

Dr Jintanat Ananworanich

US Military HIV Research Program in Bethesda
Maryland, USA

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Speaker Name	Statement
Dr Jintanat Ananworanich	acts as a speaker for a Gilead-sponsored event in October 2013. Her institution has received payment for her consultancy capacity at the ViiV Healthcare pediatric advisory meeting in May 2014 and her former institution has received an educational grant from Gilead in 2010-2012.
Date	October 2014

HIV Persistence and Pediatric HIV Cure: Where do we go after the Mississippi baby?

Jintanat Ananworanich, MD, PhD

Associate Director for Therapeutics Research
US Military HIV Research Program (MHRP)
Maryland, USA



The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.



Outline

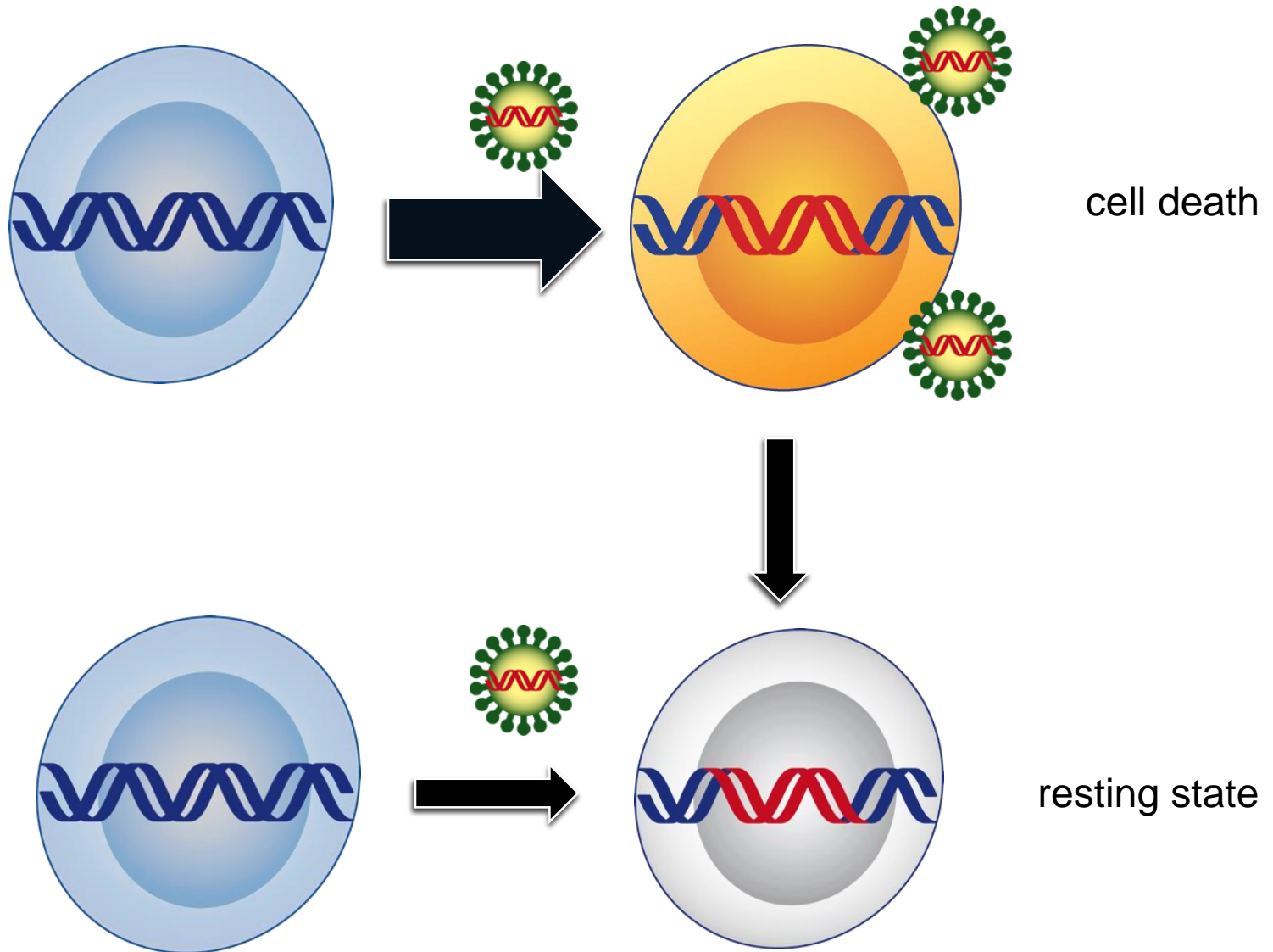
- Goals of HIV Cure research
- Mississippi, California, Canadian and Milan babies
- Strategies to eliminate HIV persistence
- Where do we go in the future?

Short video on patients' perspectives on cure

Goals vs. Current Reality

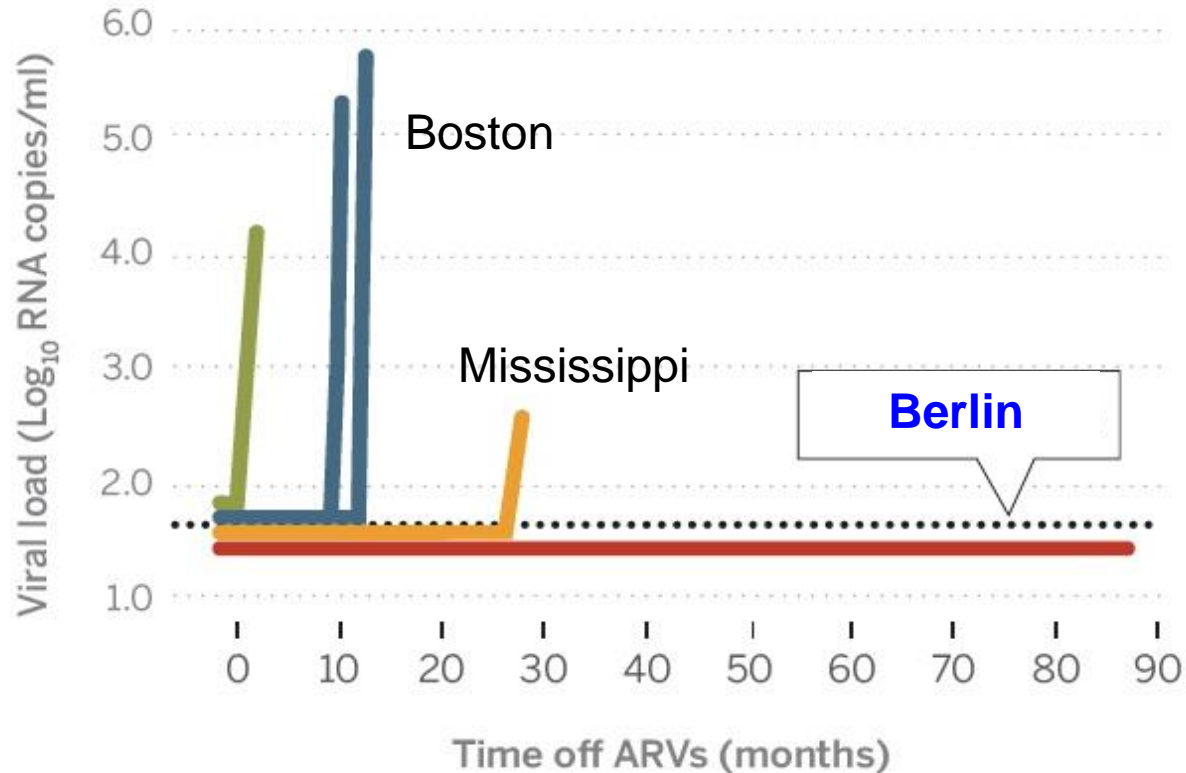
Eradication	Remission
No HIV detected	HIV detected
Test HIV negative	Test HIV positive
Not HIV infectious	Maybe HIV infectious
No need to take ARV	No need to take ARV
Healthy	Healthy
	Ongoing viral load monitoring
Reality of Current Therapies	
Normal/near normal life span	
Propensity for co-morbidities	
Control of HIV viremia and infectiousness But with strict adherence and daily medications	
Stigma and discrimination	

