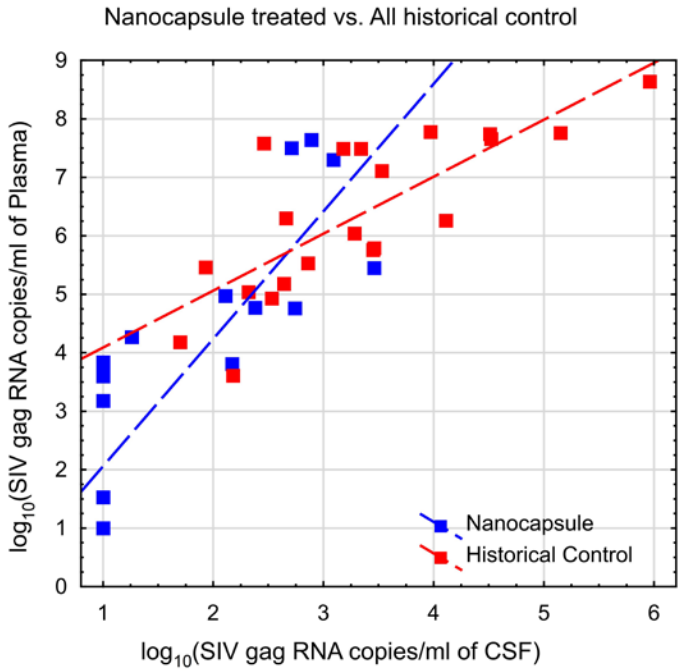
PGT121 nanocapsule-targeted delivery at 48 hours significantly reduces virus in CSF in infants relative to plasma

Irvin Chen, UCLA

p-value = 0.4989



p-value = 0.0020

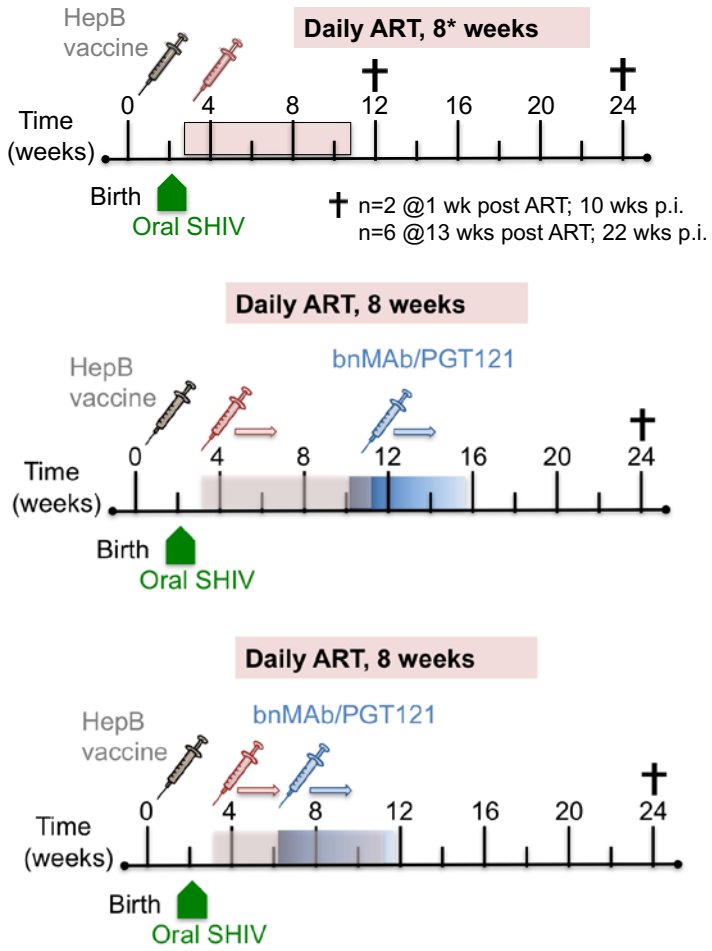


Penetrance and expression of SHIV suggests it is a good model for cure research

- Lymphoid tissues appear most heavily infected; nearly all tissues are positive for viral DNA, e.g. gut
- Tissue viral DNA correlated with plasma virus production
- Infectious virus is produced in LN and splenic CD3 cells (so far)
- Level of viral DNA in LN at week 12 predicts tissue integration at 24 week and level of adaptive immunity
- Moderate/high viremia positive in QVOA; Low level viral DNA/RNA does not yield infectious virus
- These models can help us to understand the level of reservoir to target in a functional cure
- In vivo imaging using PET can allow real-time monitoring of reservoir sources and reduction(s) per treatment

How to augment the standard of care (cART)

- cART initiated at 72h does not prevent rebound in older macaques *(D. Barouch)*
- With <u>low dose challenge</u>, cART initiated at 48h for 3 weeks suppresses viremia in infants for at least 10 weeks, re-exposure results in infection *(Haigwood, in prep)*
- Determine if reservoirs will be impacted with bNAbs given after/during ART
  - Test in conjunction with cART in IMPAACT network
  - Idea is to reduce or eliminate a life-long dependency on cART
- Intervention after established infection with LRAs and killing strategies



Macaques as Models for Pediatric HIV Cure Research

Primate models: SIV and SHIV infection both provide relevant models to measure how much virus remains in the body with and without treatment

Good news: Very early antibody treatment without ART prevents SHIV infection or severely blunts the infection with no viral rebound

Bad news: Treatment in the first 1-2 days is critical to clear the infection

Relevance for cure: Antibodies can prevent or limit SHIV reservoirs and prevent rebound without ART; models can be helpful to define tissue levels for a functional cure after ART +/- bNAb treatment (or other strategies)

Excitement? Yes. Cocktails of antibodies, bispecifics, and other killing strategies as a post-exposure treatment merit further exploration for PrEP and PEP so that ART can be discontinued

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Tracy Cheever
Rececca Lewinsohn

Nancy Haigwood
Mariya Shapiro
Philip Barnette
Heidi Henderson

Postdoctoral Positions available

University of Rochester
James Kobie

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Health research throughout the lifespan

Elizabeth Glaser Pediatric AIDS Foundation

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