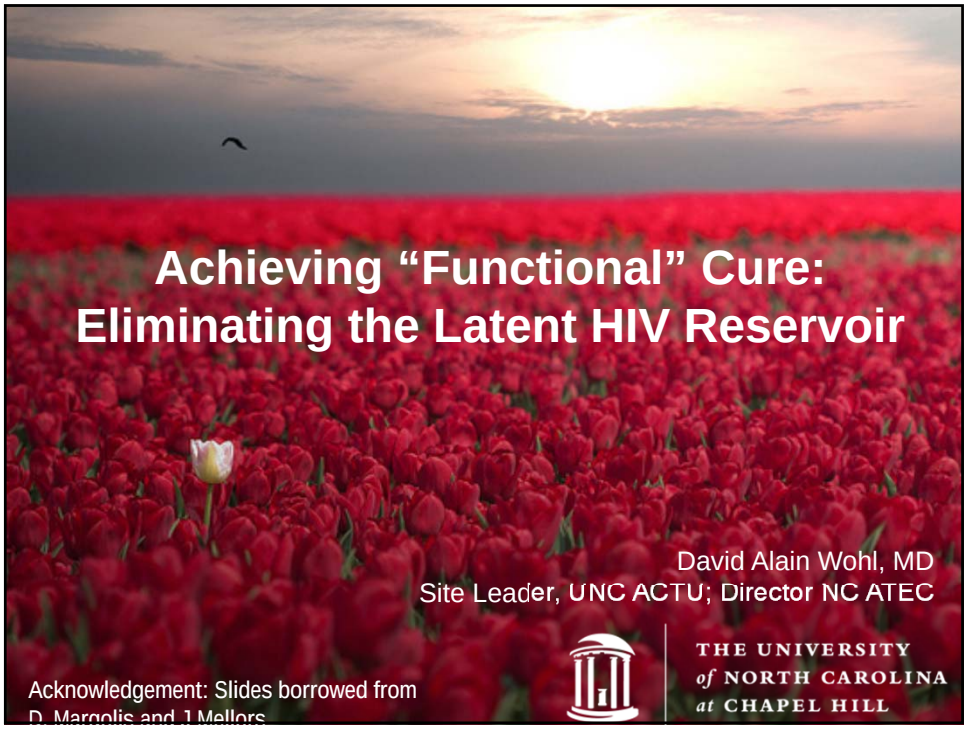
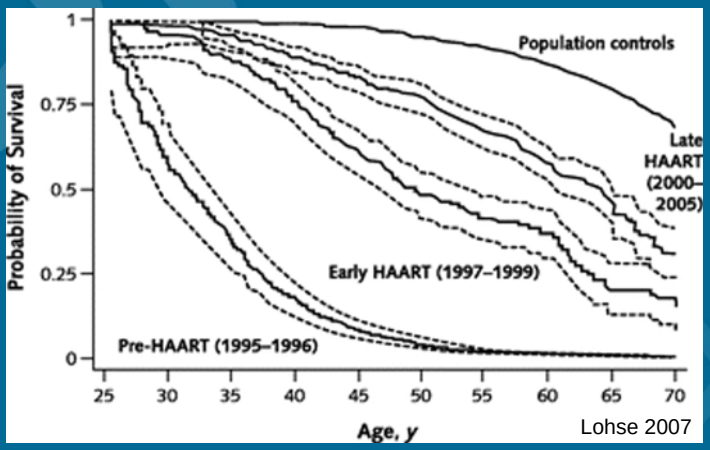


The Scope of the Global HIV/AIDS Pandemic – Current Estimates

Cumulative HIV infections	65 million
People living with HIV/AIDS	34 million
New HIV infections in 2009	2.6 million
Deaths due to AIDS in 2009	1.8 million
Cumulative AIDS deaths	~30 million

Source: UNAIDS, 2011

Predicted Survival if HIV+ at age 25 years



Lohse 2007

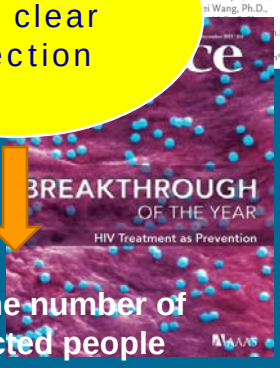
US military cohort (n = 2327, mean age 35) who started ART after 2000, 5-year mortality 0.3%

