

# Progress and Strategies for HIV remission and Cure

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Distinguished Professor and Chief  
Global Pediatric Infectious Disease  
DGSOM at UCLA, Mattel Childrens

# Time for a **CURE**



**[AIDSPolicyProject.org](http://AIDSPolicyProject.org)**



*CURE!*  
*REMISSION*

# Challenge for path to the CURE

- Mission from NIH DAIDS
  - Innovative approaches ( use of nanoparticle delivery of drugs to key sites)
  - Adults, children, newborns
  - Barriers” latent reservoirs HIV”
  - Early treatment ( more potent) reduce establishment of latent pool
  - Purge HIV reservoirs and treat / therapeutic vaccine
- Host resistance cord stem cells CCR5 delta 32 or gene therapy with resistant phenotype
- Autologous stem cell transplant with manipulation of CCR5 and CxCr4 co receptors - C Jung et al
- Other immune combination approaches

# Can we cure HIV infection?

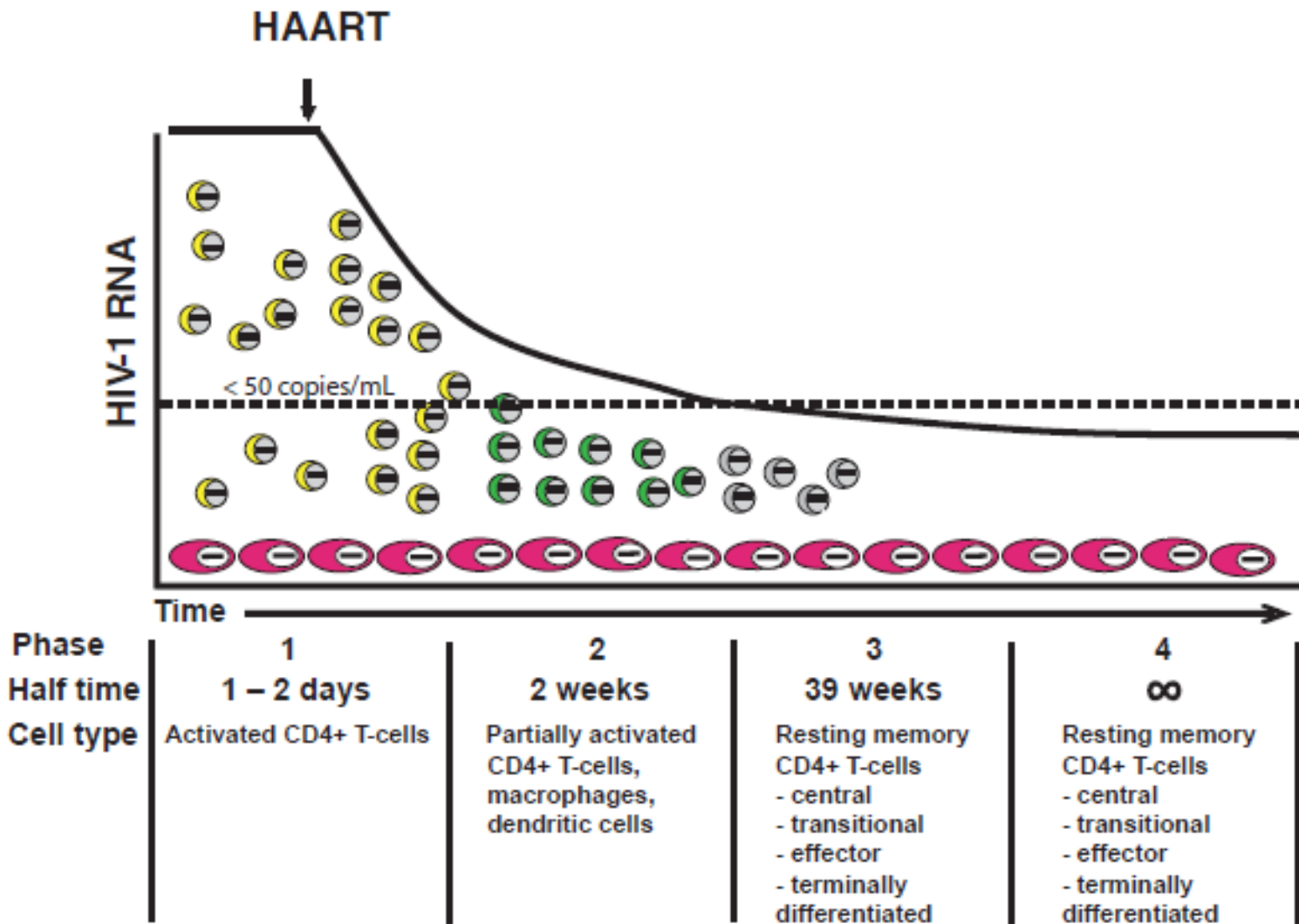
- Barriers to a cure or “functional cure” or prolonged remission

Early establishment of a latent pool of HIV reservoirs (CD4T cells, other sites)

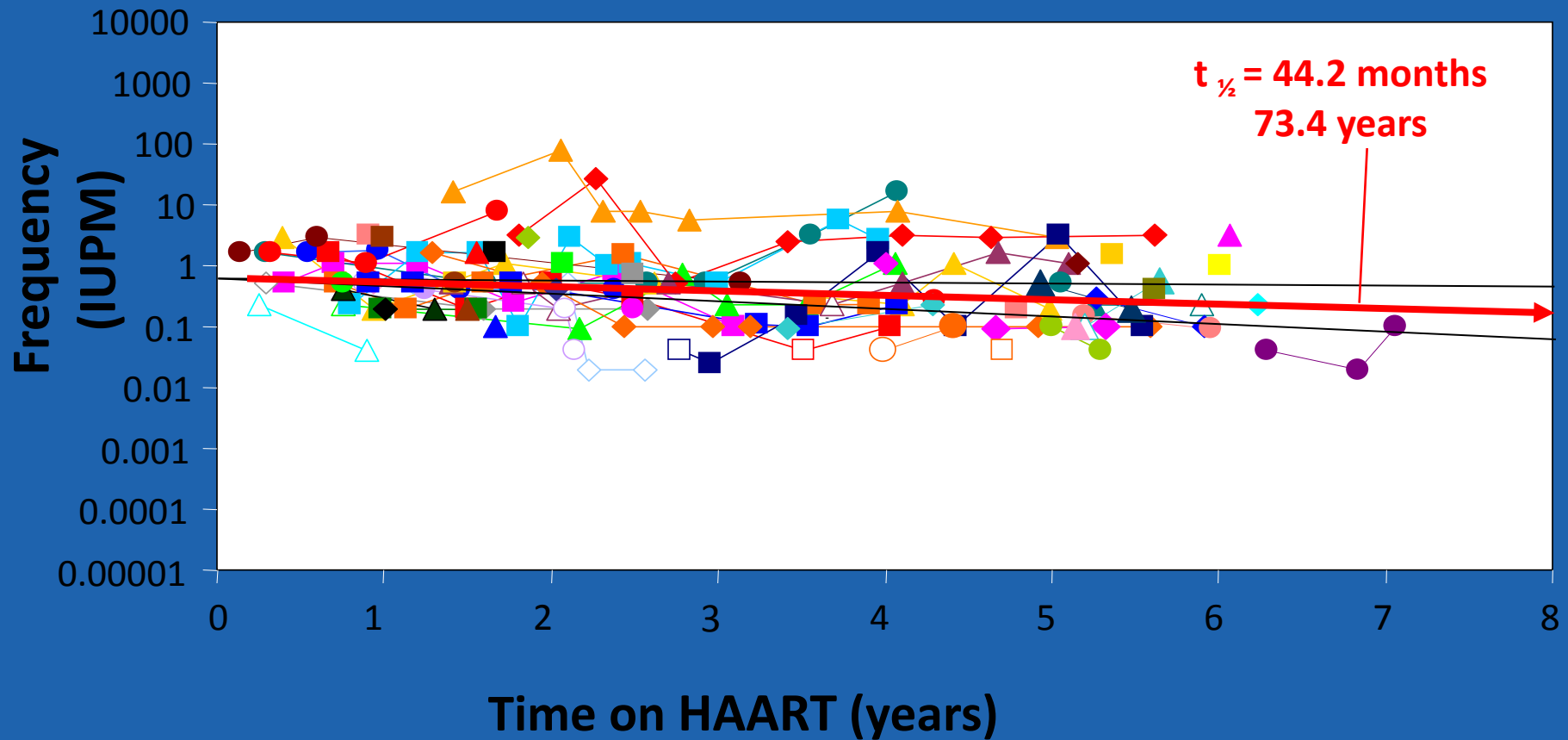
Continual low level HIV replication despite potent HAART and perpetual refill of viral reservoirs. Intermittent and incomplete reactivation of latent virus reservoirs

Long lived “latent HIV reservoirs”

# HIV Cure Elusive: Persistent Latent Infection in Long-Lived Cells (HIV- Reservoirs)



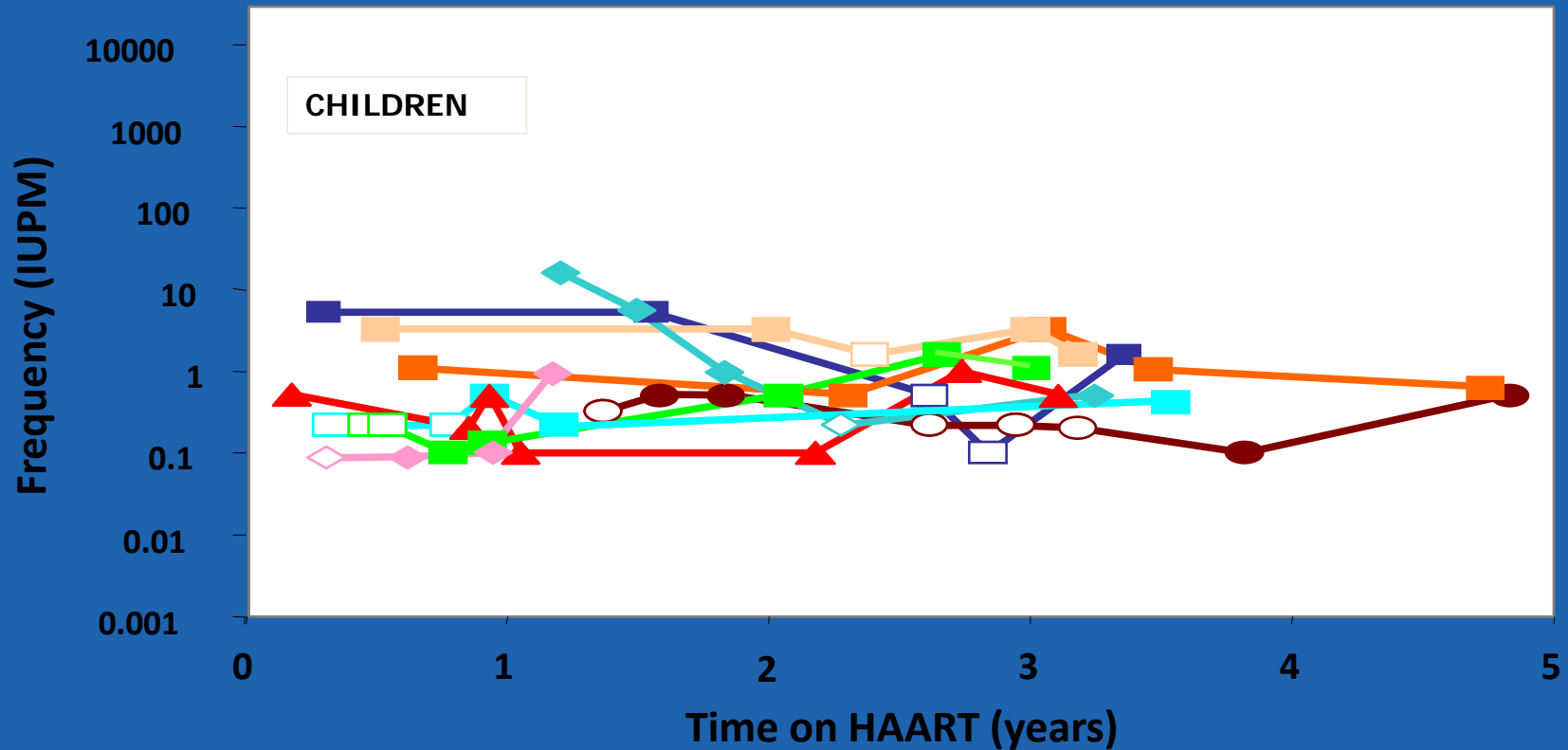
# No Decay of Latently-Infected Resting CD4+ T Cells Despite Long-term Suppression of Virus Replication with HAART (Adults)



Courtesy of Siliciano RF



## Similar Frequencies of Latently Infected Resting CD4+ T Cells Detected in Children Initiating HAART During Chronic HIV Infection as in Adults



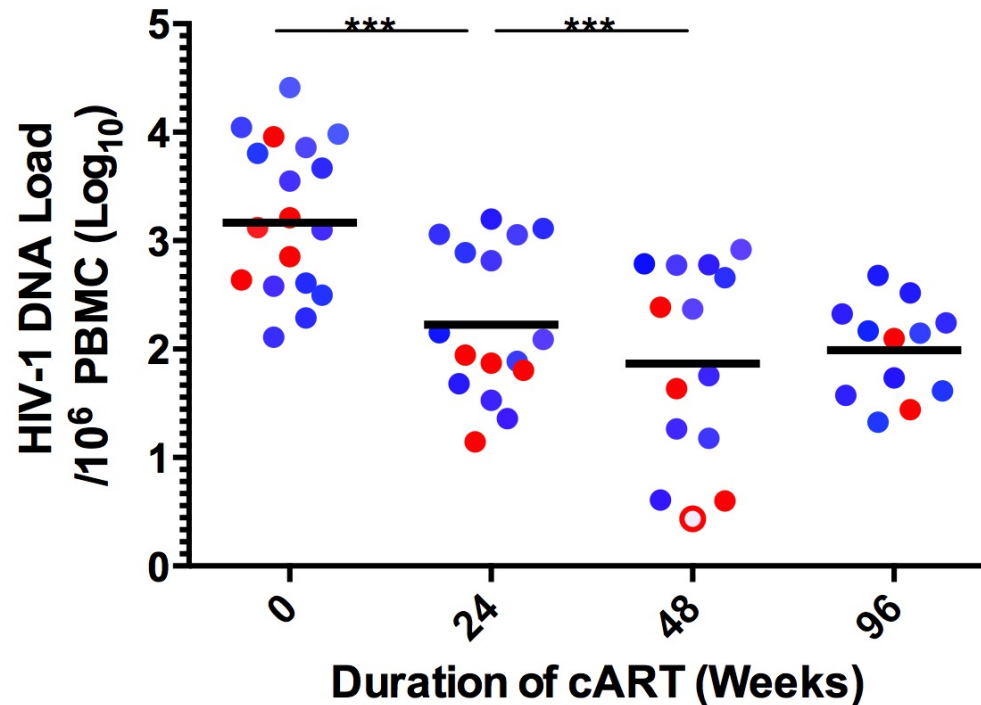
Median Frequency: 1 per million resting CD4+ T Cells (range 0.4-1.6)