HIV Persistence



ARVs stopped, HIV rebounds

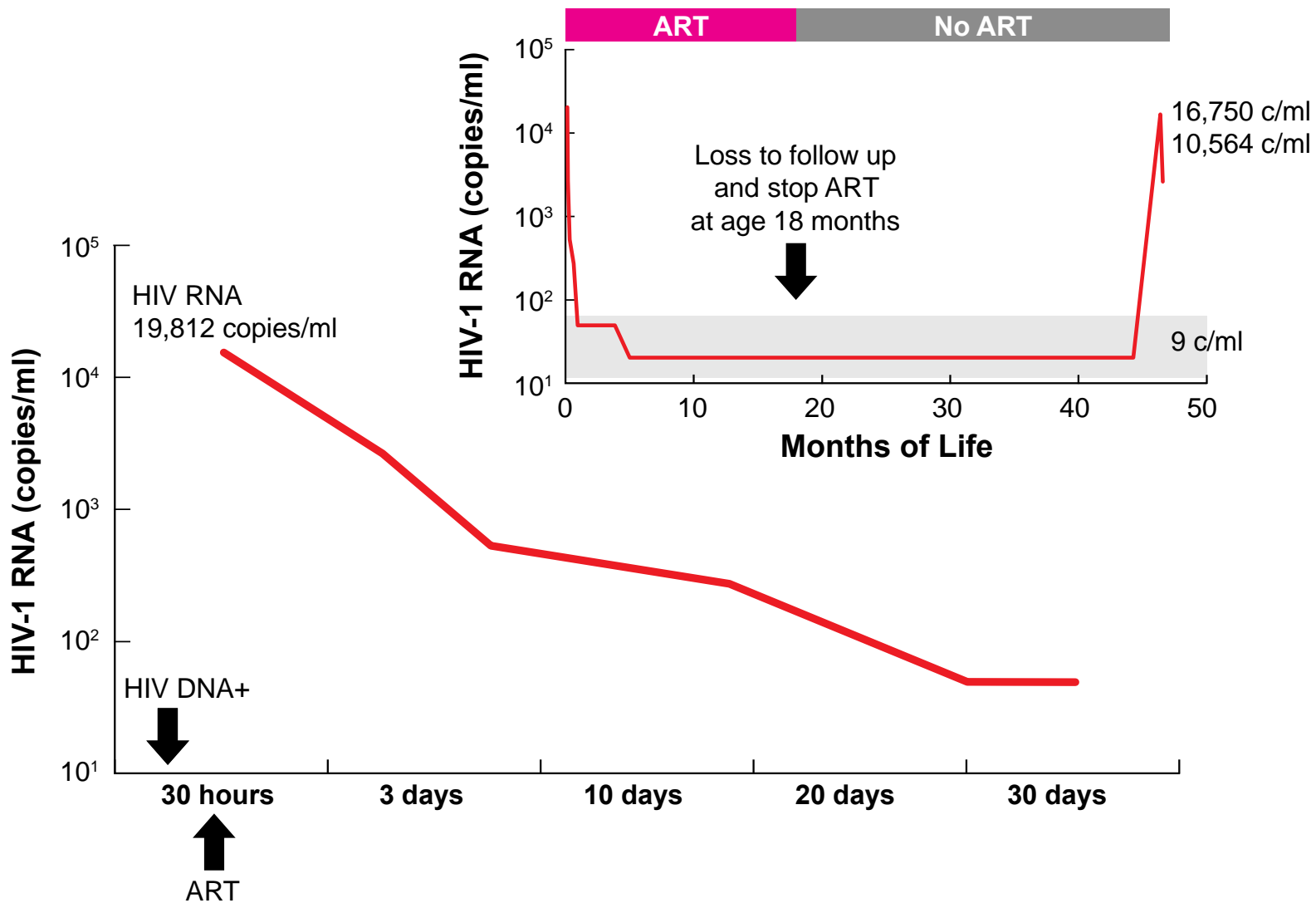
Only one person has been “cured” of HIV.