Marconi 2010

Two-Pronged Approach

Combination HIV Prevention

Treatments that clear Infection



Reduce the number of new HIV infections

Reduce the number of HIV-infected people

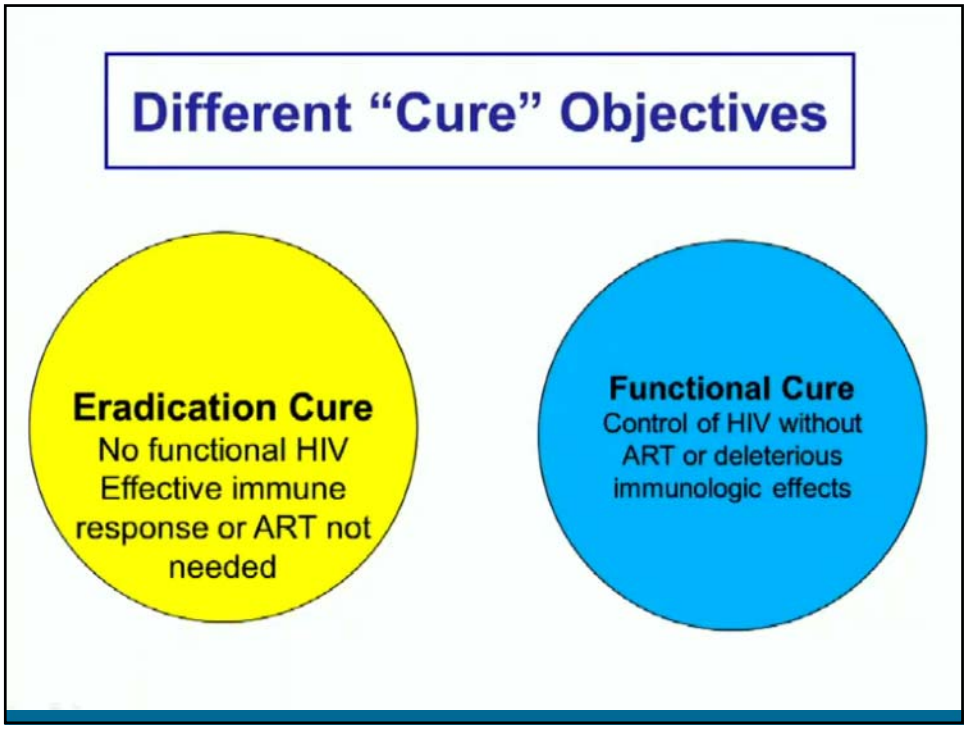
Last public appearance of the entire AIDS Quilt, 1996

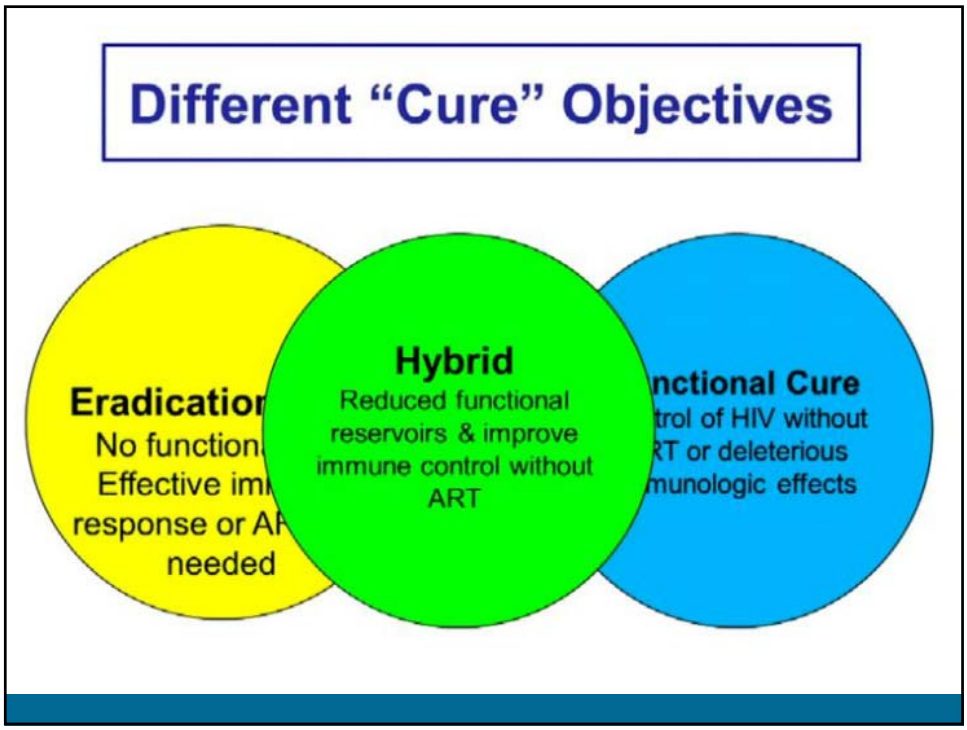
Why Try To Cure HIV?