# Summary persistence of HIV reservoirs

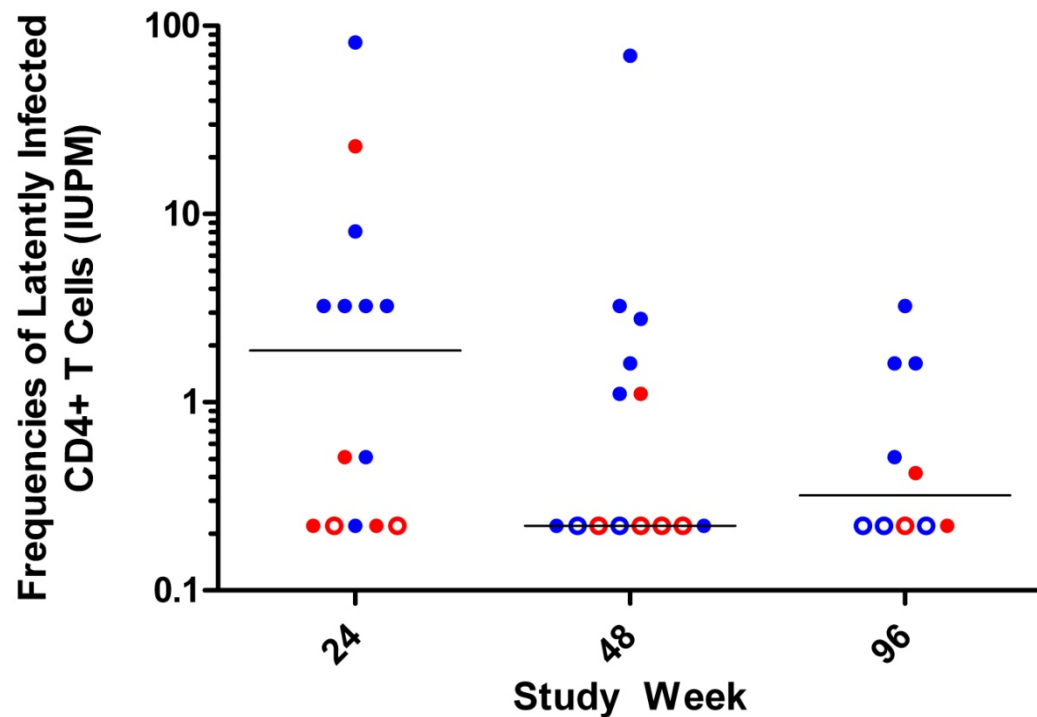
- Previous data in adults and children who were treated initially during **chronic** infection had stable levels of replication competent virus for years  $\frac{1}{2}$  life over 75 years
- **New emerging data from early treated infants** <3months of age who remain virus suppressed viral decay over time teenagers with no detectable HIV however still on treatment  
Luzariaga 2014

# HIV-1 DNA Load with Early cART in Infected Infants



N	18	16	14	12
Mean	3.24	2.23	1.87	1.99
IQR	2.6, 3.88	1.71, 3.01	1.04, 2.78	1.59, 2.30

# Effects of Early HAART on HIV Persistence in Infants



N=	14	14	10
Median	1.88	0.22	0.32
[IQR]	[0.22-3.25]	[0.22-1.61]	[0.22-1.61]

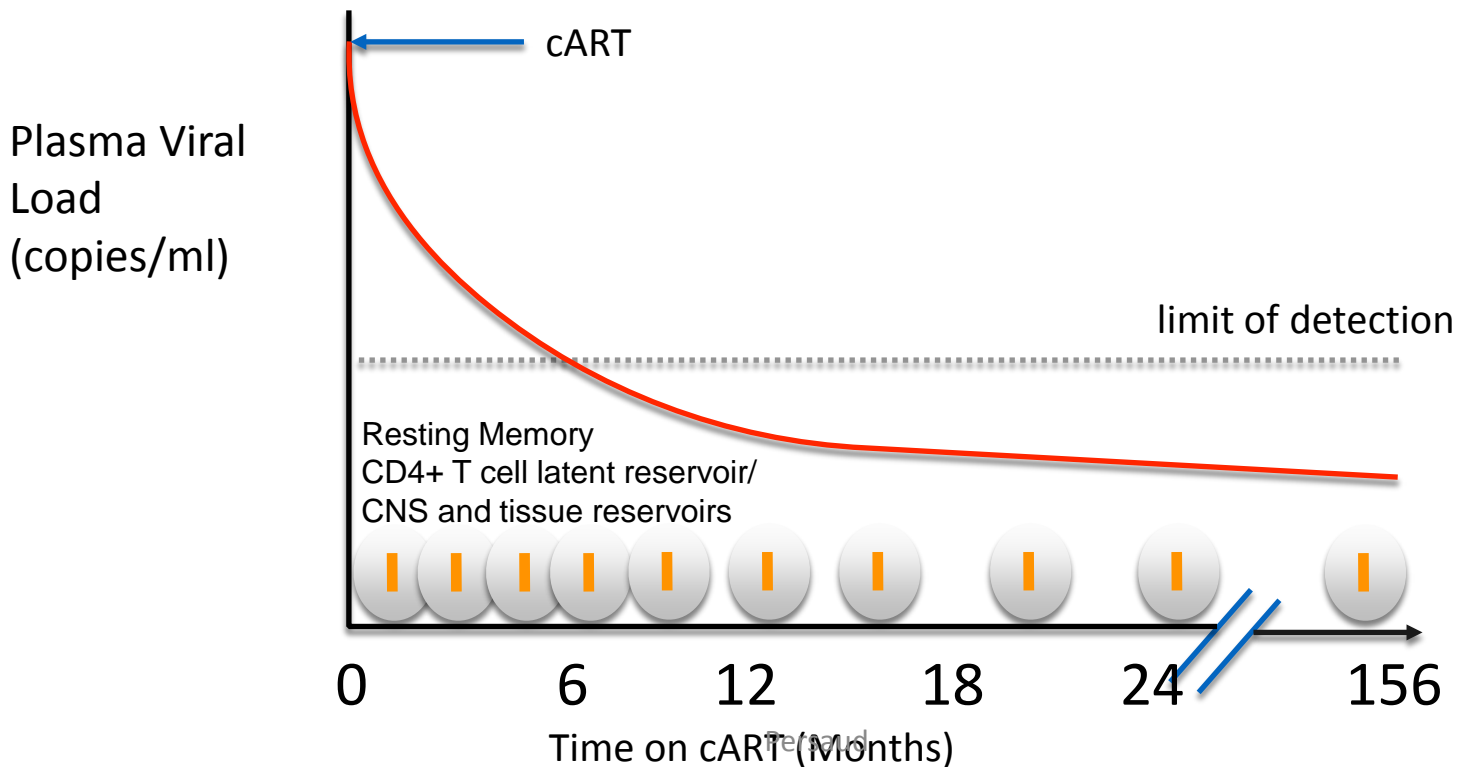
Reservoir detectable in most infants at 24 weeks of HAART  
 Declined, from 24 to 96 weeks of HAART, at an estimated mean rate of 0.028  $\log_{10}$  IUPM per month, corresponding to a half-life of 11 months [95% CI: 6 to 30 months].  
 Infants treated before six weeks of age (red circles) had restricted reservoir size

# New information from perinatal HIV infected children treated early

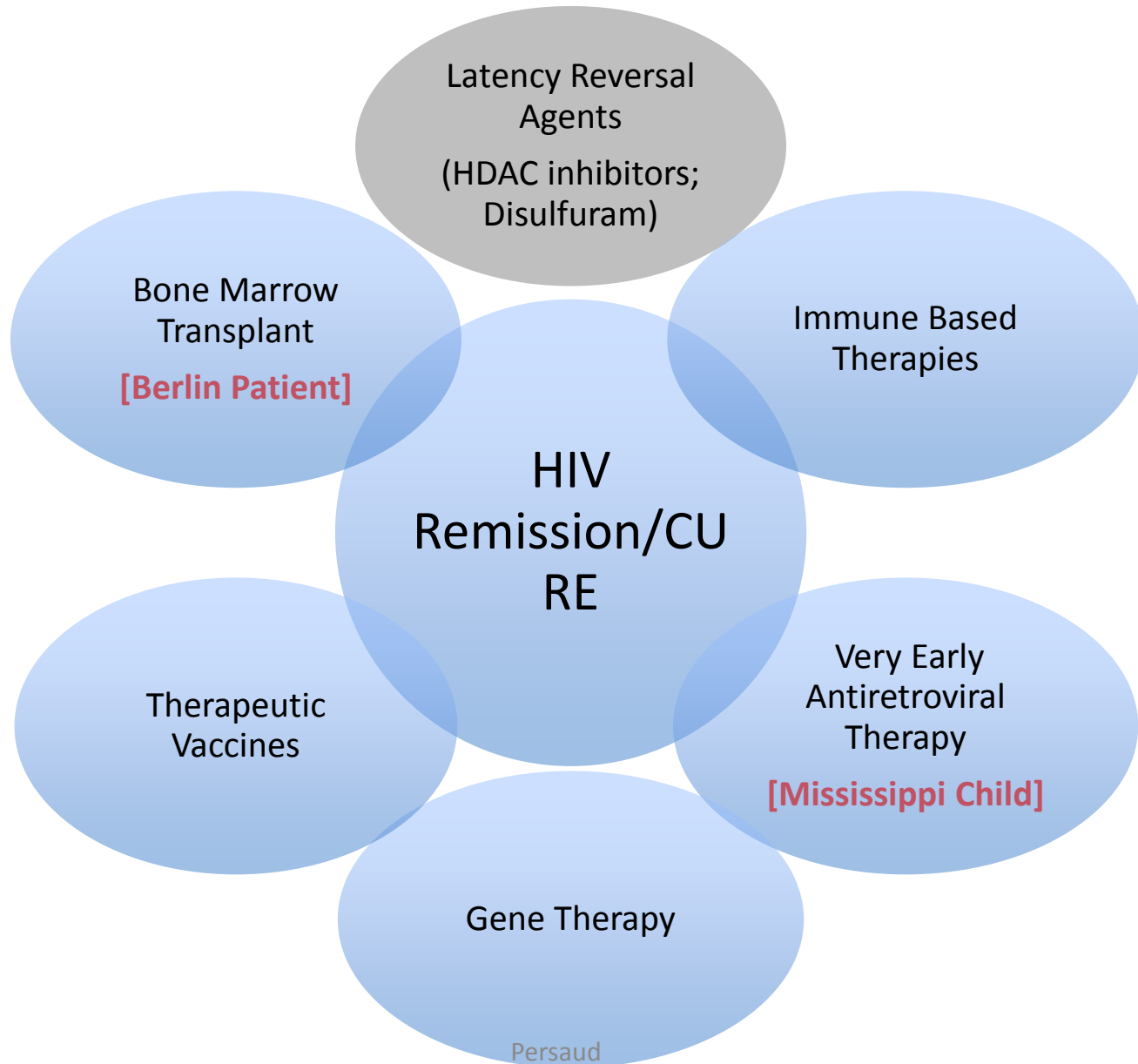
- The half life of reservoirs is significantly shortened if treated during acute infection
- The decay curves are accelerated- if the HIV replication is suppressed over time
- More information needed on youth and adults
- Long term follow up needed
- More hope for remission/cure with combined approaches

# Mission

Identify interventions to block the establishment and/or maintenance of HIV reservoirs in infected infants, children and adolescents, leading to viral remission and “cure”



# Approaches



# Approaches for acute infection/chronic HIV infection

- Multipronged
- Identify and treat as early as possible
- Requires new strategies ( “early” prior to antibody identification )especially in adults
- Maximize rapid reduction of virus to reduce establishment of reservoirs children / adults
- Reduce reservoirs in chronic infection combine with enhanced immunity ( vaccine , bNAB
- Host resistance engineering of cells



# The New England Journal of Medicine

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## **CLEARANCE OF HIV INFECTION IN A PERINATALLY INFECTED INFANT**

YVONNE J. BRYSON, M.D., SHEN PANG, PH.D., LIAN S. WEI, M.S., RUTH DICKOVER, PH.D., AMADOU DIAGNE,  
AND IRVIN S.Y. CHEN, PH.D.

# Boy beats AIDS virus, UCLA researchers say

**SCIENCE:** The case is unique, and some scientists are skeptical.

From Register news services

Scientists in California report that a child infected with the AIDS virus at birth successfully cast off the HIV infection by the age of 1, a finding that if true could hold a vital clue to defeating the disease.

But some other experts doubt that the case has been fully proved.

The boy is now a healthy 5½-year-old kindergarten pupil who is developing normally and re-

mains free of the virus, researchers from the University of California, Los Angeles, are reporting today in *The New England Journal of Medicine*.

They say the boy evidently fought off the HIV infection with his natural immune defenses. The boy's blood test is now HIV-negative, no virus can be grown from his blood and there is no laboratory or clinical evidence of HIV infection, the authors said.

The case is the first of its kind to be documented, and researchers say it may provide new clues to improving the immune system's ability to fight off HIV, the

Please see **CASE Page 20**

## AIDS virus in 2 infants disappeared in months

By Doug Levy  
USA TODAY

Two Los Angeles children have done what doctors thought was impossible: They have cleared the AIDS virus from their bodies.

Both were born infected from HIV-positive mothers. Tests in the months after birth confirmed infection, then that infection was gone.

"It sounds amazing," says UCLA's Dr. Yvonne Bryson, who reports in today's *New England Journal of Medicine*. "At first we thought it was a laboratory mistake."

But tests and retests prove HIV is gone from the first child, now 5. Tests are under way on the second, now 4. Symptoms normally appear within three years of birth.

"This tells us that in certain circumstances, one can actually get infected and then (be) completely clear," says Dr. Anthony Fauci of the National Institute of Allergy and Infectious Diseases. Possible explanations:

► The infants had a defective form of HIV.

► Antibodies passed from mother to infant were strong enough to combat the virus.

► A small amount of virus infected the baby, fought by a maturing immune system.

The report raises debate on whether recovery from HIV infection is ever possible, say Drs. Kenneth McIntosh and Sandra Burchett of Children's Hospital, Boston.

And it suggests a transient HIV infection - one that comes and goes - may exist.