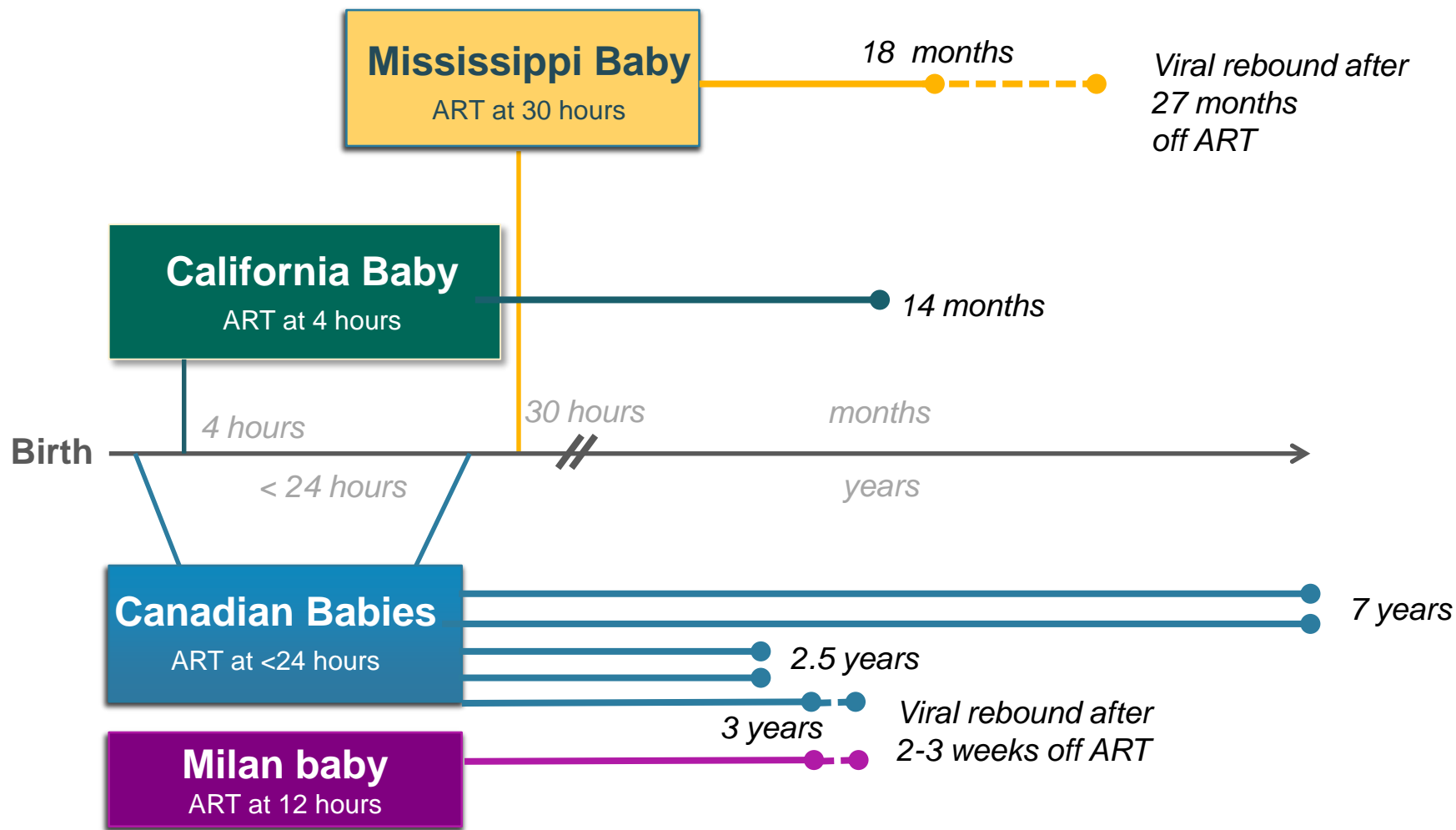
- Timothy Ray Brown
- Boston bone marrow transplants
- Mississippi child
- Typical person suppressed 1 year

From Cohen J, Science 2014; Courtesy of Diana Finzi (NIAID/NIH)
(Hutter, NEJM 2009; Henrich, Annals Internal Medicine 2014; Persaud, NEJM 2013)

The Mississippi Baby



Cases of Early Treated Infants



Modified from Rainwater-Lovett, Luzuriaga and Persaud, Current Opinion HIV/AIDS (in press)
 Bitnun A, CID 2014; Brophy J, IAS 2014; Persaud D, CROI 2014, Giacometti V, Lancet 2014

Early-treated pediatric cases with different time to viral rebound

Parameters	Mississippi ¹	Canadian ²	Milan ³
Time to VL rebound	27 months	< 1 month	< 1 month
ART onset	30 hours	< 24 hours	12 hours
Baseline VL	19,812	808	152,560
Time to VL < 50 on ART	1 month	6 months	3 months
Time on ART	18 months	3 years	3 years

¹Persaud, NEJM 2013; ²Brophy, IAS 2014; ³Giacomet, Lancet 2014

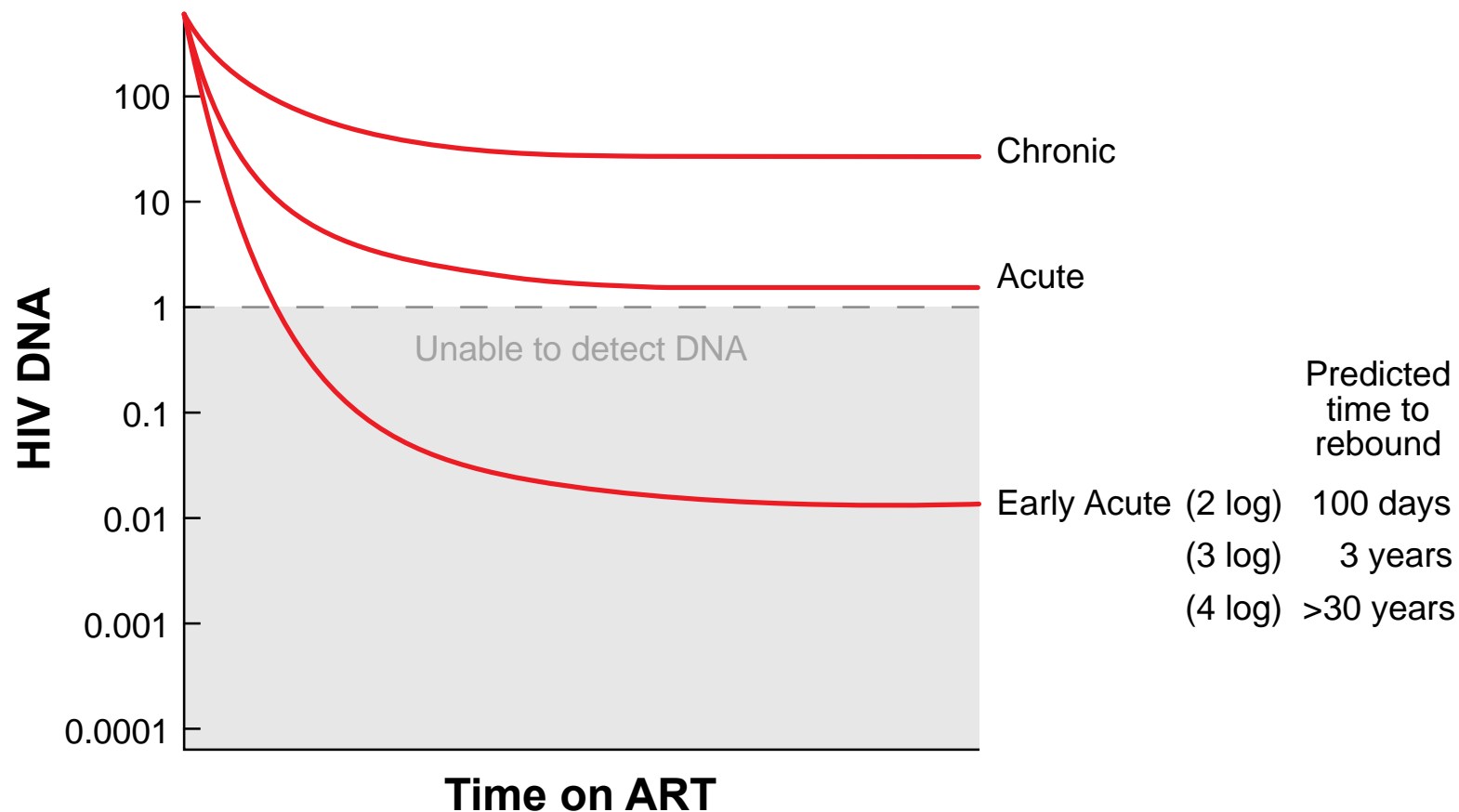
Early-treated pediatric cases with different time to viral rebound