Which would you rather take?

Different "Cure" Objectives

Eradication Cure
No functional HIV
Effective immune response or ART not needed

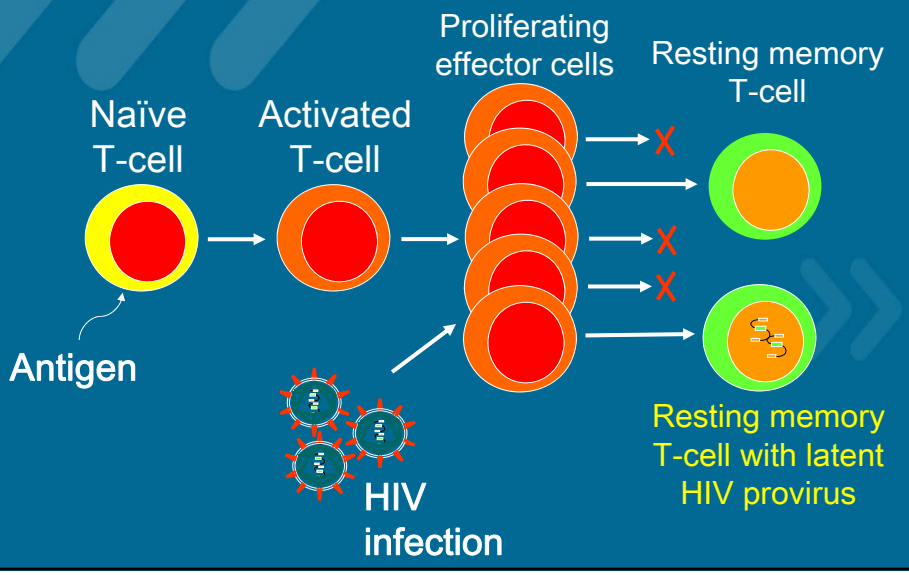

Different "Cure" Objectives
Eradication Cure
No functional HIV
Effective immune response or ART not needed
Functional Cure
Control of HIV without ART or deleterious immunologic effects


Different "Cure" Objectives
Hybrid
Reduced functional reservoirs & improve immune control without ART

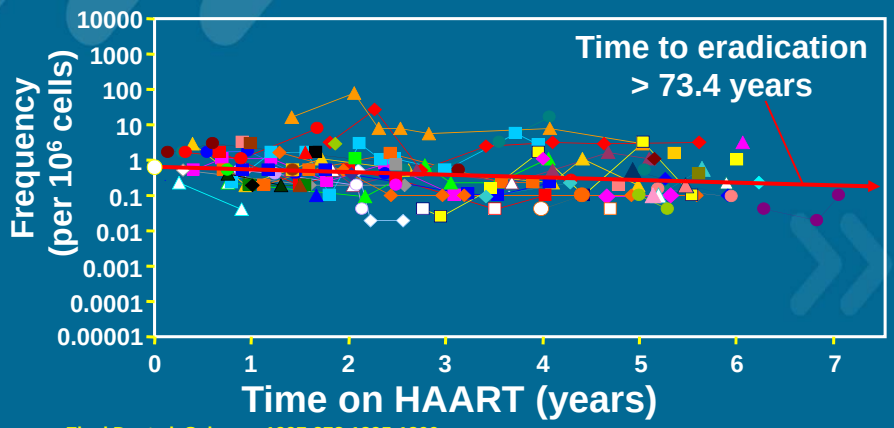
Different "Cure" Objectives

Eradication Cure
No functional HIV
Effective immune response or ART not needed

Generation of latently infected cells is probably the result of transcriptional silencing during memory cell differentiation



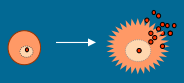
Why does infection persist despite ART:
Part 1: Resting CD4⁺ cell infection



Finzi D, et al. Science. 1997;278:1295-1300.
Wong JK, et al. Science. 1997;278:1291-1295.
Chun TW, et al. PNAS. 1997;94:13193-13197
Finzi D, et al. Nature Med. 1999;5:512-517.
Siliciano JD, et al. Nature Med. 2003;9:727-728.
Chun TW, et al. Nature Med. 1995;1:1284-1290.
Chun TW, et al. Nature. 1997;387:183:188.