# Neonates and HIV remission/Cure?

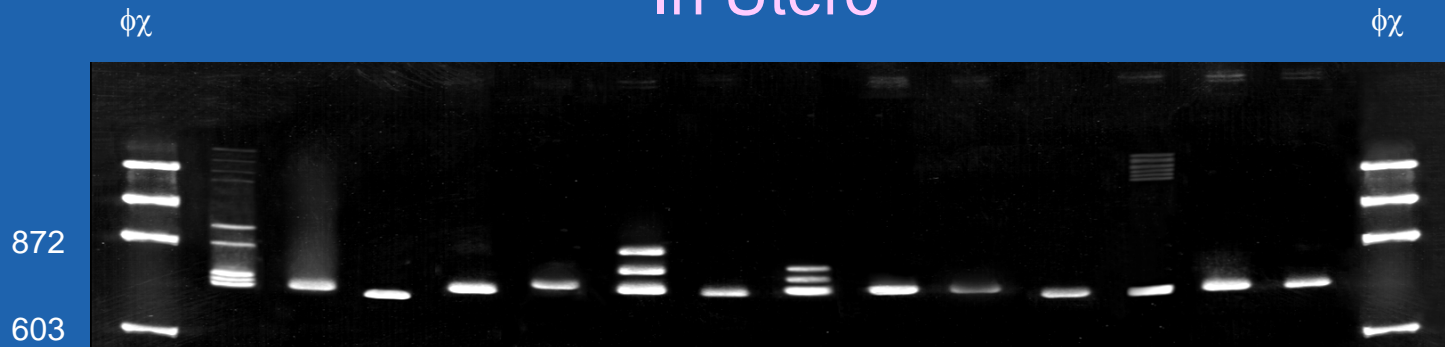
- **Why neonates?** Excellent model for effect of early treatment
- **Timing of infection is known**
- MTCT of HIV can occur in utero - the majority of transmission from 28 weeks to delivery in live born infants –6- 8 % of infected infants of untreated HIV positive pregnant women. These infants have HIV virus present at birth ( DNA PCR, RNA PCR and culture)
- % of HIV exposed infants at birth also acquire HIV 0-4 weeks) BF 0-12
- Virus is homogeneous at birth easier to treat
- Early ARV treatment infected infants <3months seronegative normal immune status – **reduced HIV reservoirs**
- Persaud /Luzariaga

# Functional CURE /HIV remission in HIV infected neonates

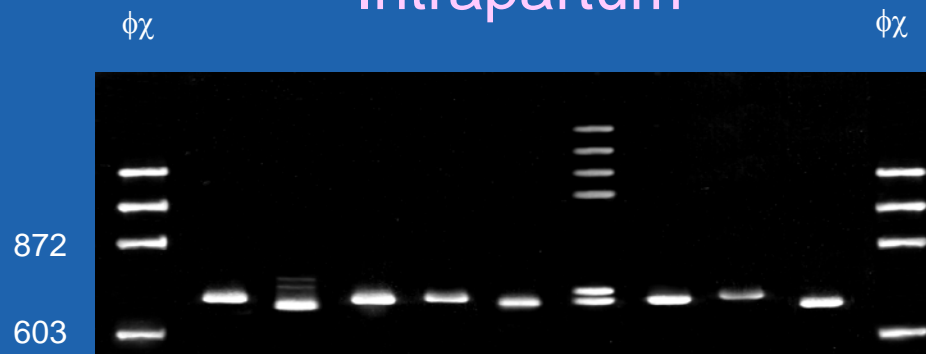
- An ounce of prevention is worth a pound of CURE Evidence for effective prophylaxis for prevention of infection in infants and pregnant women
- Effective ARV prophylaxis given at the time of birth or during early breastfeeding can prevent HIV infection in HIV exposed neonates/infants
- ARV prophylaxis during pregnancy can reduce both in utero and intrapartum MTCT of HIV

# HIV-1 Env Gene Diversity in Infected Infants at Their First Positive Timepoint

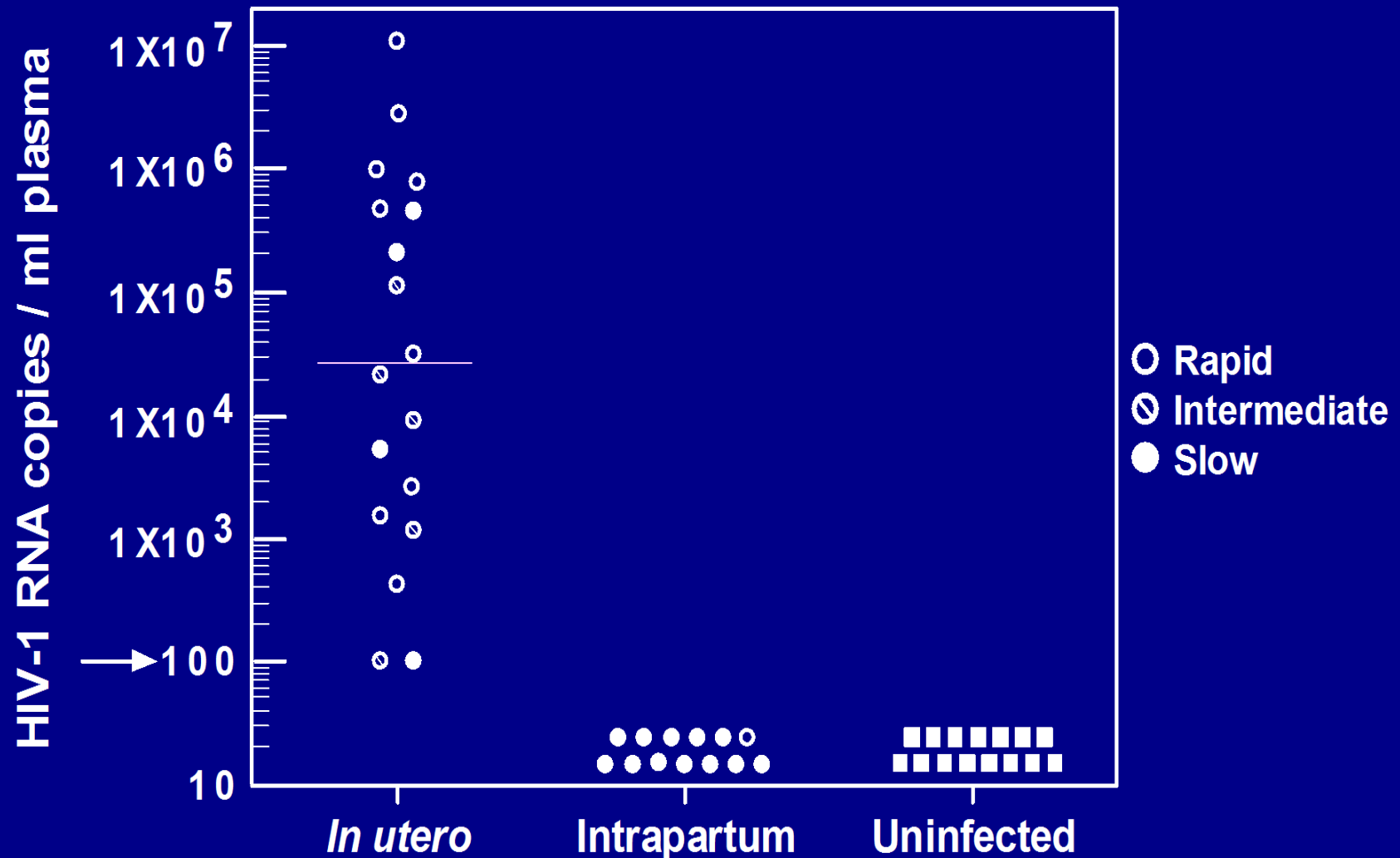
In Utero



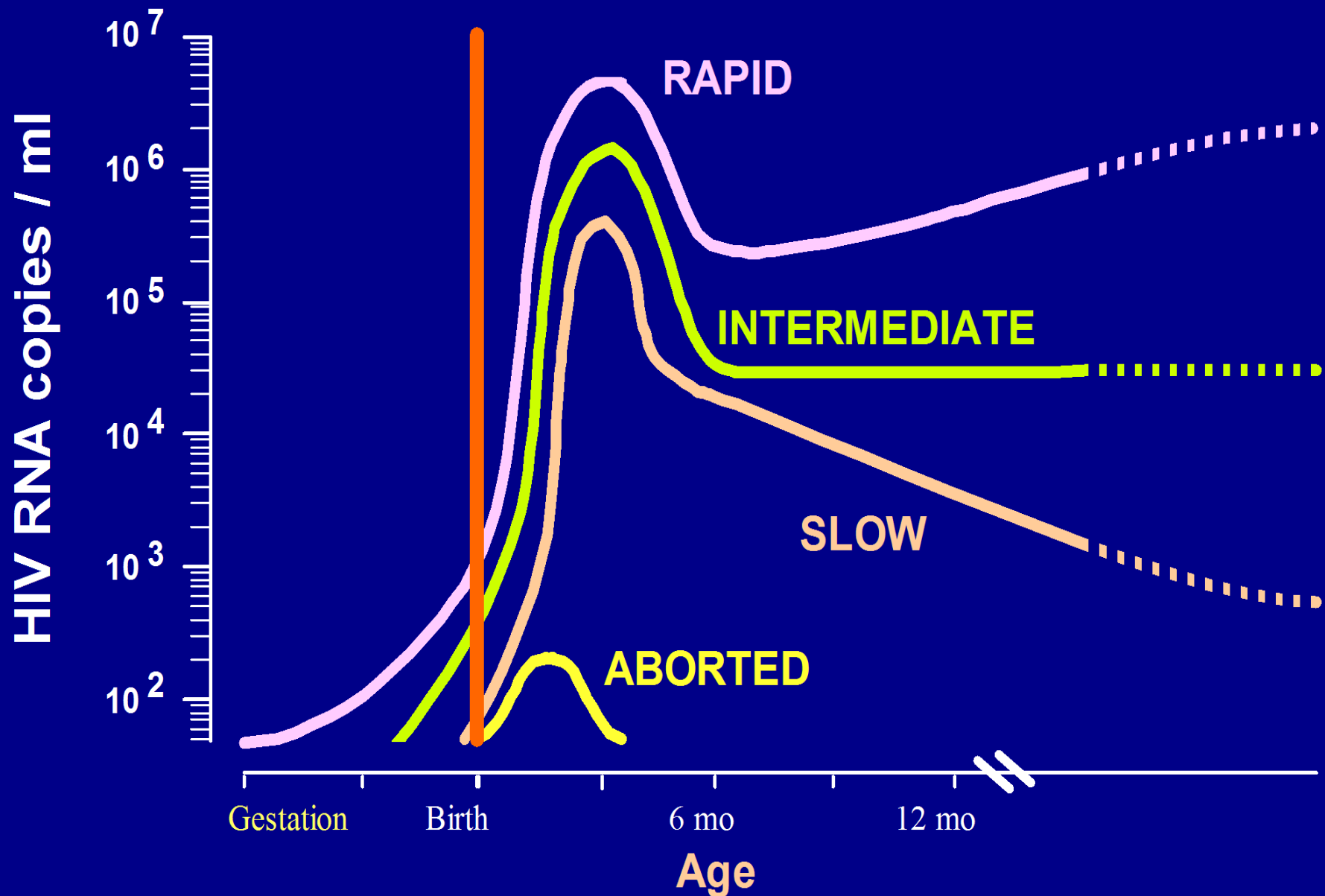
Intrapartum



# Plasma HIV-1 RNA Levels at Birth in Infants of Infected Mothers



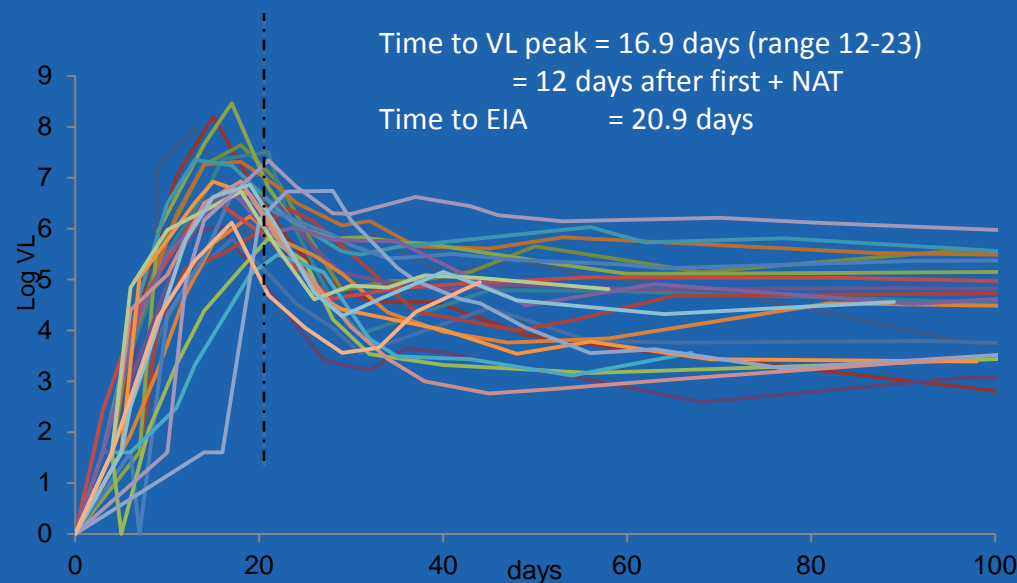
# Hypothetical Model of HIV Perinatal Infection





# RV217 Acute HIV Infection Study in Thailand and East Africa

- Prospective cohort of HIV negative sex workers
- Thailand, Kenya, Uganda and Tanzania
- Finger stick twice weekly for nucleic acid testing
  - Compliance in 89%
  - AHI incidence of 3.7%
- USMHRP study funded by NIAID/MHRP

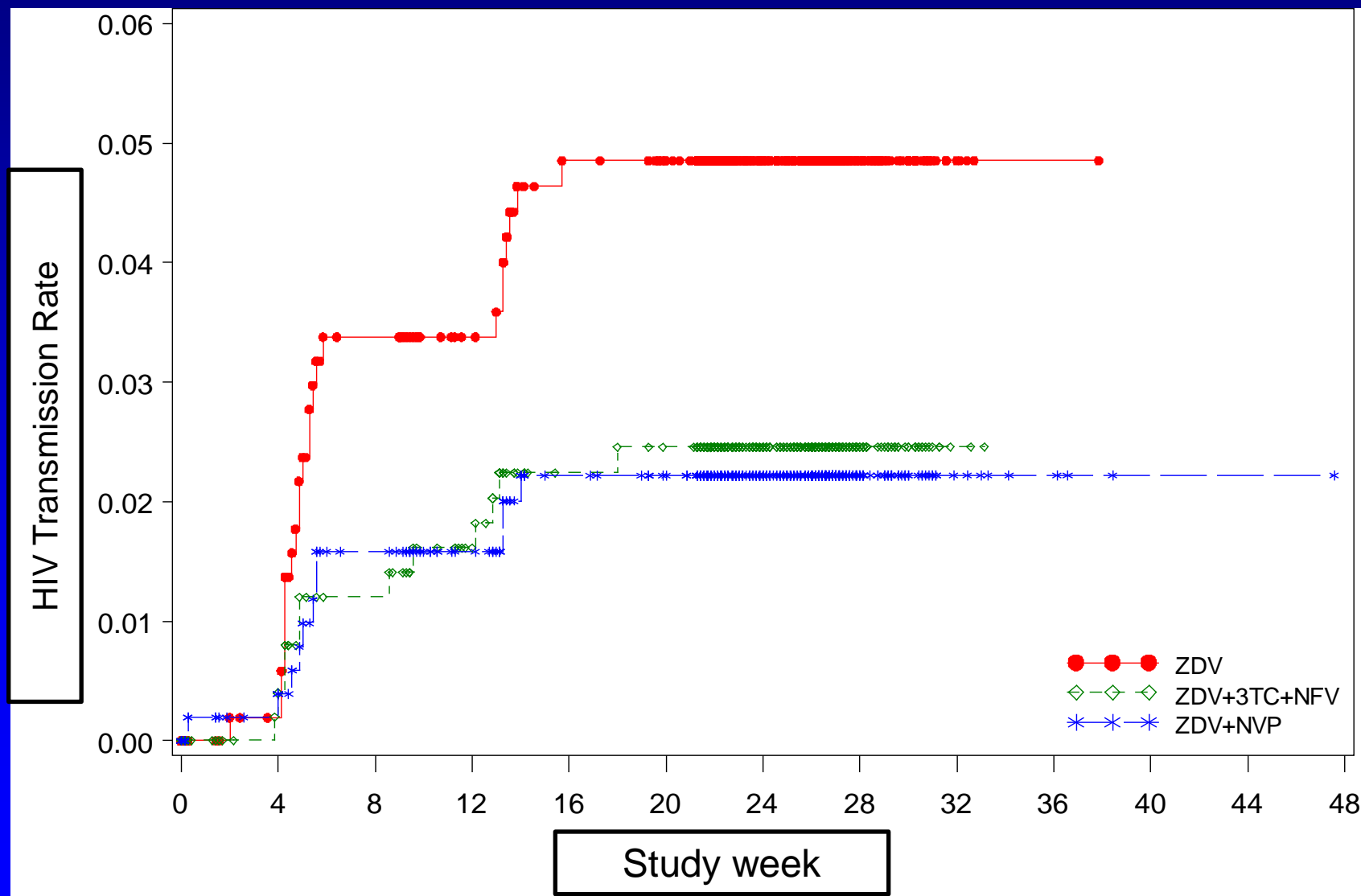


2011	HIV-infected pregnant women	HIV-infected children on ART
Kenya (Kericho)	81,451	1910
Tanzania (Mbeya)	157,239	3667
Tanzania (Dar es Salaam)	10,350	493