Parameters	Mississippi ¹	Canadian ²	Milan ³
Time to VL rebound	27 months	< 1 month	< 1 month
HIV DNA	Undetected*	Undetected	Undetected
Replication competent virus	Negative*	Negative	Negative
HIV antibody	Non-reactive*	Non-reactive	Non-reactive
HIV-specific T cells	Undetected*	Undetected	Detected
Others	Normal % activated T cells*	Detected cell-associated HIV RNA	High % activated T cells

*Off ART

¹Persaud, NEJM 2013; ²Brophy, IAS 2014; ³Giacomet, Lancet 2014

Predicting time to viral rebound: Limitation of current tools



Sharon Lewin (Doherty Institute, University of Melbourne)
based on Hill AL, PNAS 2014

HIV Persistence and Immunity in Early Life

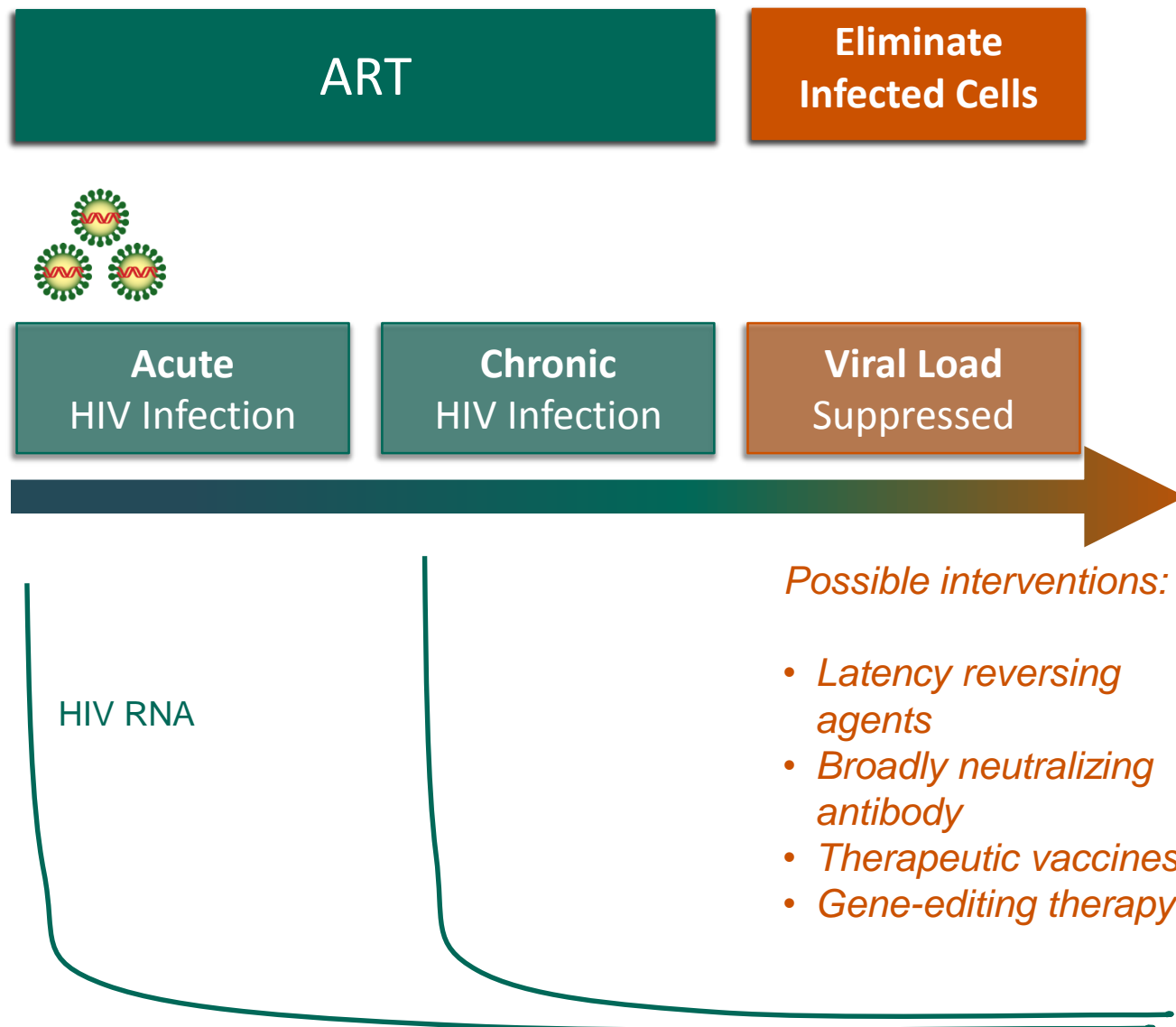
↓ Persistence

- Few memory CD4+ T cells
- Fewer activated CD4+ T cells

↑ Persistence

- Abundance of target cells (CD4+CCR5+ T cells in the gut)
- Immature innate and adaptive immune responses
- High viremia
- Memory-like T cells in cord blood

Strategies to Eliminate HIV Persistence



VISCONTI Cohort of Post-Treatment Controllers

14 people
ART in first
3 months

Control VL
after
stopping ART

Why are these patients able to control HIV without ART?