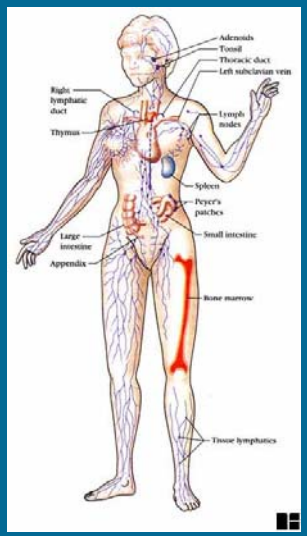
Residual Virus Reservoirs

- Resting CD4 cells

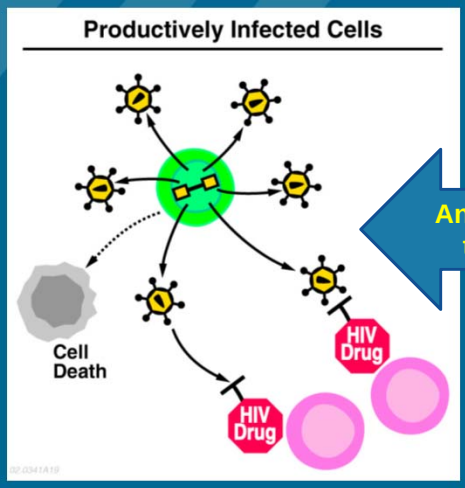


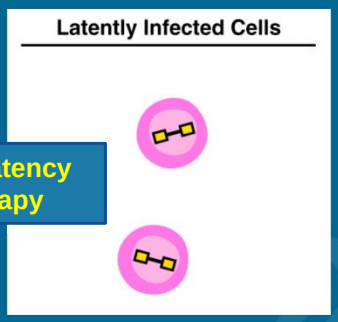
- Other cellular compartments?

- Protected anatomical sites?



Primary strategy to eliminate latent HIV infection





Anti-latency therapy

Other Challenges:

- Clearance of infected cells
- Clearance of virions
- Complete block of new infection

The New York Times 2008

AIDS Patient Is Reported Cured in Berlin With a Rare Treatment

By DONALD G. McNEIL Jr.

Doctors in Berlin are reporting that they cured a man of AIDS by giving him transplanted blood stem cells from a person naturally resistant to the virus.

But while the case has novel medical implications, experts say it will be of little immediate use in treating AIDS. Top American researchers called the treatment unthinkable for the millions infected in Africa and impractical even for insured patients in top research hospitals.

"It's very nice, and it's not even surprising," said Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases. "But it's just off the table of practicality."

The patient, a 42-year-old American resident in Germany, also has leukemia, which justified the high risk of a stem-cell transplant. Such transplants require wiping out a patient's immune system, including bone marrow, with radiation and drugs; 10 to 30 percent of those getting them die.

"Frankly, I'd rather take the medicine," said Dr. Robert C. Gallo, director of the Institute of Human Virology at the University of Maryland School of Medicine, referring to antiretroviral drugs.

Moreover, the chances of finding a donor who is a good tissue match for the patient and also has the rare genetic mutation that confers resistance to H.I.V., the virus that causes AIDS, are extremely small. Nonetheless, the man has been free of the virus for 20 months even though he is not using antiretroviral drugs, and the success in his case is evidence that a long-dreamed-of therapy for AIDS — injecting stem cells that have been genetically re-engineered with the mutation — might work.

The cure was announced Wednesday by Dr. Gero Hütter and Dr. Eckhard Thiel, blood-cancer specialists at Charité Hospital in Berlin. The case was described last week in The Wall Street Journal.

Attempts to use bone-marrow transplants in AIDS treatment have been made since the 1980s. In one case, a patient with both AIDS and lymphoma died of the cancer two months later, but was found to harbor no H.I.V.; it was not known if something in the transplant had protected him.

And in a famous 1995 case, Jeff Getty, a prominent San Francisco advocate for AIDS patients, received bone marrow from a baboon, which is resistant to the human virus. He survived 11 years, but died of AIDS and cancer; the transplant had not protected him but antiretroviral triple therapy had been invented in time to help.

Dr. Hütter said one of the 80 potential donors who matched his patient closely enough for leukemia treatment also happened to have the mutation.