# NICHD O40 protocol

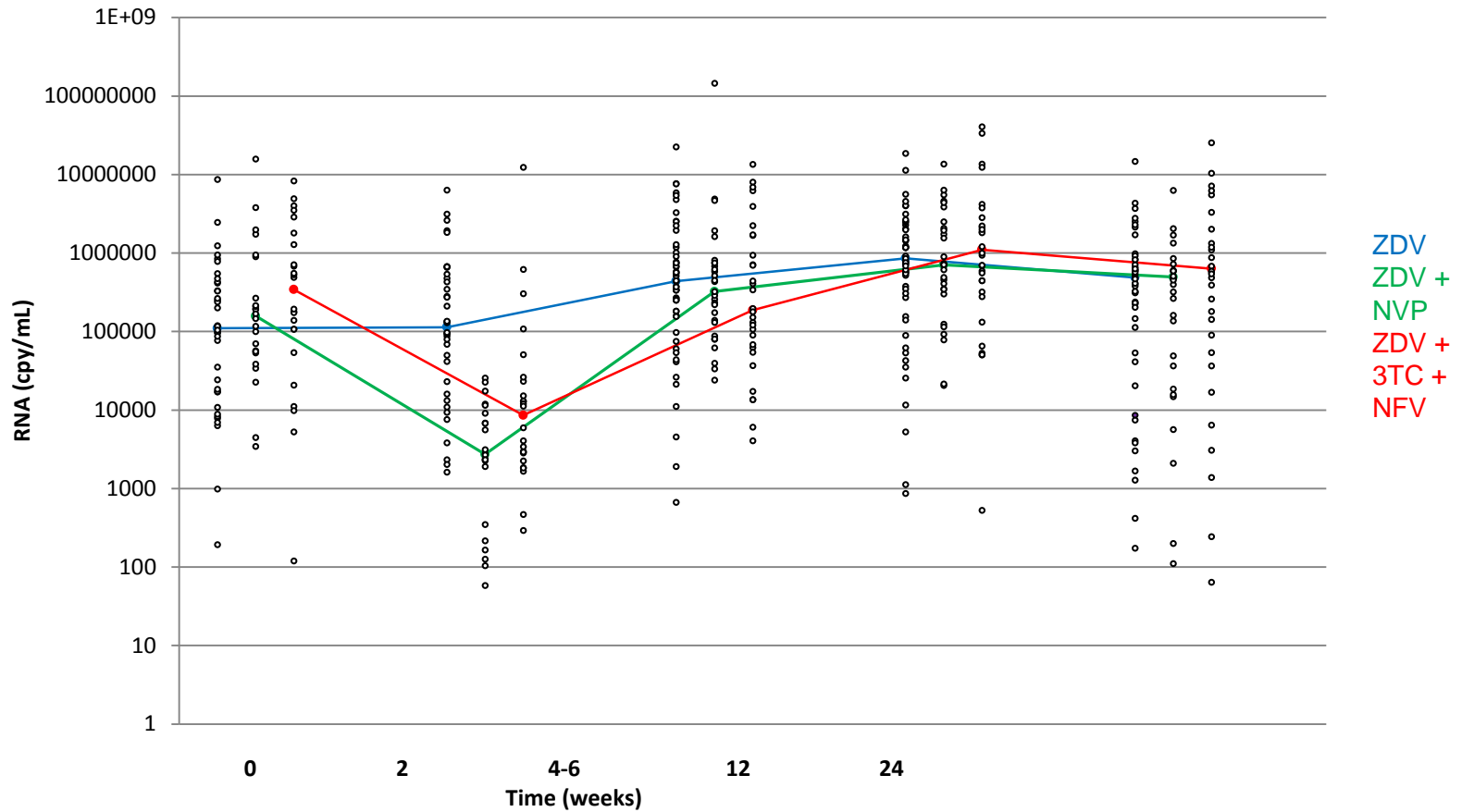
- Mothers entered who did not receive ARV prior to delivery and infants randomized to 3 ARV arms within 48 hours of birth ( 1,700 entered) Brazil, South Africa, USA , Argentina
- Approximately 6-8% infected at birth
- Samples available at birth and up until 6 months with HIV RNA levels- cell pellets

# Timing of HIV Infection for Infants Testing Positive After Birth by Study Treatment Arm (Intrapartum Only)



040

VL of *in-utero*- and intrapartum-infected infants separated by treatment arm.



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## Researchers: Toddler cured of HIV

By **Sandra Young**, CNN

updated 4:54 PM EST, Mon March 4, 2013

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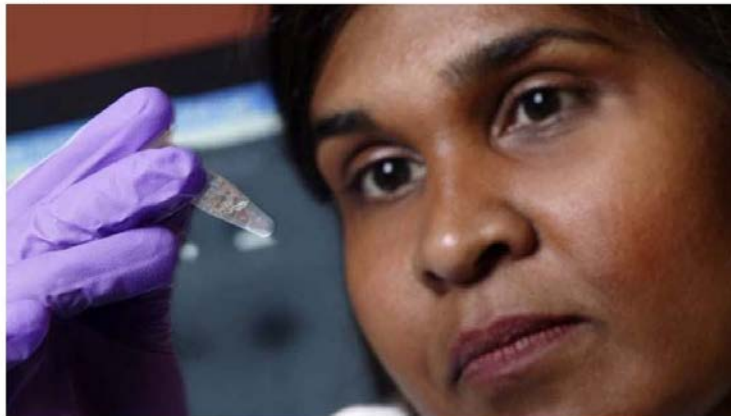
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### Mississippi Baby Born With HIV 'Functionally Cured,' Doctors Say



This image shows Dr. Deborah Persaud of Johns Hopkins' Children's Center in Baltimore. A baby born with HIV appears to have been cured, scientists announced Sunday, March 3, 2013. (AP Photo/Johns Hopkins Medicine)

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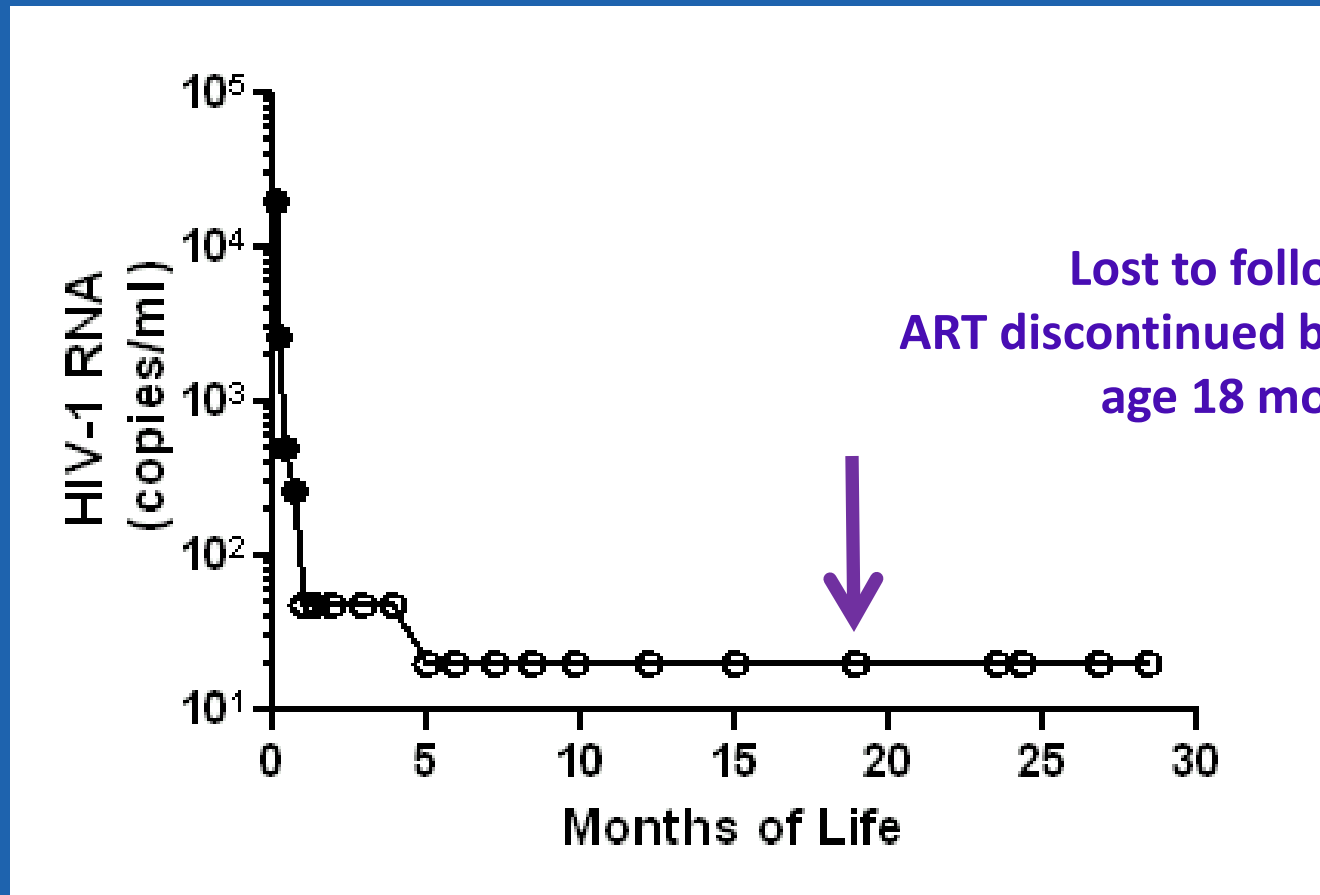


By ANTHONY CASTELLANO

# Absence of detectable HIV viremia after treatment cessation in an infant (Persaud NEJM 2013)

- Report of the “Mississippi baby” ,a high risk HIV exposed infant treated with ARV (triple)at 31 hours of age
- In utero infection. Infant had numerous HIV RNA PCR positive Viral load reduced from 19,800 at birth to undetectable by 21 days
- Kaletra substituted for NEV at one week and continued on Rx until 18 months when Lost to follow up caretaker stopped meds
- Persaud D Gay H,Ziemniak,Chen,Piatak,Chun et al NEJM 2013

# Effective Control of HIV Replication During ART and Even after ART Discontinuation



Lost to follow-up;  
ART discontinued by caretaker at  
age 18 months

Regimen #1: AZT/3TC/NVP (31 hours-7 days of life)

Regimen #2: AZT/3TC/LPV/ritonavir (7 days-18 months of life)



# Mississippi baby

- Remained HIV seronegative, HIV RNA negative, DNA negative replication competent virus negative and clinically well through 27 months post cessation of ARV
- Traces of HIV Nucleic acid at limits of detection of assays.
- Met definition of HIV remission which is > one year
- rebound HIV at 27 months and then seroconverted and responded to ARV quickly

# Implications from Mississippi baby

- RX started < 48 hours in in utero infected infant reduced viral reservoirs to unheard of low levels ( below current level of detection in peripheral blood) for over 3 .5 years and 27 months without ARV
- Even though rebound occurred **major advance**
- Improve on this –other agents depends on how long the virus infected the infant prior to birth
- Therapeutic HIV vaccine to prolong remission

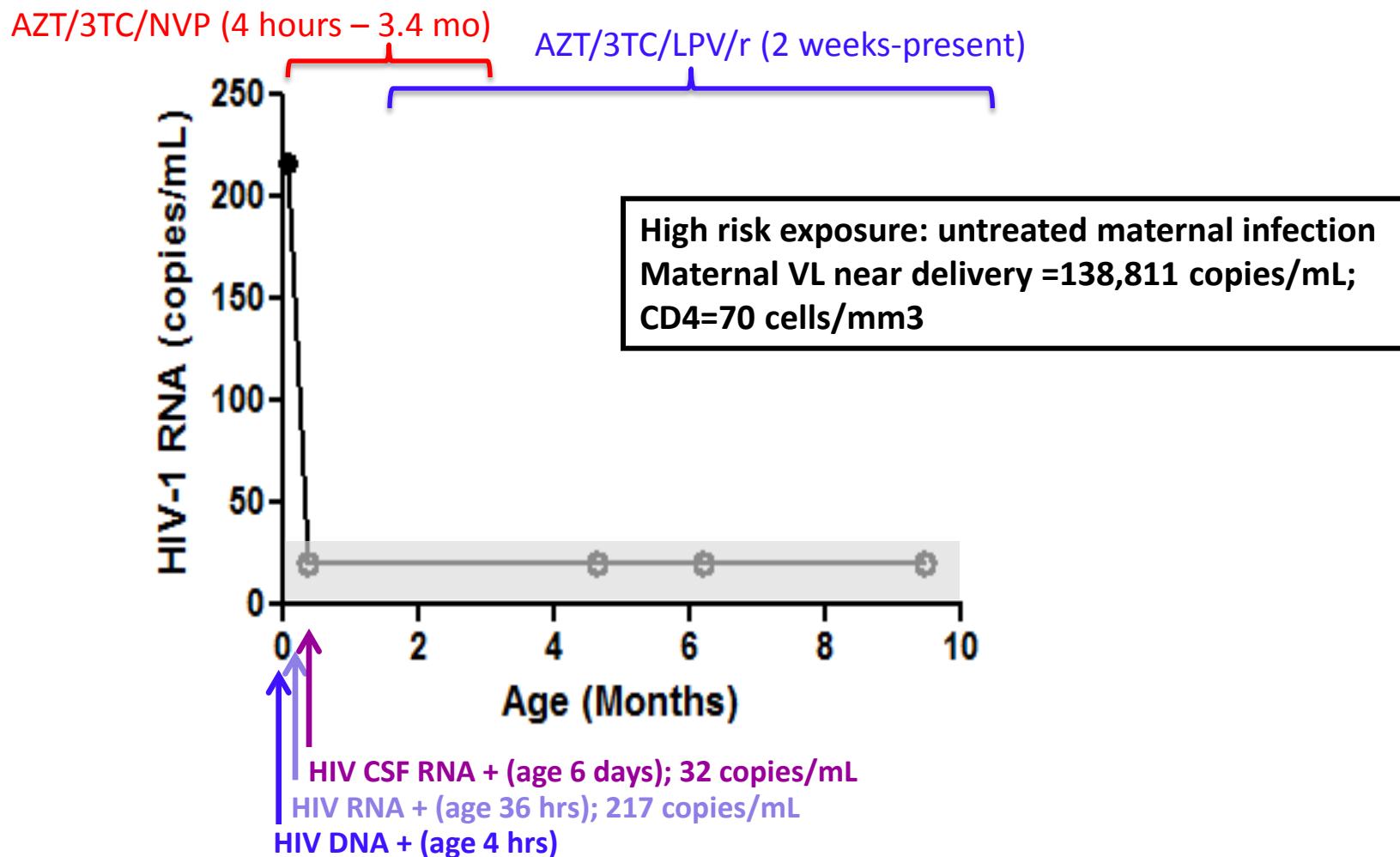
# In utero HIV infected infant LA baby

- Premature infant -36weeks precipitous vaginal delivery from known HIV infected mother inadequate RX (CD4 Tcells70,HIV RNA 138,000)
- Started on 3 drugs AZT,3TC and NEV BID treatment doses at 4 hours of age after blood sample drawn for DNA PCR: confirmatory sample for HIV RNA day 2 septic work up CSF day 6
- Kaletra added at two weeks to regimen( 4 drugs for 3.5months) then 3 drugs AZT,3TC Kal until present 12 months