**HIV reservoir amount
and location?**

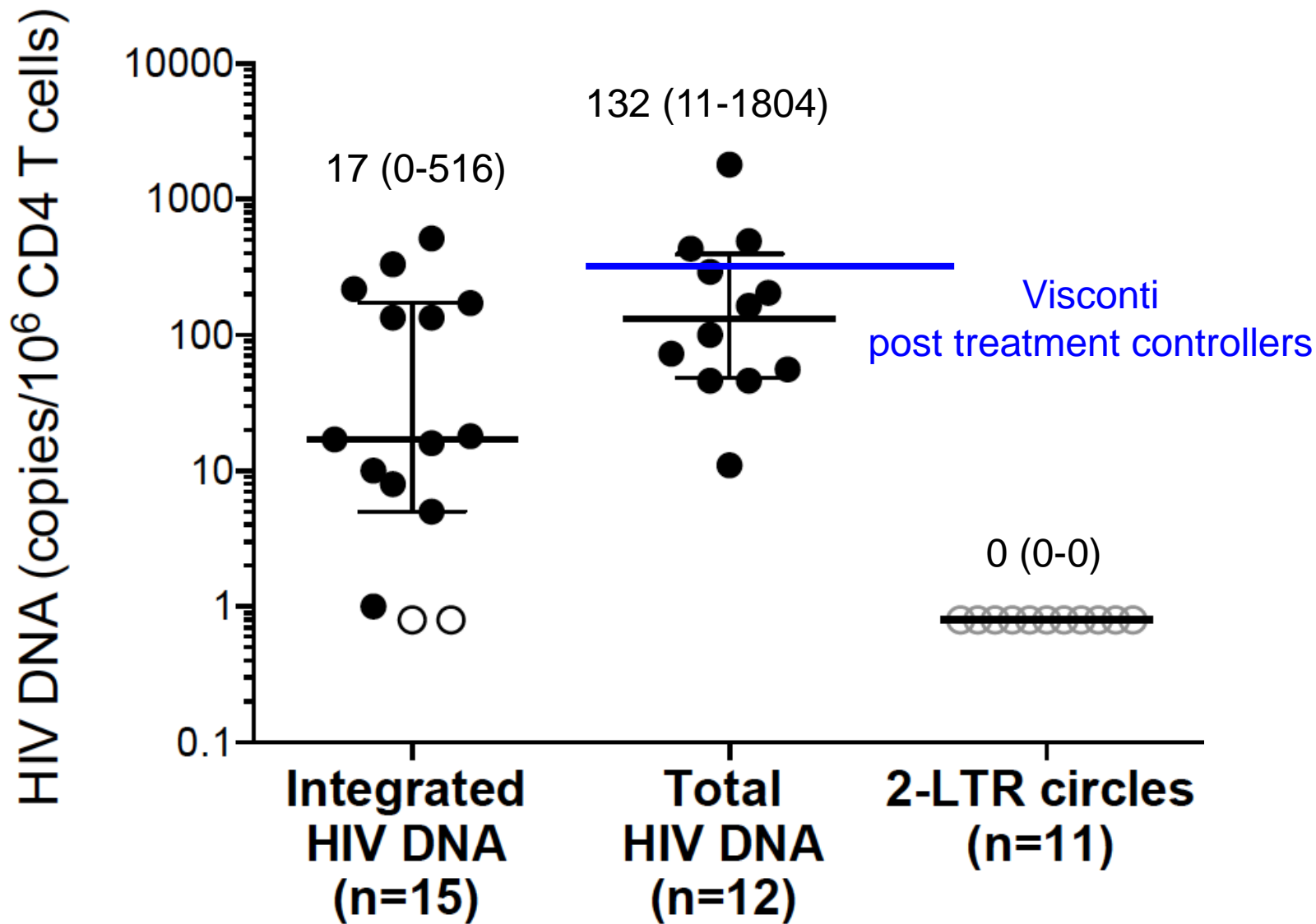
✓ **Low HIV DNA**
✓ **In shorter-lived CD4 cells**

Saez-Cirion A, Plos Pathogens 2013

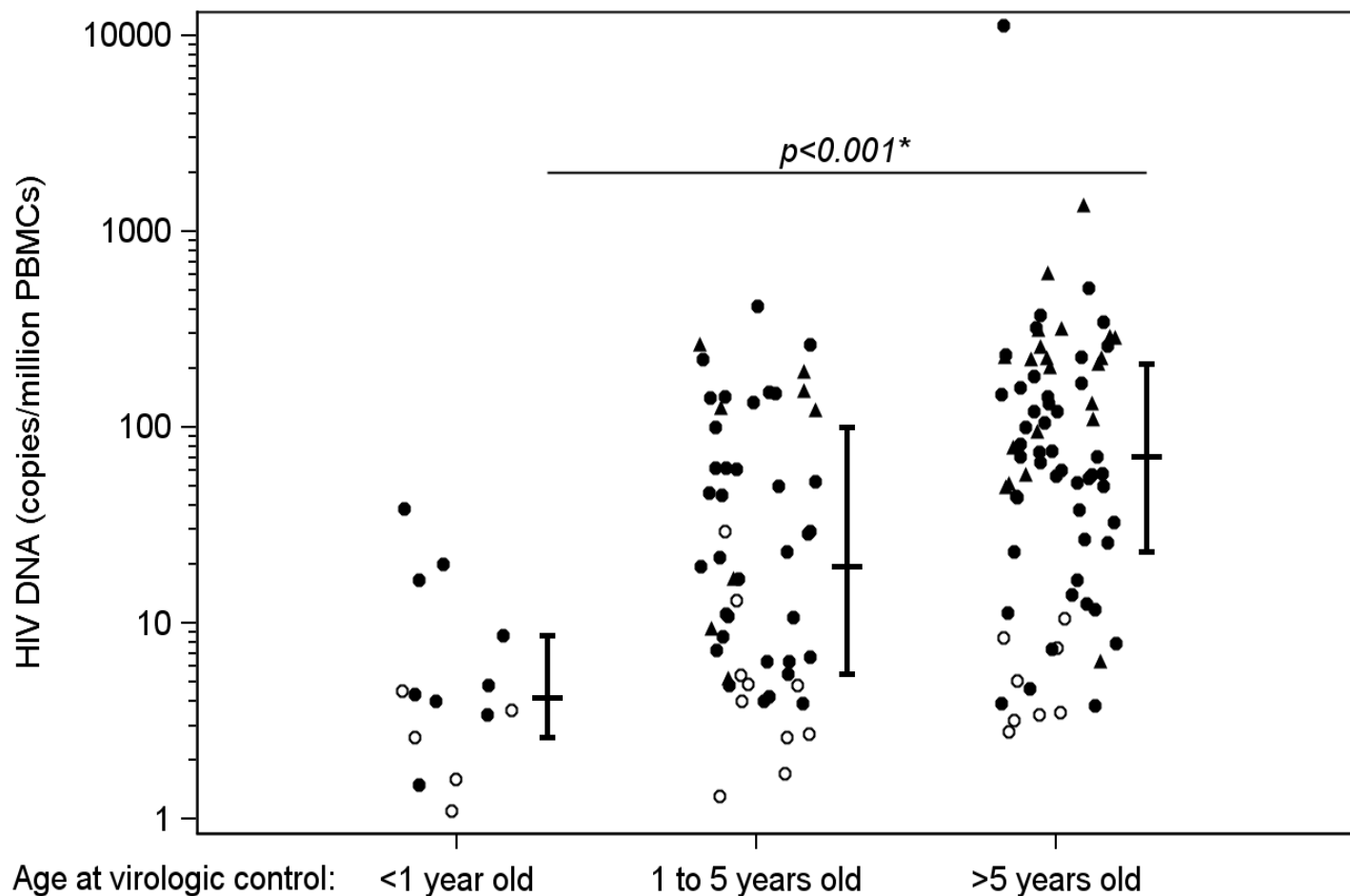
Limited infection in long-lived CD4+ T cells after treatment in acute HIV infection