That mutation, discovered in a few gay men in the 1990s and known as Delta 32, must be inherited from both parents. With it, the white blood cells produced in the marrow lack the surface receptors that allow H.I.V. to invade the immune system.

Even if it is prevented from replicating by drugs, the H.I.V. can lie dormant in lymph and nerve cells for years. But without the necessary receptors, any virus coming out of dormancy has no way to infect them.

Doctors say the case gives hope for therapies that artificially induce the Delta 32 mutation.

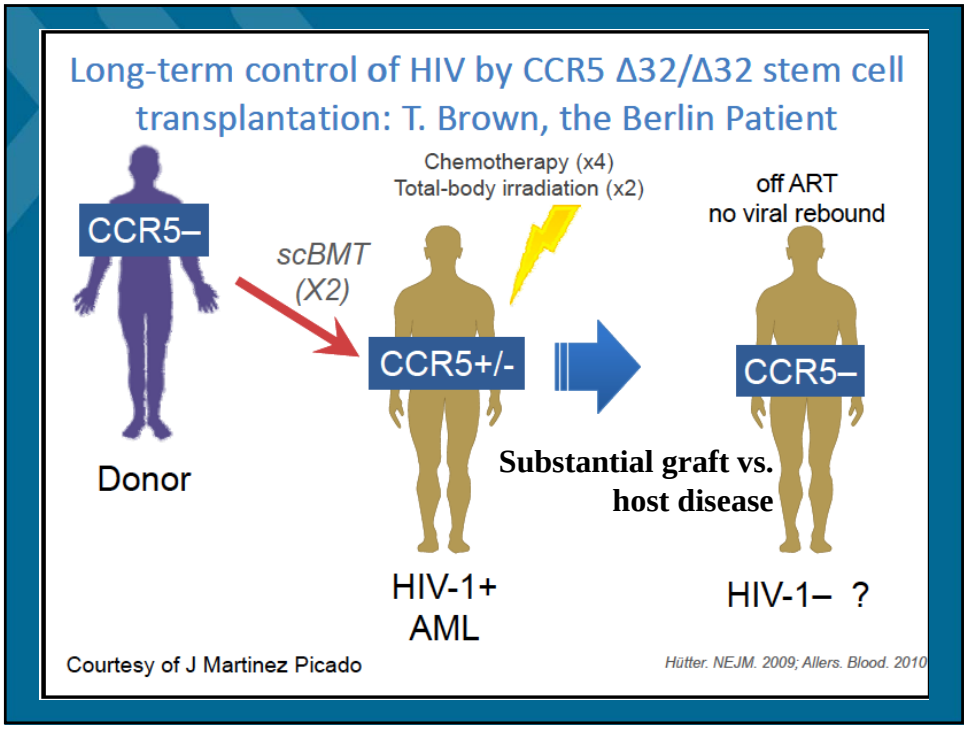
For example, Dr. Irvin S. Y. Chen, director of the AIDS Institute at U.C.L.A. , is working on using RNA "hairpin scissors" to cut out the bits of genetic material in blood stem cells that code for the receptors. The concept is working in monkeys, he said. Eventually, he hopes, it will be possible to inject them into humans after wiping out only part of the immune system with drugs. "I think that would carry no risk of death," he said.