# LA baby

- Infant tolerated treatment well without side effects
- HIV DNA positive day 1, HIV RNA positive 217cp/mm<sup>3</sup>, CSF positive day 6 HIV RNA 37cp/ml
- HIV RNA viral load was undetectable by 10 days and HIV DNA PBMC undetectable day 6
- Seronegative by 9 months
- Met definition of in utero HIV infected 2 positive NAT from two different time points

# Very Early Treatment of a in utero HIV- Infected Infant (4 Hours of Age)



# Methods

- Standard HIV DNA (Roche) and HIV RNA and CD4 and CD8 T cells HIV western blot
- Proviral DNA ( droplet digital PCR)
- Replication competent purified resting CD4 T cells limiting dilution viral outgrowth
- Non induced proviral DNA ( no virus production)
- Full length sequencing maternal virus/infant

# Rapid Loss of Detection of Infection During Very Early cART in Perinatally HIV-1 Infected Infant LA

Biomarker	Age at Testing (months)	cART Duration (months)	Finding
Plasma viral load (copies/ml)	0.36 (11 days)	0.36	<20
	1.6	1.6	<20
	2.2	2.2	<20
	4.6	4.6	<20
	6.2	6.2	<20
	9.5	9.5	<20
Proviral DNA (Clinical Assay)	0.2 (6 days)	0.2 (6 days)	negative
	1.6	1.6	negative
	2.2	2.2	negative
Infectious Virus Recovery (IUPM)	1	1	<0.13
	3	3	<0.20
	9	9	<0.15
Non-Induced Proviral Genomes	1	1	positive
	3	3	negative
	9	9	negative
Proviral DNA (ddPCR)/per Million PBMCs	3	3	<6.3
	9	9	<1.6
HIV Serostatus (Western Blot)	3	3	Indeterminate
	9	9	Negative



# Summary

- This infant is still on treatment with cART at 24 months of age and clinically well- normal CD4 T cells for age and HIV seronegative
- Extremely rapid reduction of HIV provirus DNA and HIV RNA viral load by 6 days, loss of detection of non-induced provirus remnants by 3 months ( Faster than Mississippi baby)
- Future discuss treatment interruption after 2 years of age to assess viral rebound off treatment ( evaluation of reservoirs)

# Working Definition for HIV “Cure”

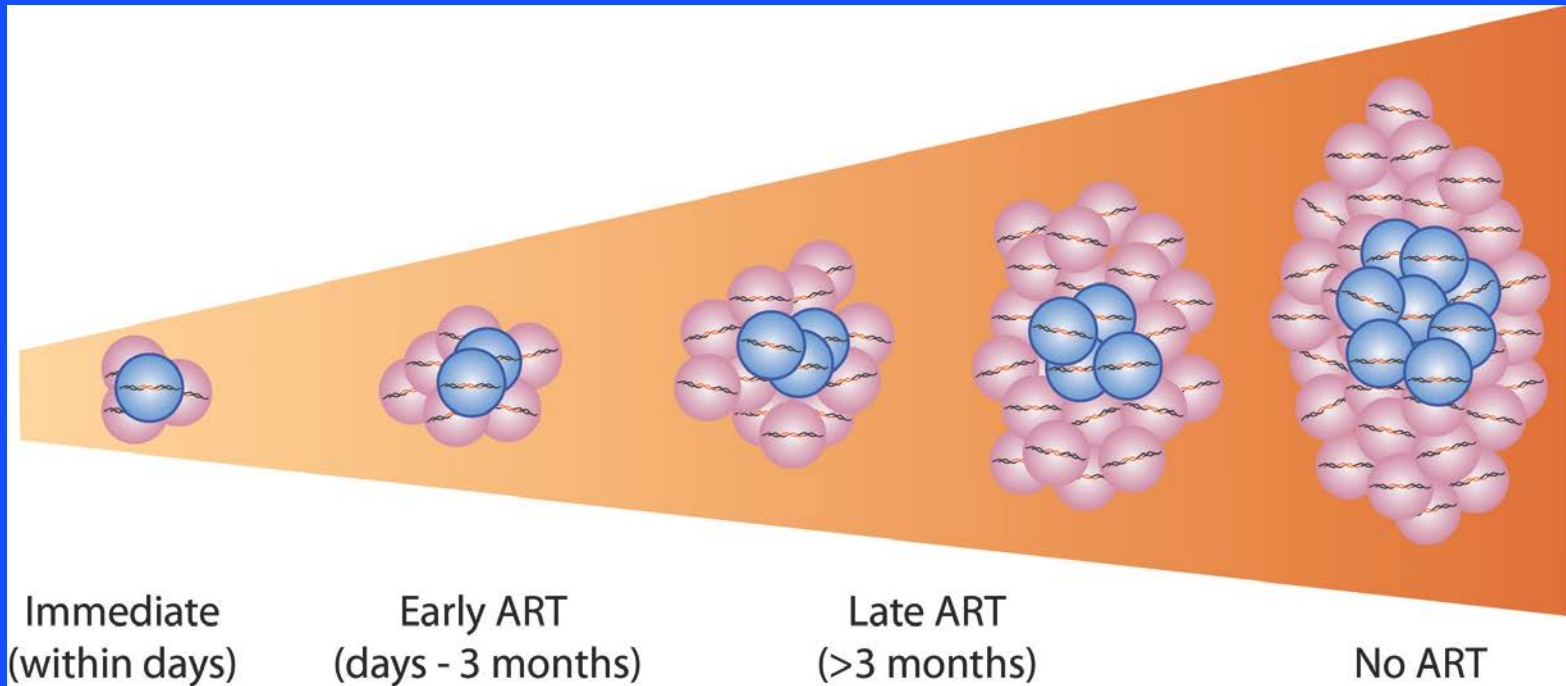
Permanent disease remission in the absence of antiretroviral therapy

Maintenance of normal CD4 T cell counts and immune function

Preservation of immune responses to routine childhood vaccines

No evidence of ongoing immune activation or inflammation

# HIV Cure in an Infant: Biologically Plausible



Immediate antiretroviral treatment blocked HIV reservoir formation, including the long-lived, central memory CD4+ T cell latent reservoir



# P1115 : Early Intensive Treatment of High Risk HIV Exposed/Infected Infants to Assess a HIV Remission

Y Bryson & E Chadwick co chairs  
open globally 47 sites

- Hypothesis: Early at birth Intensive( multiple targeted including integrase inhibitor) ARV therapy/prophylaxis in HIV infected/exposed infants will significantly alter primary acute infection , reduce the latent viral reservoirs,preserve immune function and potentially result in **Prolonged HIV remission “functional cure”**

# Overall design

- RX high risk infants ARV <48 hours 3 drugs ZDV,3TCNVP
- If PCR + at birth add Kaletra (4 drugs)
- If PCR – continue for 6 weeks then stop
- Follow for HIV viremia/quantitative DNA PCR latent HIV reservoirs HIV antibody
- Criteria for treatment Interruption ( Test of CURE) after 2 years of age

# SUMMARY

- Unique opportunity to assess earliest and most potent intervention in primary infection Proof of concept
- Feasible high risk population similar to 040 which has completed enrollment of 1,700 infants whose mothers were not treated with ARV) prior to delivery and given ARV < 48 hrs
- Even if does not result in CURE/potential functional cure will provide greater information on neonatal HIV pathogenesis
- Cohort of children low HIV reservoirs , normal immune system Therapeutic HIV vaccine planned

# Bid to cure HIV ramps up

*Clinical trial will aim to replicate virus-expunging therapy that worked in US infant.*

BY ERIKA CHECK HAYDEN

**H**IV-positive mothers who take anti-retroviral therapies while pregnant can be prevented from transmitting the virus to their babies 99% of the time — a resounding success story in the decades-long fight against the virus. But what about infants whose mothers do not receive the drugs? Energized by the case of the ‘Mississippi baby’ — who seemed to be cured of HIV after aggressive treatment was begun within hours of birth — researchers are hoping to show that these infants, too, can get off to a healthy start.

At a symposium on HIV cure research on 29 June at the International AIDS Society’s

focused on adults. In 2012, the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, spent US\$18 million on HIV cure research in adults and adolescents, and just \$45,000 on children. Yet 3.3 million children worldwide have HIV.

“Children have been an afterthought,” says Jeffrey Safrit, director of clinical and basic research for the Elizabeth Glaser Pediatric AIDS Foundation, who is based in Los Angeles, California. “But the immune system of the child might be more easily manipulated to allow a cure.”

This was highlighted in March, when virologist Deborah Persaud of the Johns Hopkins Children’s Center in Baltimore, Maryland,



A baby in Lesotho is given anti-HIV drugs at birth.

GIDEON MENDEL/CORBIS FOR UNICEF

# IMPAACT HIV CURE Scientific Committee Members



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# Key Scientific Questions

Evaluate **very early ART** to reduce viral reservoirs in neonates to achieve viral remission and cure

Evaluate specific interventions in chronically infected-youth to reduce HIV reservoirs

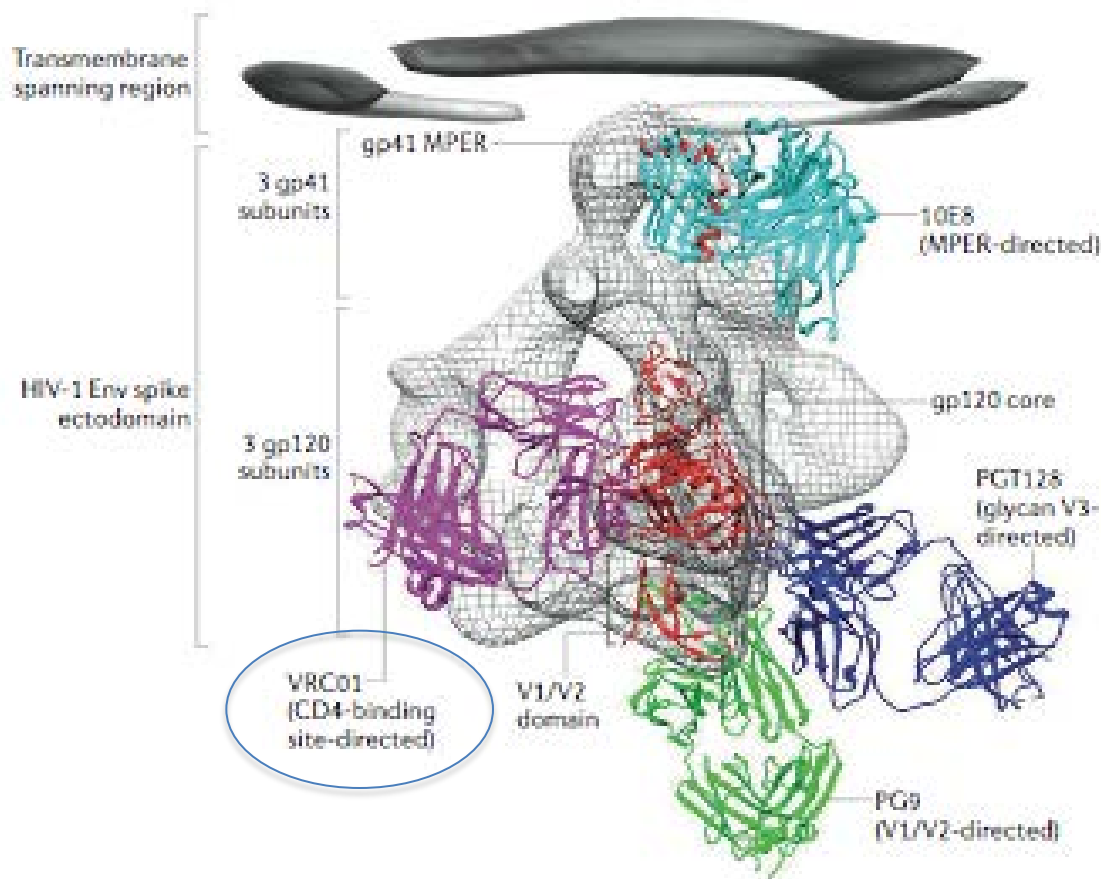
(broadly neutralizing antibodies, HIV vaccines, immunomodulatory agents, inflammatory blockade, target cell modification strategies)

Elucidate relationships between viral reservoirs and the developing immune system