Ananworanich J, Plos One 2012, CROI 2013

Restricted Reservoir Size in Early Treated Thai Children

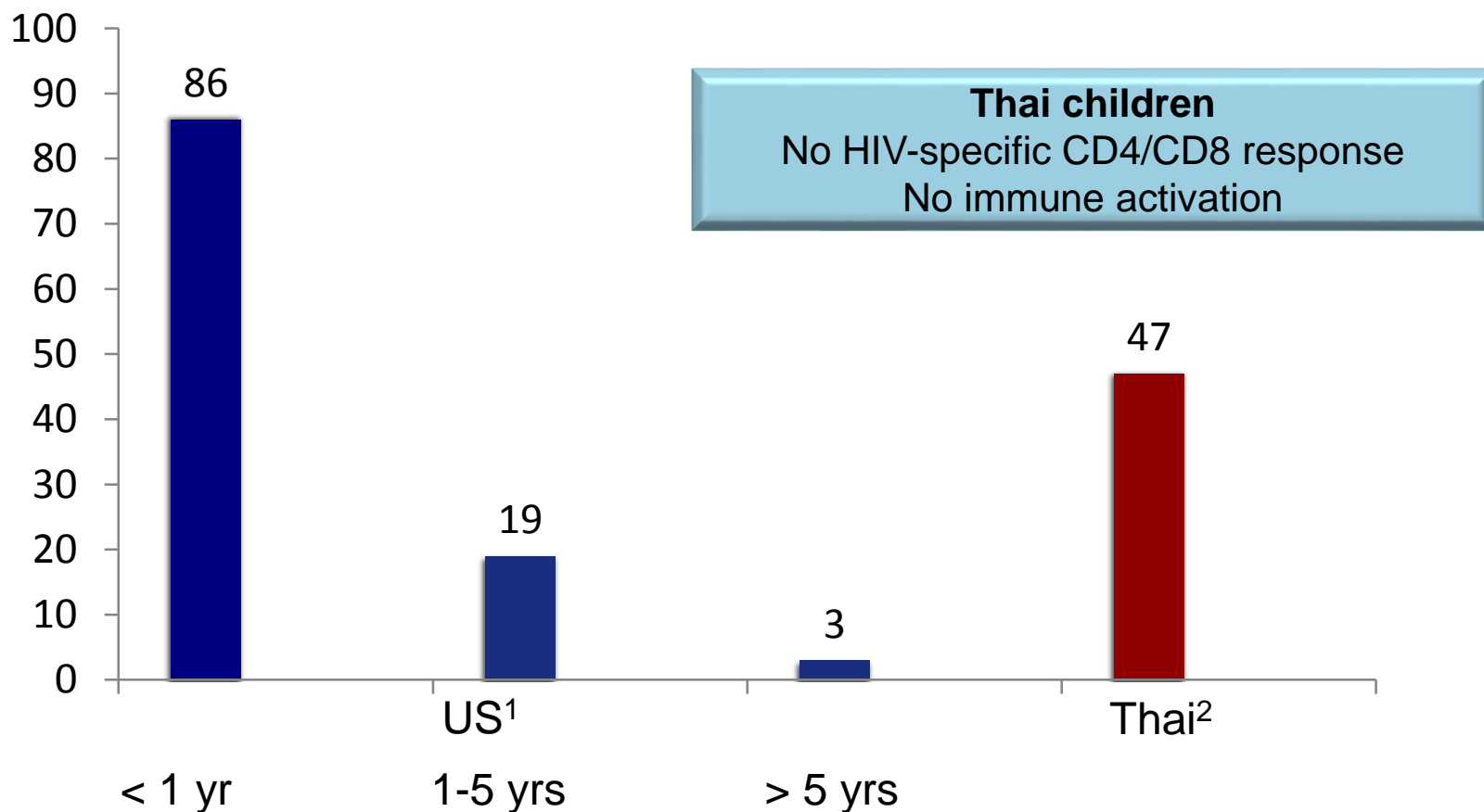


Low HIV DNA in Children who Achieve Viral Suppression by Age 1 Year



HIV Seronegativity in Early-treated Children: Marker for Low HIV Reservoir

% Non-reactive
HIV antibody



¹Persaud D, CROI 2014 and JAMA Peds 2014 (in press); ²Ananworanich J, AIDS 2014

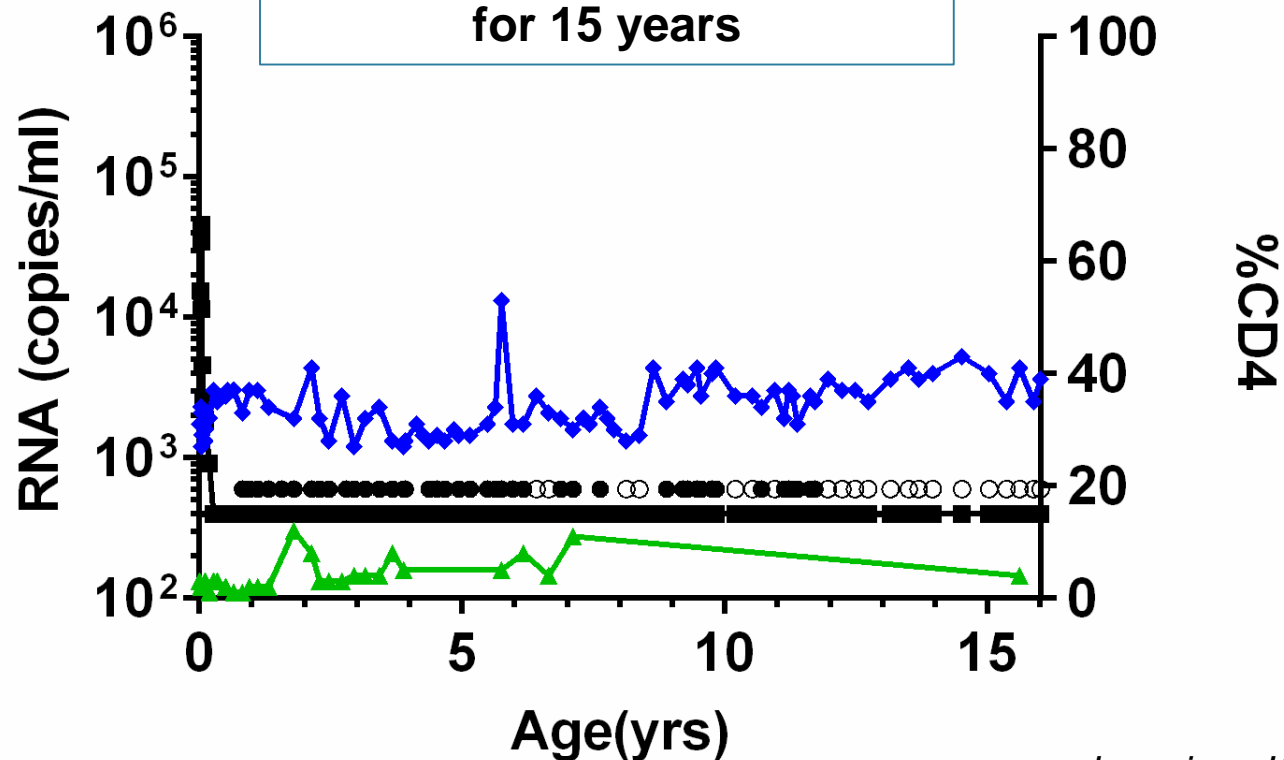
Long-term Treated Adolescents with No Detectable HIV