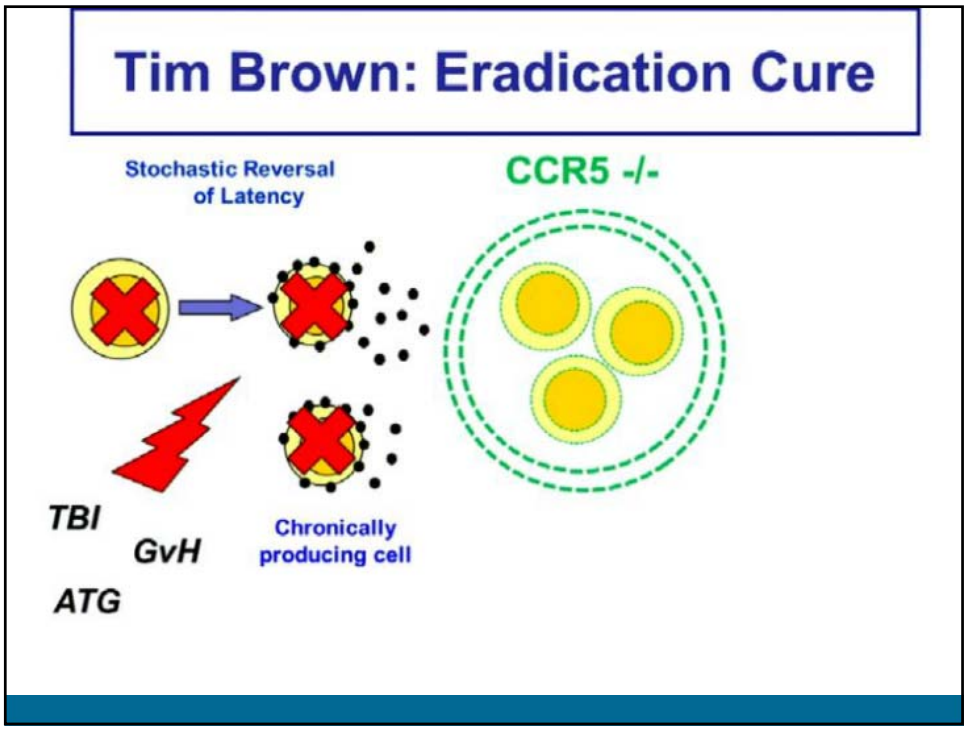
Patient No More

Timothy Brown—a.k.a. "the Berlin Patient"—is the Man Who Once Had HIV. Recovered from a deadly form of leukemia and now virus-free, Brown embodies the hopes of scientists and millions of people living with the virus. Brown's road to a cure is unlikely to be traveled by others. But his journey provides critical proof of a concept that just may lead to the end of AIDS—by offering clues for how to develop a safe, affordable cure for all.

How was Tim Brown cured?

- Cytotoxic chemotherapy?
  - Modest to no long-term effects on HIV reservoirs
    - Cillo PLoS 2014 (in press); Henrich #418 CROI 2014 **(Session TD14)**
- Hematopoietic stem cell transplantation?
  - Autologous transplantation ineffective despite cART
    - Cillo JAIDS 2013; Mavigner #416 CROI 2014 **(Session TD14)**
- Allogeneic CCR5 Δ32/Δ32 stem cell transplant
  - **Replacement of host hematopoietic and immune system**
  - **Donor cells resistant to infection by CCR5 tropic virus**
- High risk (7-25% mortality)
  - Last resort for specific cancers
  - primarily inspiration!


Long-term control of HIV by CCR5 Δ32/Δ32 stem cell transplantation: T. Brown, the Berlin Patient
CCR5–
Donor
scBMT
(X2)
Chemotherapy (x4)
Total-body irradiation (x2)
CCR5+/-
HIV-1+
AML
Substantial graft vs.
host disease
off ART
no viral rebound
CCR5–
HIV-1– ?
Courtesy of J Martinez Picado
Hütter. NEJM. 2009; Allers. Blood. 2010


Tim Brown: Eradication Cure
Stochastic Reversal
of Latency
CCR5 -/-
TBI
GvH
ATG
Chronically
producing cell

Boston Patients (Henrich #144 LB; Session O-12)

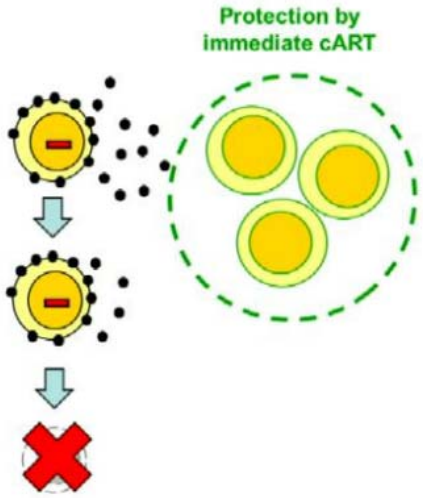
HSCT/Patient Factor	Patient A	Patient B
Mode of acquisition	**Perinatal**	**Sexual (adult)**
CCR5 genetics	**Δ32 Heterozygous**	**Δ32 Heterozygous**
Favorable HLA alleles?	**No**	**No**
Pre-HSCT HIV-1 DNA	**144 copies/10^6 PBMC**	**96 copies/10^6 PBMC**
Type of Allogeneic HSCT	**HLA C-mismatched unrelated; $CCR5^{wt/wt}$**	**Matched related donor; $CCR5^{wt/wt}$**
HSCT Conditioning	**Reduced intensity**	**Reduced intensity**
GVHD	**Chronic, mild (skin)**	**Chronic, mild (skin)**
Length of ART post-HSCT	**4.5 years**	**2.8 years**
Chimerism	**<0.001% host PBMC**	**<0.001% host PBMC**
Post-HSCT HIV-1 DNA	**undetectable**	**undetectable**

REUTERS

Relapse of 'cured' HIV patients spurs AIDS science on
By Kate Kelland, Health and Science Correspondent
LONDON Thu Jan 2, 2014 5:21am EST

(Reuters) - Scientists seeking a cure for AIDS say they have been inspired, not crushed, by a major setback in which two HIV positive patients believed to have been cured found the virus re-invading their bodies once more.

