
NIAID Workshop, May 22-23, 2018

Nancy L. Haigwood, Oregon Health & Science University
“Mississippi baby” case brought attention to the need to treat continuously after peripartum infection.

Los Angeles Times

HIV appears again in child thought cured
Finding dashes hopes of way to treat infants
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

**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

*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 $\text{SHIV}_{SF162P3}$ 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?**

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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.)**

Day 1
No NmAb

Day 2
NmAb 10 mg/kg

Day 7, no Tx

Day 7; 10 mg/kg

Day 14
No NmAb

Day 14
NmAb 40 mg/kg

**SIV copies/µg DNA**

- 0.01 - 0.99
- 1 - 299
- 300 - 2,999
- 3,000 - 29,999
- > 30,000
No evidence of viral DNA in a panel of 33 lymphoid, mucosal and organ tissues,
CD8 depletion yielded no viral outgrowth
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

Time (weeks) following SHIV oral inoculation

SIV gag RNA copies/ml of plasma

Plasma viremia (0.5 mL virus)

Plasma viremia (2 mL virus)

Plasma viremia - SHIV-only controls (0.5 mL virus)

Plasma viremia - SHIV-only controls (2 mL virus)

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Plasma viremia - SHIV-only controls (2 mL virus)

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

- 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

Nishimura, Martin et al., 2017 *Nature*
**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 et 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

- 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

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
**SHIV is expressed in tissue-resident splenic CD3+ cells**

_C. Kieffer and P. Bjorkman, Caltech_

Spleen Animal# 35255 (High VL)  

Spleen Animal# 35159 (Low VL)
Correlation of CSF, brain, and plasma virus in infant rhesus macaques

**SHIV-infected Infants**

$P < 0.0001; r = 0.7535$ (Spearman)

**SHIV-infected Infants**

$P < 0.0001; r = 0.7729$ (Spearman)

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**SIV gag RNA/ml of plasma**

**SIV gag RNA/ml of CSF**

**SIV gag DNA/10^6 cells of brain tissue**

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

\[ p-value = 0.4989 \quad p-value = 0.0020 \]
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 low dose challenge, 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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