ART at 15 days of life

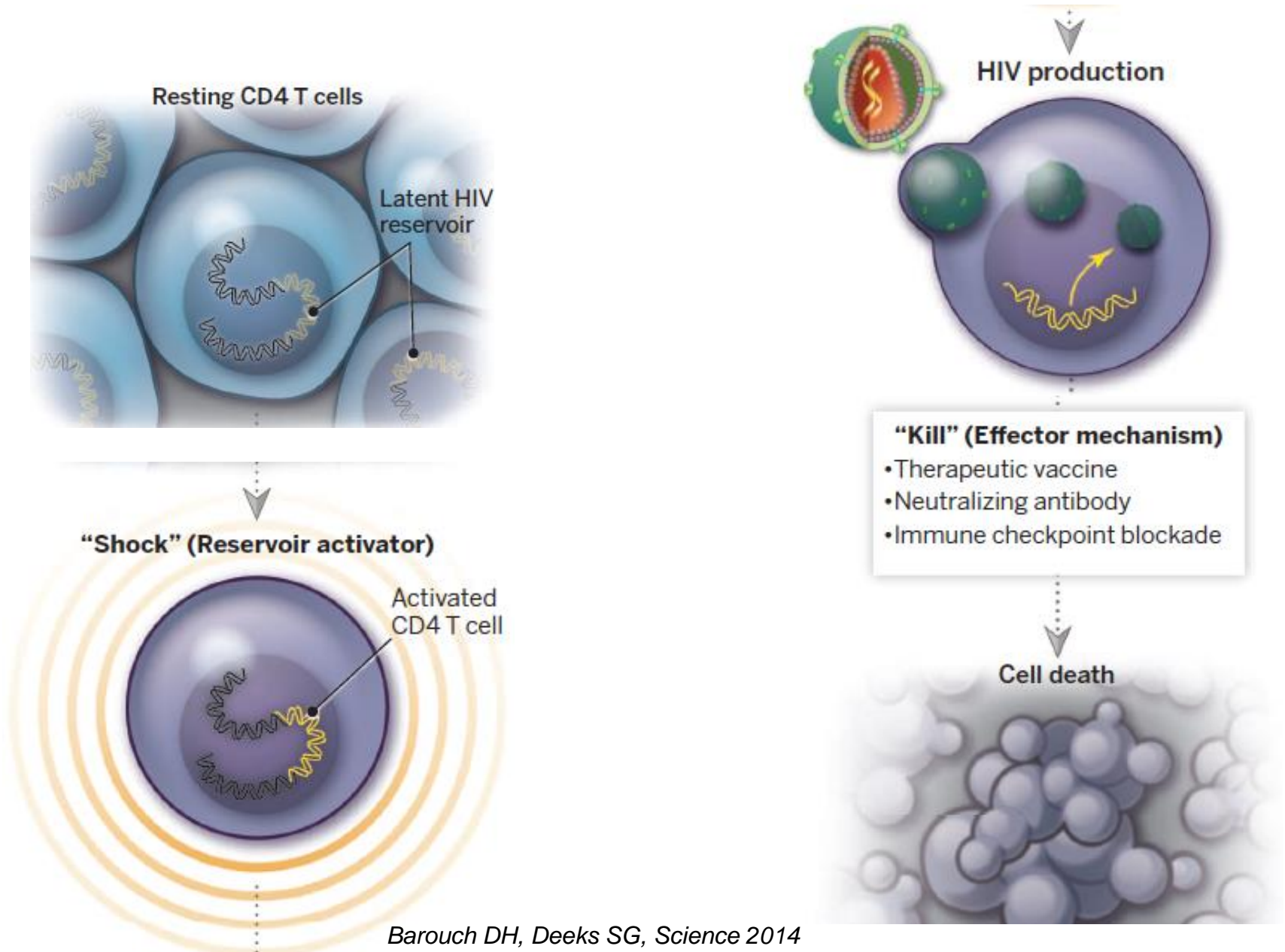
VL < 400 by 3 months of age

VL suppression on ART
for 15 years

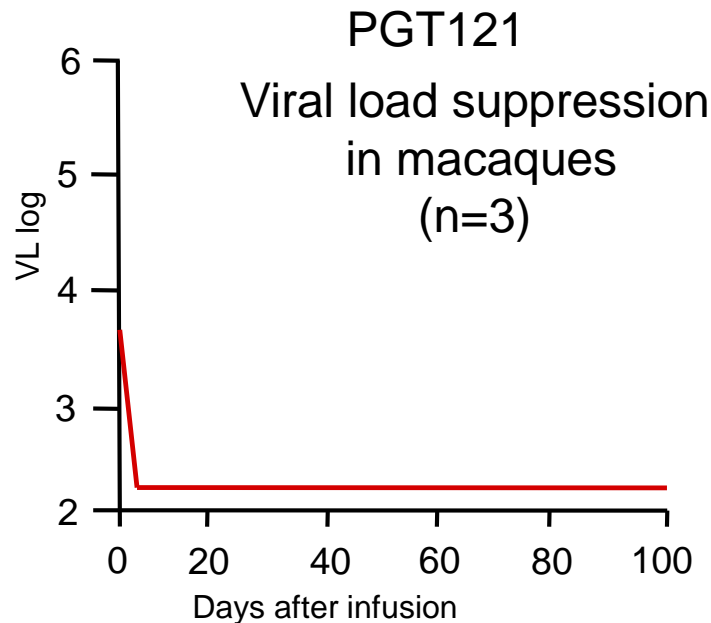
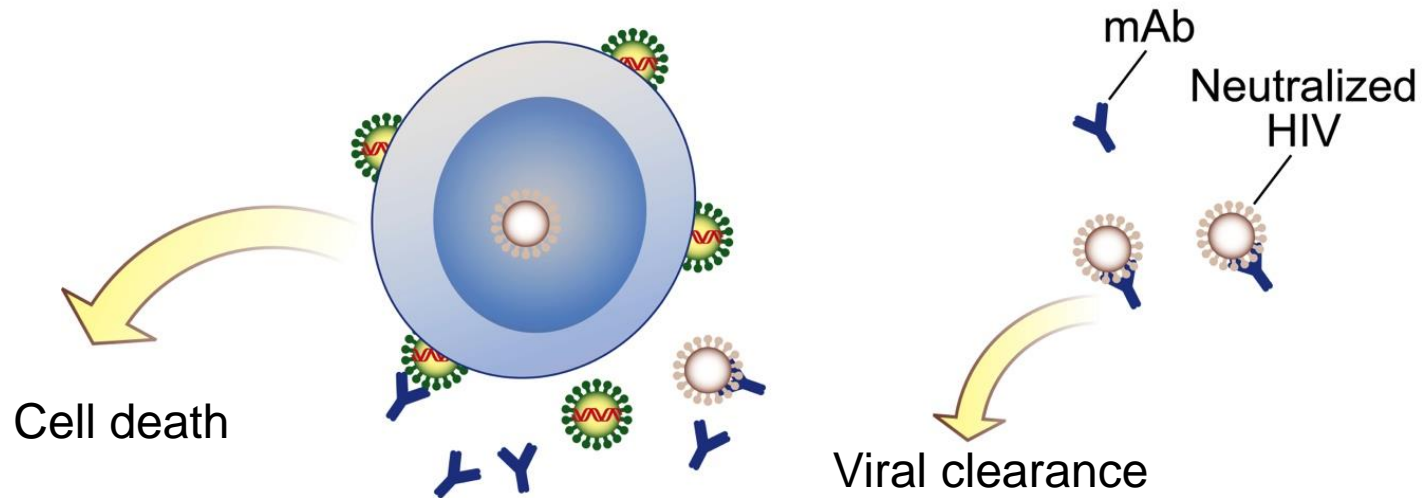
No detectable
RNA
DNA
Replication competent virus
HIV-specific immunity
Immune activation