Prevent Long-lived Reservoirs



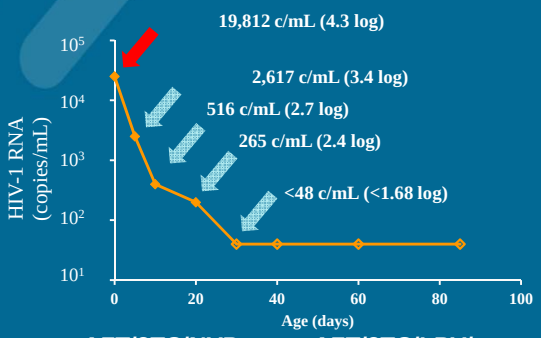
The Second Cure?

- Infant born at U. Miss Medical Center
- Mother HIV+ (EIA, WB); no prenatal care
- Maternal VL: 2,423 c/mL, CD4 644/mm^3
  - Infant born 35 weeks; NSVD
  - Rapid test HIV+ in neonate
- Standard testing of exposed infants:
  2 HIV+ tests from 2 samples

Sample	Age	Test	Result
Blood	30 hours	HIV DNA	positive
Blood	31 hours	HIV RNA	19,812 c/mL

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Virologic Response to HAART Regimen

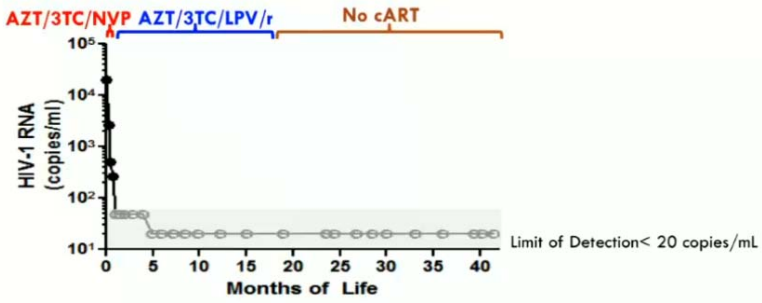


AZT/3TC/NVP **AZT/3TC/LPV/r**
31 Hours – 7 days → 7 days – ~18 months

- Mother stops ART about month 18 – LTFU until month 23
- HIV testing of infant done before restarting ART

Persaud D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 48LB.

Sustained HIV-1 Remission (23 months off cART)

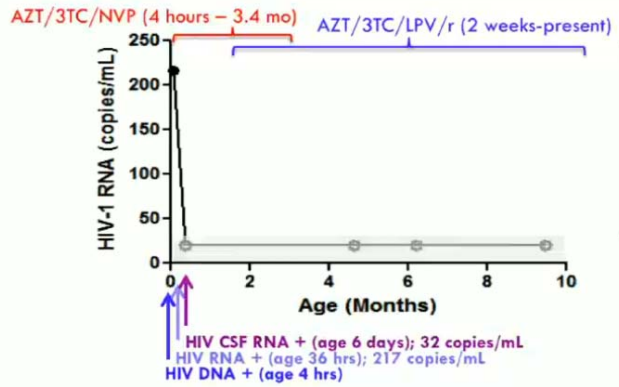


Remains under the care of Dr. Hannah Gay of the University of Mississippi Medical Center

Absent Residual Viremia and Replication-Competent Resting CD4+ T Cell Latent Reservoir

Biomarker	Age at Testing (months)	Months Post-cART cessation	Finding
Residual Viremia (copies/mL)			
	24	6	1
	26	8	<2
	33	15	<1
	36	18	<1
	39	21	<1
	40	22	<1
Infectious Virus Recovery (Infectious units per Million Resting CD4+ T cells)			
	24	6	<0.03
	33	15	<0.04
	36	18	<0.03

Very Early Treatment of a Second Perinatally HIV-1 Infected Infant (4 Hours of Age)