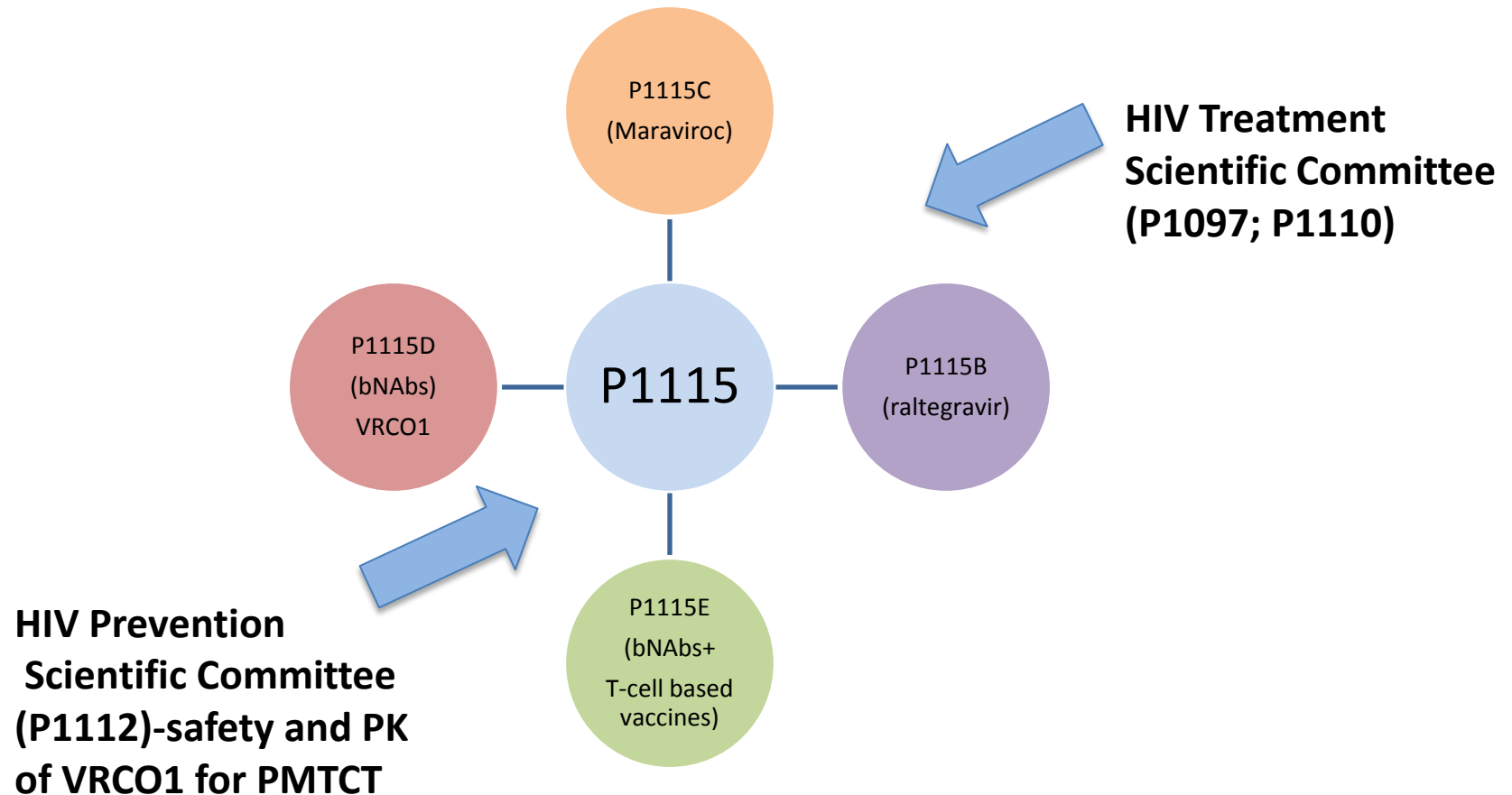
# Accomplishments

Protocols/Capsules	Title	Status
Infants		
P1115	Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study	Open to accrual
CAP 512	A Phase I/II safety and efficacy study of monoclonal antibody VRC01 with combination antiretroviral therapy for HIV-1 infected infants between age > 2wks to $\leq 12$ weeks to promote faster clearance of HIV-1-infected cells	Under Review
Children and Youth		
CAP 5002	bNAb VRC01 to clear residual viremia in perinatally HIV-infected youth	Hold
CAP 503	Autologous Virus Dendritic Cell Vaccine (ARGOS Therapeutics)	Hold pending adult data
CAP XX	CNS reservoirs in perinatal infection	underdevelopment

# Broadly Neutralizing Monoclonal Antibodies



# Building on P1115



# Single Case of HIV Cure (Chronically-Infected Adult)

**Strategy that led to cure:**

Treatment of relapse AML

Chemotherapy

Radiation

Stem cell transplant with CCR5  $\Delta 32$   
homozygous donor cells (HIV-resistant)

Graft versus host disease

**Provided proof-of-concept for cure**



**Timothy Brown  
(" Berlin  
Patient")**

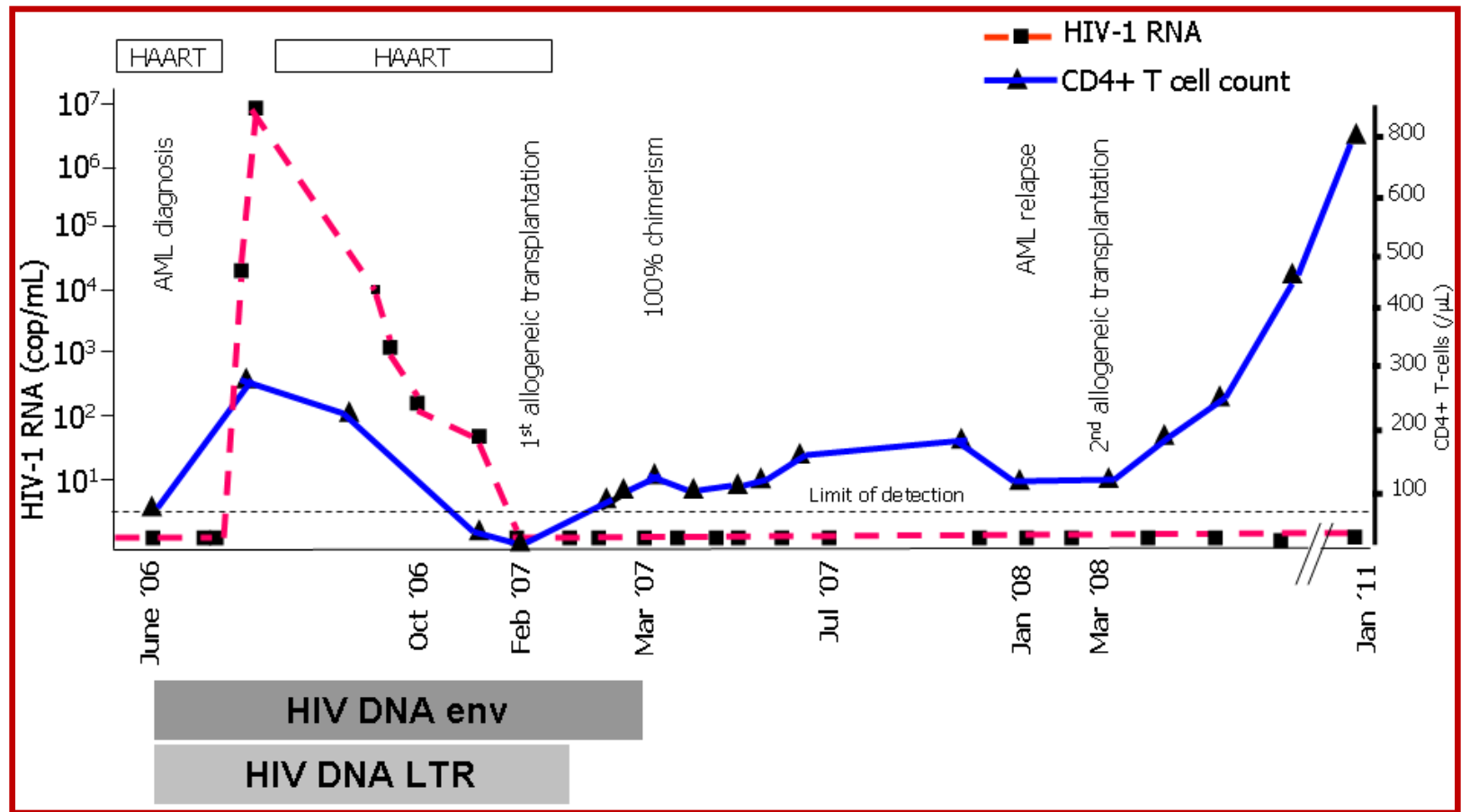
Hutter G et al.;NEJM  
2009;360:292

*Photos from Science 2012*

# Case report -Cure of HIV Blood 2010

- 7 year follow up of patient post BMT
- No evidence of HIV at any site GI , multiple bx
- No evidence of switch of HIV to X4
- Off all antivirals
- In vitro resistance of PBMC to R5 HIV but not CXCR4 HIV.
- Clinically well

# Defining HIV Cure in the “Berlin Patient”



No rebound in HIV viremia (up to four years) after HAART stopped  
No detectable HIV DNA in peripheral blood

# Host resistance

- Berlin patient CURE received CCR5 delta 32/32 BMT lost HIV antibody, no detectable HIV RNA,DNA or CD4 T cell replication competent virus 5+ years out from transplant
- New approaches, autologous transplant with zinc finger Removal of CCR5 co receptor and re-infuse Phase 1
- Genetic manipulation for resistant stem cells



# Acquired Host resistance-Approach

## CCR5 $\Delta$ 32 mutation

- Prevalence
  - varies with population:
  - greatest in Caucasian (1% homozygous)
  - 15-20% heterozygous ( $\Delta$ 32/CCR5)
- Homozygosity leads to resistance to R5 HIV infection; heterozygosity associated with decreased rate of disease progression
  - The plan to assess the use of cord blood transplant with CCR5delta 32/32 for treatment of HIV in children/ adults was proposed in **2002**  
**Cord blood transplants common in children for RX immune deficiency malignancy**
  - Stemcyte International Cord Blood bank initiated screening of cord blood units for CCR5delta 32/32 homozygotes
  - has tested over 20,000 units to date- cord units from other banks
  - identified **>220** CCR5 delta 32/32 units
  - Plan to acquire **300 units**

# Feasibility of finding a match: Stemcyte International Cord Blood Bank

- Stemcyte Screen:
  - Existing aliquots of cord blood that are HLA typed and stored at Stemcyte International Cord Blood bank
  - Donors are from diverse racial backgrounds
    - Including hispanic, african American from the Los Angeles area
  - Feasibility study to assess potential for finding a cord blood match for HIV infected children from **diverse ethnic backgrounds to known units at Stemcyte (Chen et al)**
  - HLA on 44 HIV infected children/adolescents
  - 7/44 (16%) with 4/6 or greater match with the identified units

# **Malignancy and Pediatric/Adolescent HIV Infection**

## **(Survey IMPAACT Domestic sites; N=19)**

- 24 HIV infected children or adolescents diagnosed with malignancy in the last 10 years
  - Age range 1 to 20 years of age
  - majority in the 8 to 10 year old age group
  - AML, ALL, Lymphoma including Burkitt's lymphoma
  - one received a BMT (succumbed)
- Aware of two perinatal HIV-infected youth with impending marrow failure awaiting transplantation

# Cord blood transplant

- Advantages

- widely available
- successful with 4/6 or greater match; therefore greater likelihood of match
- lower rates of GVH

- Disadvantages:

- More problems with late engraftment
- cell dose critical
- double cell dose if necessary with a different unit
- - new plan use with Haplo stem cells with cord

Three recipients of  $\Delta 32$ CCR5/ $\Delta 32$ CCR5 donors were found from 1995-2001 (City of Hope)

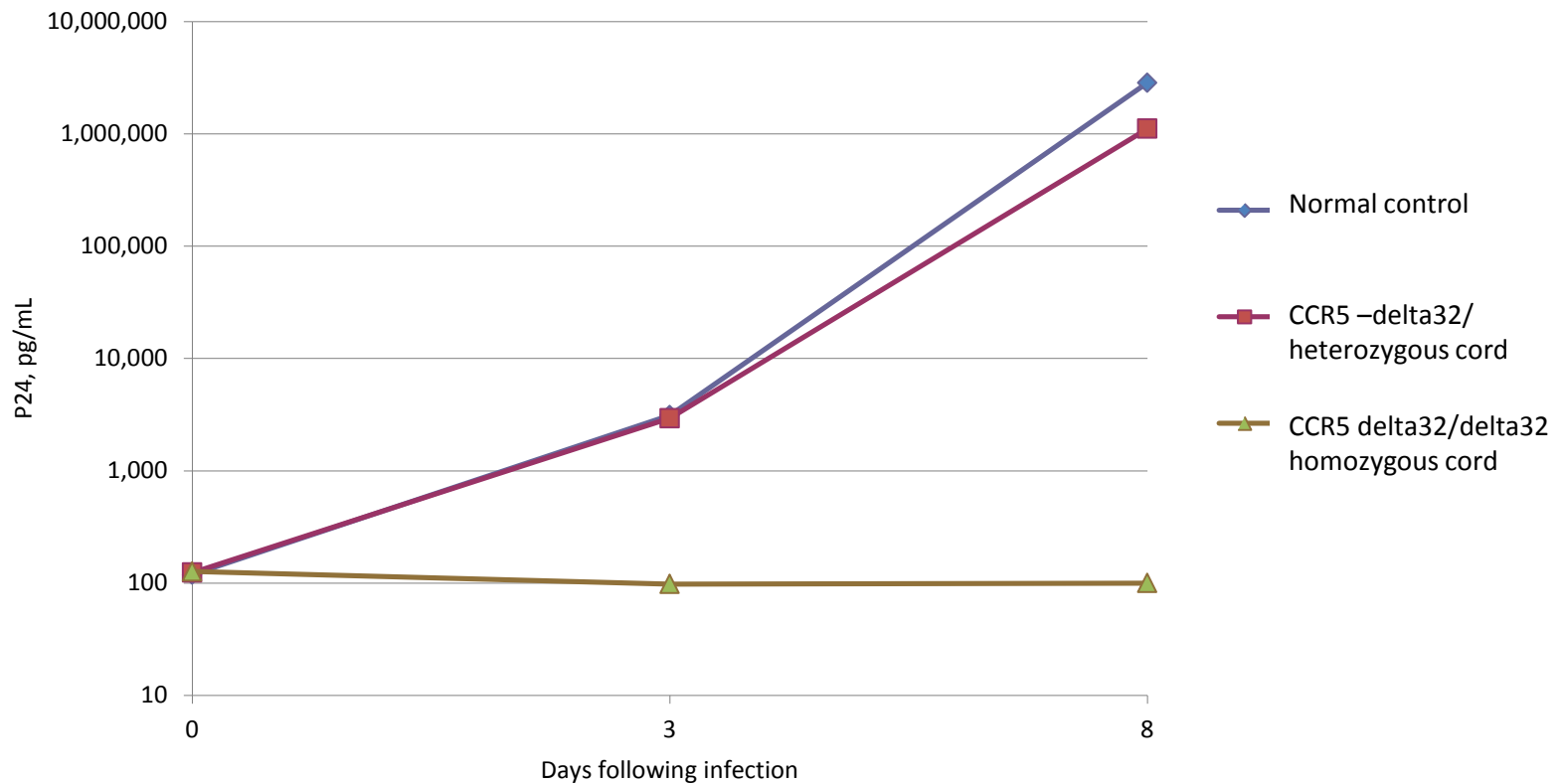
All three recipients engrafted and had no unusual complications post-HCT.