Shock and Kill Strategy



Broadly Neutralizing Antibody



Barouch DH, Nature 2013

- > 30 antibodies identified
- Human studies
 - VRC01
 - RV397/398 in acute HIV
 - ACTG in chronic HIV
 - IMPAACT in chronic HIV
 - 3BNC117, 10-1074, PGT121

Examples of Strategies Currently in Human Studies

MINIMIZE RESERVOIR

Limit reservoir with early treatment

Antiretroviral therapy
Broadly neutralizing antibodies

SHOCK

Reactivating latently-infected cells

Inhibit histone deacetylase
Inhibit bromodomain
extraterminal
Activate toll-like receptors
Activate protein kinase C

KILL

Viral clearance by the immune system

Broadly neutralizing antibodies
Therapeutic HIV vaccines
Anti programmed cell
death (PD)1
Anti PD ligand 1

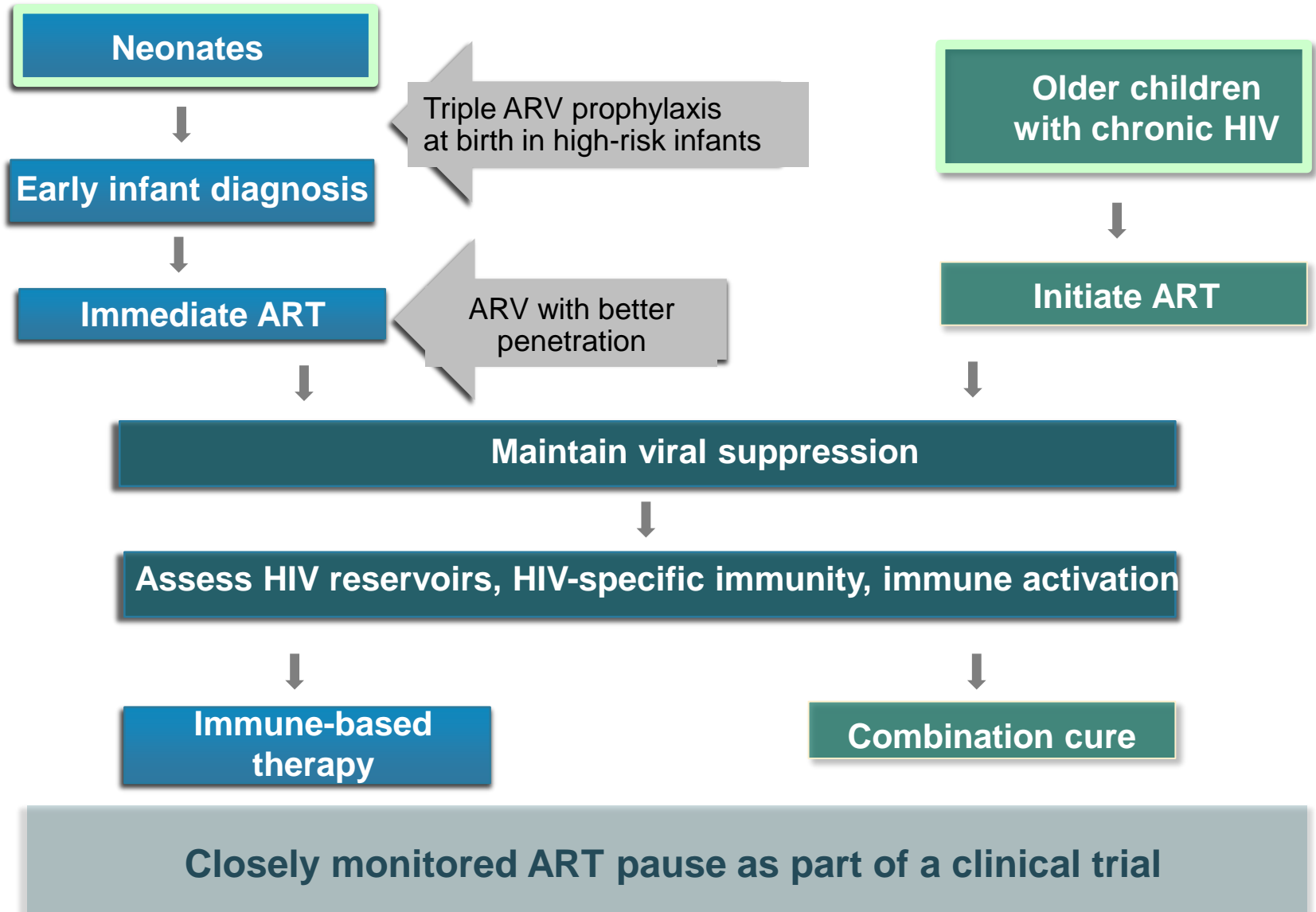
**Combination
Cure**

HIV RESISTANT CELLS

Transfusing cells without CCR5 gene

Gene-editing therapy
Bone marrow or cord blood transplantation

What will it take to cure children with HIV?



Ethics of HIV Cure Research in Infants and Children

- Enrolling mothers at high risk of transmitting HIV
 - Informed consent during labor
- Treatment interruption
 - Biomarkers for viremic control is unknown
- Early phase trials
 - High risks and low/no benefits
- Research in low and middle income countries
 - Cost and accessibility

Acknowledgements

Study Volunteers and Research Teams

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Associate Director for Therapeutics Research, US Military HIV Research Programme, USA

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What does HIV cure mean to me?

“*It would be like my baby and I are born again. My baby will have a normal life and people will not stigmatize us.*”

- Thai widow living with HIV