# Estimates of probability of finding a match

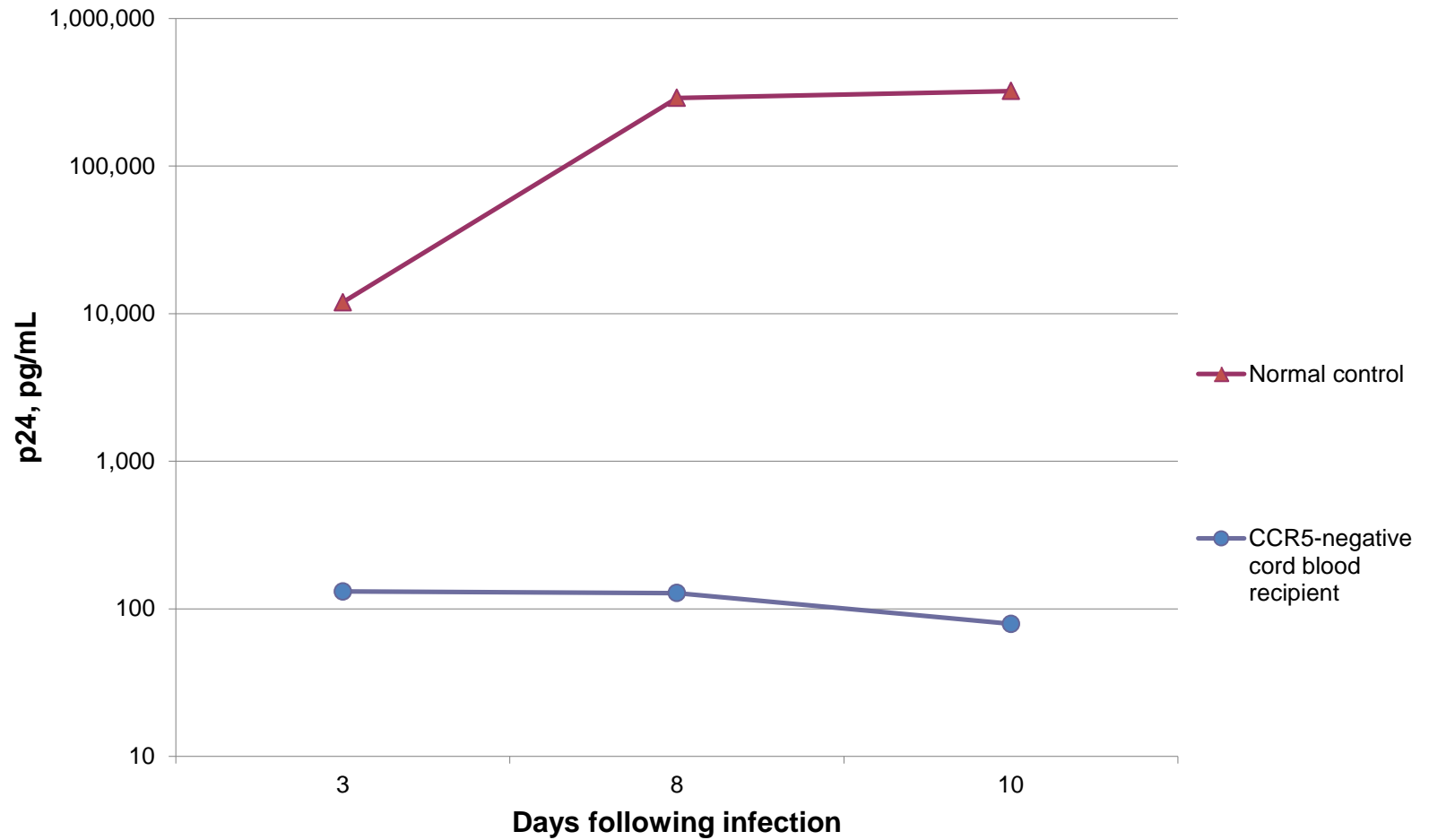
- Adult patients with sufficient cells  $2.5 \times 10^7$  TNC/kg with a 300 unit bank is:
  - .01% for 6/6
  - 4.49% for 5/6
  - 27.92% for 4/6 matches.
- For pediatric patients it is estimated at TNC of  $2.5 \times 10^7$  cells /kg :
  - .01% 6/6
  - 10.58 for 5/6
  - 73.6% with 4/6

# In vitro HIV1( BAL) infection cord blood

HIV-1 (BaL)-infected PBMC



### HIV-1 (BaL)-infected PBMC



# IMPAACT P1107

Goal: Recapitulate the “ Berlin Patient”





# IMPAACT P1107

Observational Study of Cord Blood Transplantation Using CCR5 $\Delta$ 32 Donor Cells For The Treatment of Underlying Disease in HIV infected patients and its effect on HIV Disease

A Multicenter, Domestic & International Trial of the  
International Maternal Pediatric Adolescent AIDS  
Clinical Trials Group (IMPAACT)

IND# Held by NIAID  
DAIDS ES#

The IMPAACT HIV-1 CURE Committee Chair: Deborah Persaud, MD

Protocol Chair: Yvonne Bryson, MD  
Protocol Vice Chairs: Debroah Persaud MD  
Theodore Moore, MD  
Diane Wara, MD

NIAID Medical Officer:	Elizabeth Smith, MD
NICHD Medical Officer:	Rohan Hazra, MD
Clinical Trials Specialist:	Anne colleti, PhD

# P1107 Schema

DESIGN: Observational, open label, multi-center study

## POPULATION

### **Prospective pretransplant cohort:**

HIV-1 infected patients  $\geq 12$  months of age, who require a HSCT for other underlying disease and for whom a suitable match heterozygous or homozygous CCR $\Delta$ 32 cord blood is available

### **Post transplant cohort:**

HIV-1 infected patients  $> 12$  months of age, who have already received homozygous CCR5 $\Delta$ 32 cord blood

SAMPLE SIZE: Prospective cohorts: **Up to 10 evaluable** subjects receiving CCR5 $\Delta$ 32 **homozygous** cells; **up to 10 evaluable** subjects receiving CCR5 $\Delta$ 32 **heterozygous** cells

Post transplant cohort: Up to 5 subjects homozygous CCR5 $\Delta$ 32 cord blood recipients

STRATIFICATION: There is no stratification as part of this study

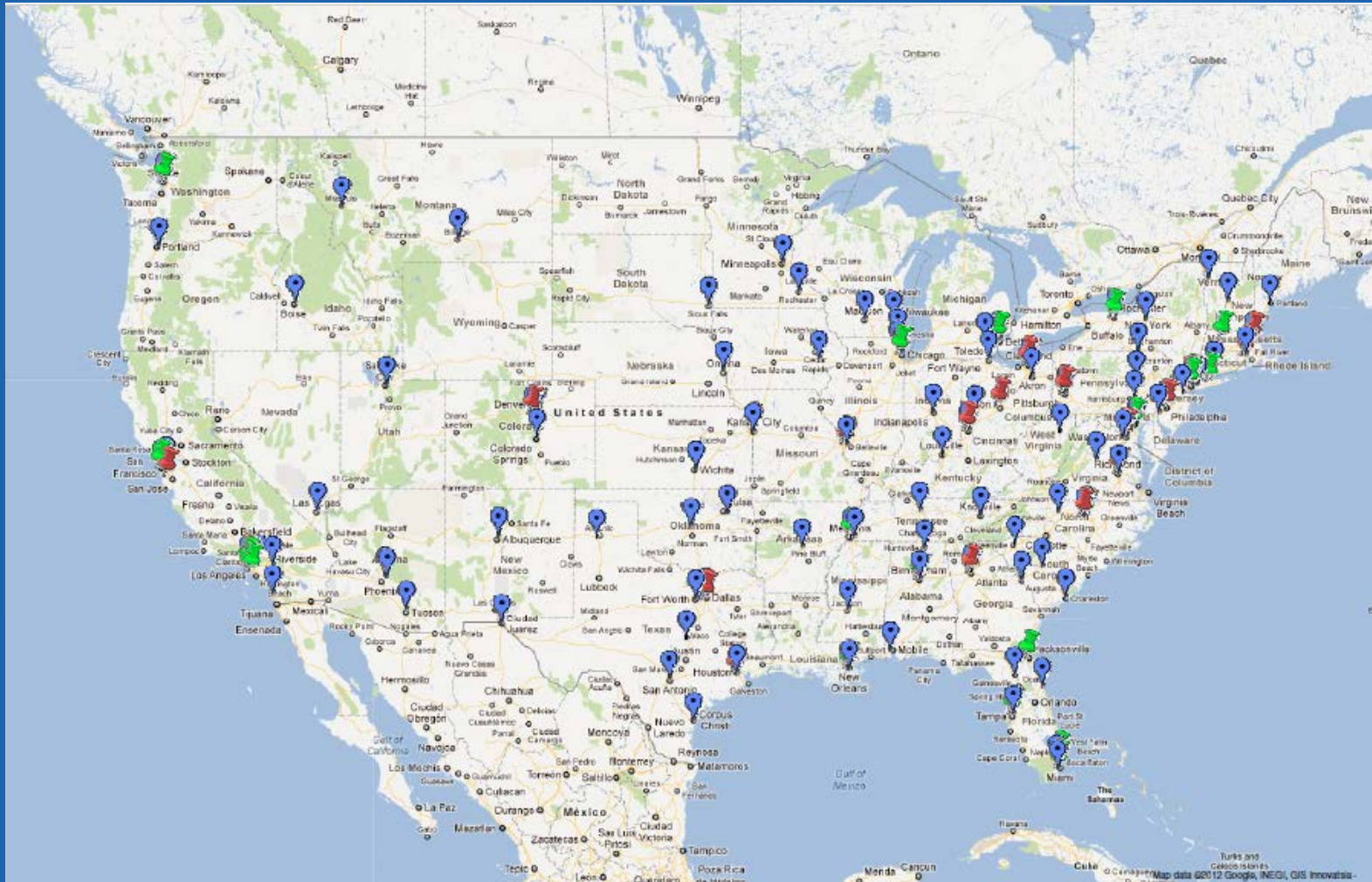
REGIMEN: There is no study drug as part of this study 5YEARS follow up

# Primary Objectives

- To determine the feasibility and safety of transplantation of CCR5 $\Delta$ 32 cord blood stem cells in HIV-1 infected subjects who require a hematopoietic stem cell transplant for underlying disease and for whom matched HSC blood is available
- To describe the **timing of hematopoietic cell and immune recovery**, incidence and severity of graft vs. host disease
- To determine the extent **of post-transplant chimerism for CCR5 $\Delta$ 32 cells** in peripheral blood by 100 days in HIV-1-infected recipients receiving CCR5 $\Delta$ 32 homozygous and heterozygous transplantation
- To describe CCR5 $\Delta$ 32 cord blood stem cell engraftment and its effect on **biomarkers of HIV infection including plasma viral load, HIV-1 DNA and replication-competent reservoirs**, and in gut and other sites if tissue samples are available

# P1107: “Opportunistic” Protocol in Collaboration with CIBMTR/ACTG/IMPAACT Sites

Blue markers – CIBMTR transplant sites; Green pins – IMPAACT sites; Red pins – ACTG sites



Created by P1107 Clinical Trials Specialist: Elizabeth Petzold

# Overall Goals of P1107

- Can we recapitulate findings of Berlin patient?
- Provide a path to further understand pathogenesis of host resistance to HIV
- Step wise knowledge for use of autologous stem cells genetically modified to be HIV resistant
  - Without need for myeloablation or cord blood units
- Provide a protocol for consistent collection of samples pre- and post transplantation
- Cord blood units available for patients as part of blood bank mission priority for HIV infected individuals
- IMPAACT/ACTG AIDS Malignancy C. serve as recruitment network for referral and follow up

# Study Plans

- Expect to enroll 3-4 children /adolescents /adults in next few years as proof of concept
- Protocol 1107 and team approved by NIH networks – >220 -cord bank units available
- This will enhance the further understanding of the host relationship to HIV infection and pave the way for other approaches which can be more generally available This is a PROOF of CONCEPT
- Gene therapy with cord or BMT , stem cells resistant to HIV
- Zinc finger technology to treat autologous cells to alter the CCR5 /CxCr4 co receptor -auto infusion



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Laboratory Data Coordinator: Anthony Bloom

Westat Clinical Research Associate: Rita Patel, MS

**Thank You!**



# Long-Term Reduction in Peripheral Blood HIV-1 Reservoirs Following Reduced-Intensity Allogeneic Stem Cell Transplantation in Two HIV-Infected Individuals

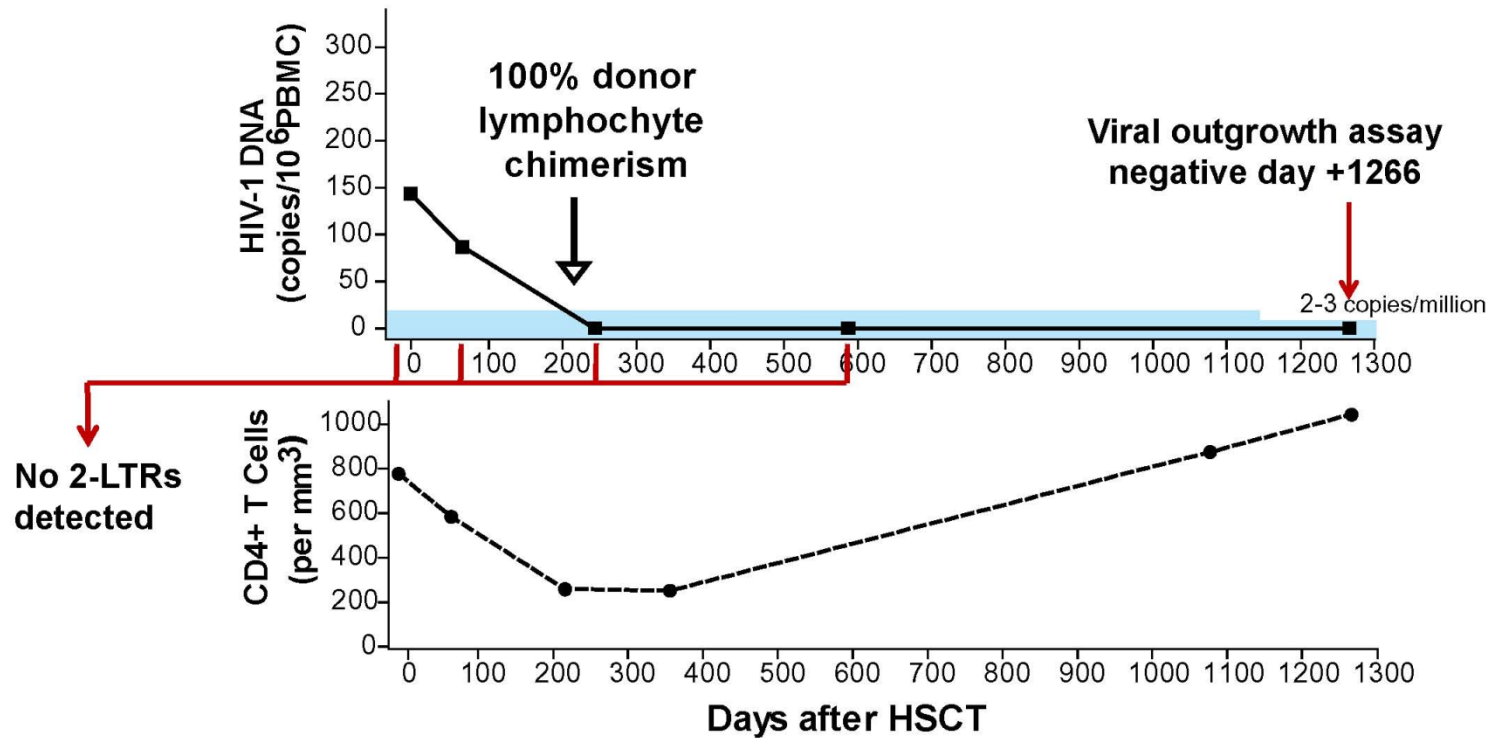
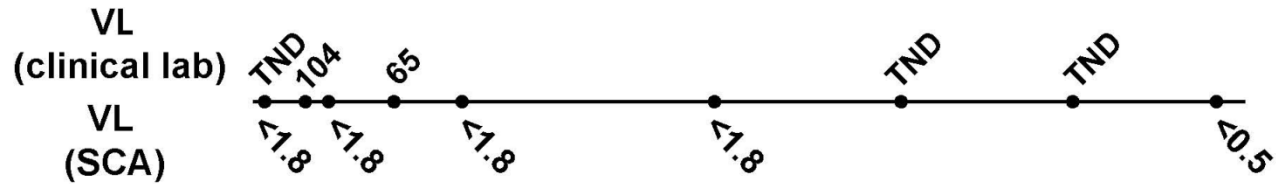
Timothy J. Henrich<sup>1,2</sup>, Gaia Sciaranghella<sup>3</sup>, Jonathan Z. Li<sup>1,2</sup>, Sebastien Gallien<sup>4</sup>, Vincent Ho<sup>5,2</sup>, Ann S. LaCasce<sup>5,2</sup>, and Daniel R. Kuritzkes<sup>1,2</sup>

<sup>1</sup>Brigham and Women's Hospital, Boston, MA; <sup>2</sup>Harvard Medical School, Boston, MA; <sup>3</sup>Ragon Institute of MGH, MIT, and Harvard, Boston, MA; <sup>4</sup>Hopital Saint-Louis, Paris, France;

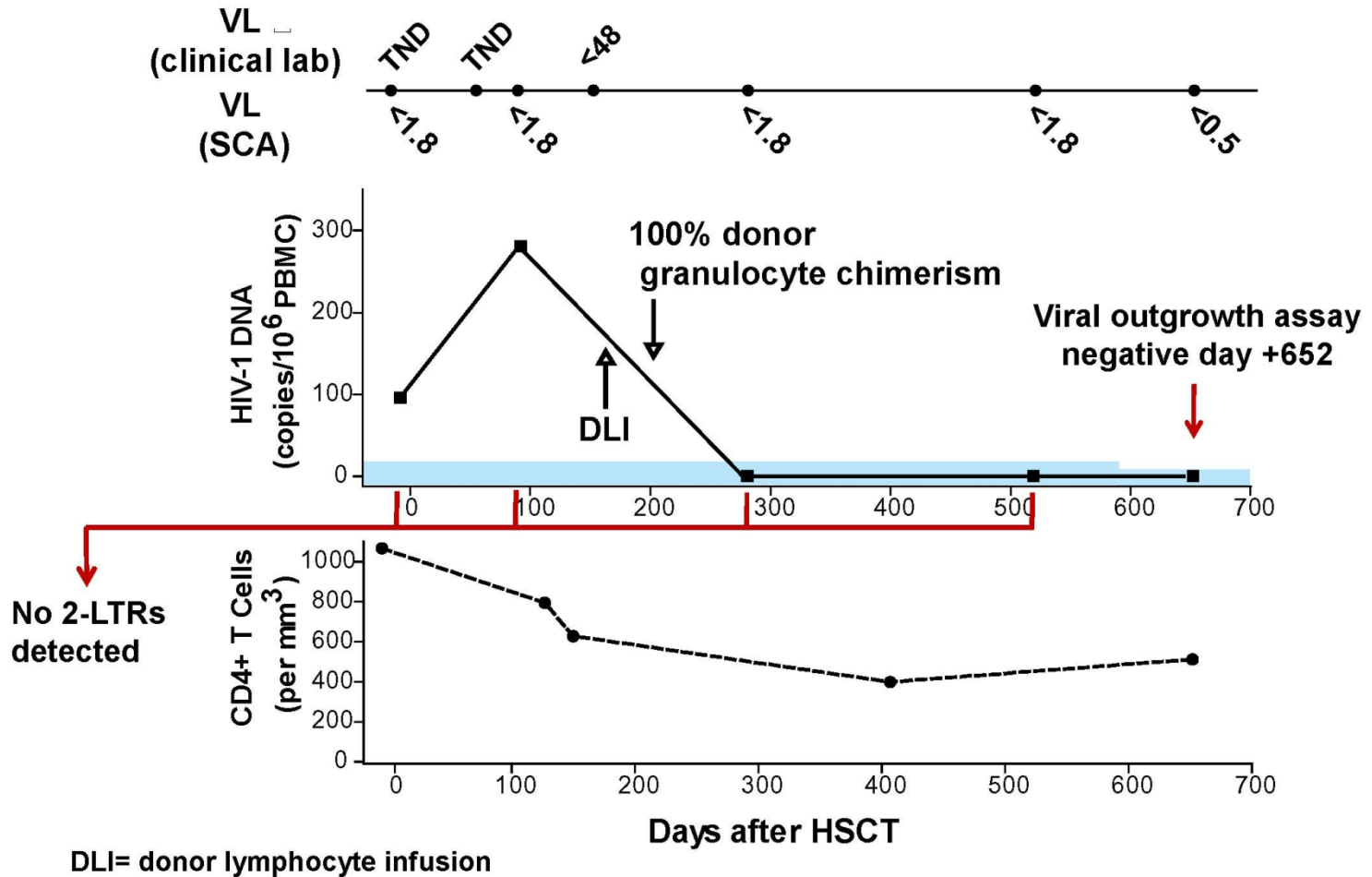
<sup>5</sup>Dana-Farber Cancer Institute, Boston, MA.



# Patient A



# Patient B



# Lessons learned

- HIV Allogeneic transplants ( Boston patients)
- myeloablation of recipient cells and stem cell transplant ( wild type cells not CCR5 delta 32/32) resulted in significant reduction of HIV viral reservoirs
- However these reservoirs were not eliminated and delayed virus rebound occurred—months
- Suggests need for additional strategy- HIV resistant cells/ immune enhancement - vaccine/neutralizing antibody

# Progress

- Reports from CRO1 Allogeneic transplants with CCR5 delta 32 /32 cells stem cells, cord blood
- Barcelona patient CCR5 cord 32/32-engrafted
- In vitro PBMC resistant to HIV decrease in HIV markers –recurrence cancer

German stem cell CCR5 32/32 slow engraftment ,stopped ARV, HIV viremia CXCR4 –  
Boston one patient with stem cell CCR532/32 engraftment following currently

## P1007 enrollment

- 48yr/old HIV infected male with Hodgkins lymphoma and HIV >12 years
- Received CCR5 delta 32/32 cord and haplo transplant from mother
- Engrafted by day 18 and was discharged from hospital day 27
- Had initial partial engraftment with cord and haplo cells but later lost grafts and his cells returned Still clinically well and cancer in remission. HIV negative on standard assay but on ARV

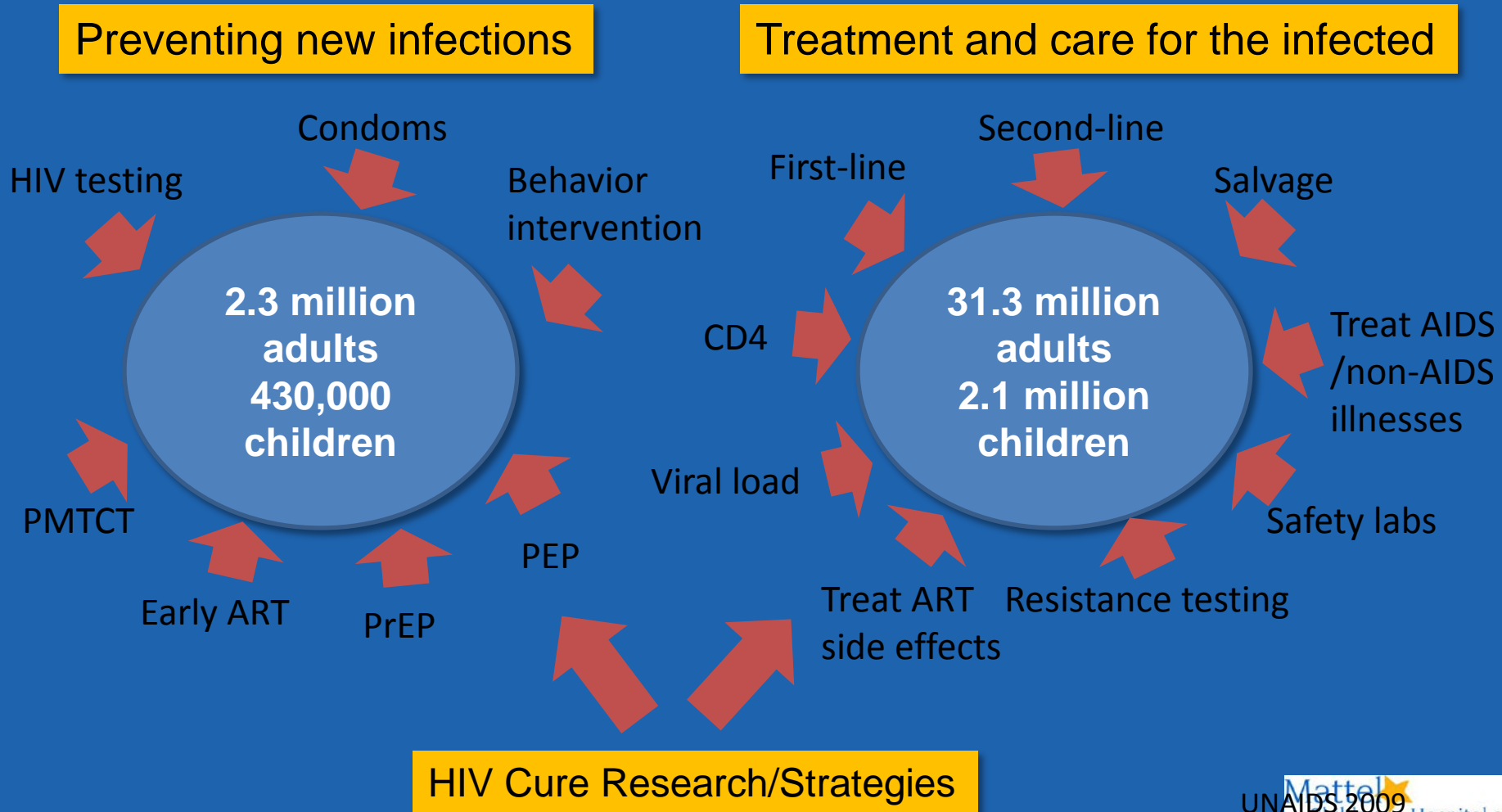
# Approach to transplant using cord plus Haplo

- Advantages of Haplo combined with cord
- More rapid engraftment 12 -28 days less time for infectious complications
- Cord takes over the haplo cells for engraftment
- No increase in relapse of underlying cancer
- Allows use of single cord in adults or adolescents with Haplo Voien Beisen et al

# Challenges ahead

- More knowledge about goals ( similar to cancer advances ) remission--- to cure
- Step wise approach
- Need better assays to assess remission and cure ( current assays not sensitive enough)
- Innovative ways to assess reservoirs
- Gut /CNS
- Enhance host resistance / immunity as a combined approach

# Ownership of HIV Cure Research in Resource-poor nations





NEVER UNDERESTIMATE THE  
POWER OF ONE

or a few good people

N. BERGER/POLARIS/EYEVINE



The 'Berlin Patient,' Timothy Brown, has been cured of HIV since 2007. His story has renewed interest in cure research.

# RYAN WHITE





Elizabeth Glazer & Yvonne Bryson



# Suit Against Cheap AIDS Drugs Ends in S. Africa

■ **Health:** Settlement with world's pharmaceutical giants is hailed as a major step in providing treatment for millions on the continent. Pretoria's critics voice doubt that distribution will come quickly.

By ANN M. SIMMONS  
TIMES STAFF WRITER

PRETORIA, South Africa—The world's biggest drug companies dropped their controversial lawsuit against the South African government Thursday, paving the way for this country to provide cheaper medication to combat diseases such as AIDS.

## Nkosi Johnson; South African Boy Sought Greater AIDS Awareness

By ANN M. SIMMONS  
TIMES STAFF WRITER

JOHANNESBURG, South Africa—Child activist Nkosi Johnson, an outspoken advocate for greater AIDS awareness and an inspiration to millions of South Africans, died Friday of complications from the disease. He was 12.

Nkosi was considered by many an ambassador for children born HIV-positive and was admired for his openness about his infection in a country where admitting to carrying the disease is still taboo.

Initially given nine months to live when his foster mother, Gail Johnson, took him in at age 2, Nkosi was labeled as the country's longest surviving child AIDS carrier five years later.

He collapsed in December with brain damage and viral infection. His foster mother brought him home in January after doctors said they could do nothing more.

A torturous struggle followed. By the end, he lay bedridden in a comatose state, his emaciated body weighing just 22 pounds.

Admirers said Nkosi's valor in the face of great suffering was an inspiration to many of South Africa's 4.7 million people who are living with the human



Reuters

NKOSI JOHNSON

He was admired for speaking out on a disease in a country where it's still considered taboo.

President Thabo Mbeki. "You can't get AIDS by hugging, kissing and holding hands."

The government has come under fire for being slow to react to the pandemic and blocking the distribution of anti-retroviral drugs. But state officials recently said that pregnant women would soon be treated with such medicines.

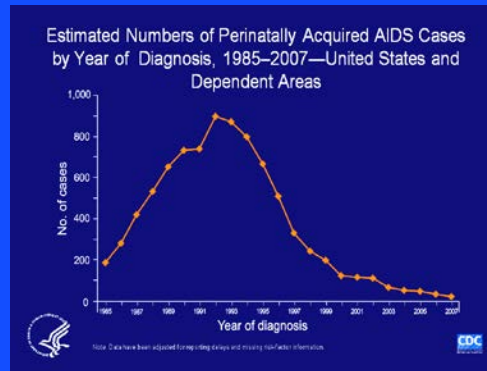
Mbeki has also been criticized for questioning the link between HIV and AIDS.

"Nkosi is a reminder to us that there are approximately 60,000 children born every year with HIV infection," said Nathan Geffen, a spokesman for the Treatment Action Campaign, an anti-AIDS drugs lobby group. "And a large number of them could be prevented if only the government didn't lack the political will to implement the necessary mother-to-child HIV-transmission-prevention program."

In April, the world's biggest pharmaceutical companies dropped a controversial lawsuit against the South African government, paving the way for the country to provide cheaper versions of anti-AIDS medication. But the state has still to take advantage of the opportunity.

Born Nolani Nkosi on Feb. 4, 1989, his mother, Daphne, could not afford to raise him. She died of AIDS-related diseases in 1997.





# Thank You





Real-time screening of 51406 VCT samples in Bangkok  
by pooled nucleic acid and sequential EIA (Apr 09-Mar12)

Acute HIV infection confirmed (n= 89)

75 acutely infected subjects enrolled

F I = 25  
F II = 10  
F III = 32  
F IV = 5

Main protocol  
(n=75)

Optional  
compartment  
Studies

ARV protocol  
(n=73)

D 0, 2, 3, 5, 7,  
Wks 2, 4, 8, 12  
then q 12 wks  
- Clinical  
characterization  
- Phlebotomy

Wks 0, 24, 96  
- Sigmoid biopsy (n=55)  
- Leukapheresis (n=55)  
- Lumbar puncture (n=52)  
- MRI/MRS (n=70)  
- Genital secretion (n=74)

MegaHAART

HAART

3 days

2 days