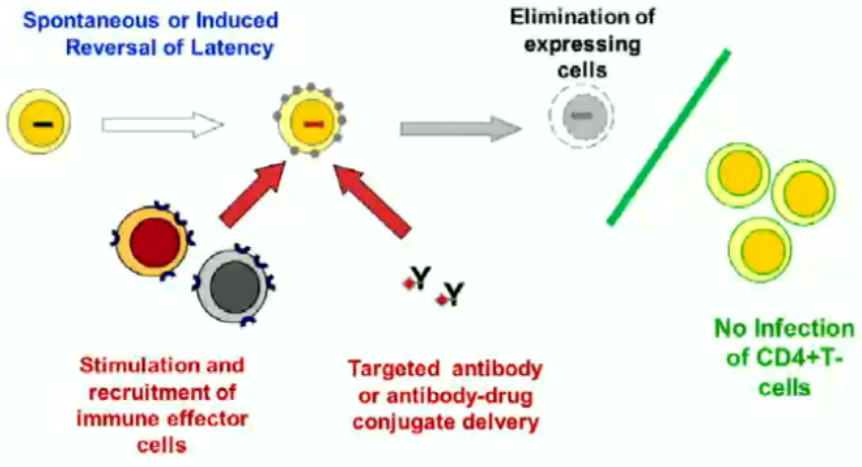
High risk exposure: untreated maternal infection
Maternal VL near delivery =138,811 copies/mL; CD4=70 cells/mm^3

Miller Children's Hospital, LA County: Deveikis A, et al.

Rapid Loss of Detection of HIV-1 Infection

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

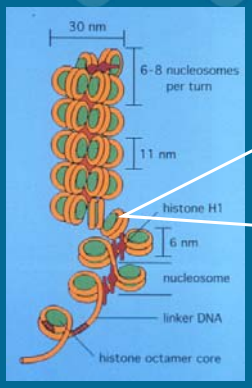
Strategies to reduce and/or control HIV reservoirs

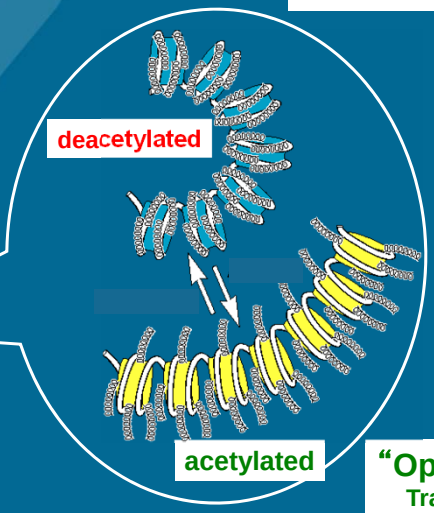


Modified from Romas Geleziunas et al.

HIV lives within chromatin: *tipping the balance towards acetylation removes a restriction at the initiation of proviral expression*

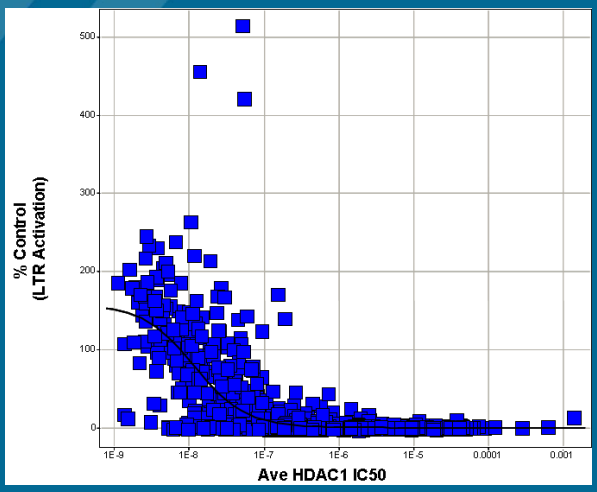
"Closed" Nucleosome
Transcription Repressed





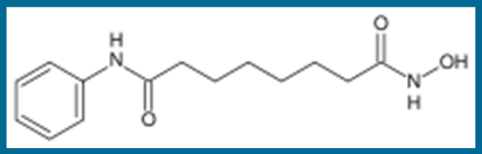
"Open" Histones
Transcription Active

Activation of HIV-1 Gene Expression Correlates with HDAC1 inhibition



Archin AIDS 2009

Vorinostat:
Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor with nanomolar potency licensed for the treatment of cutaneous T cell lymphoma

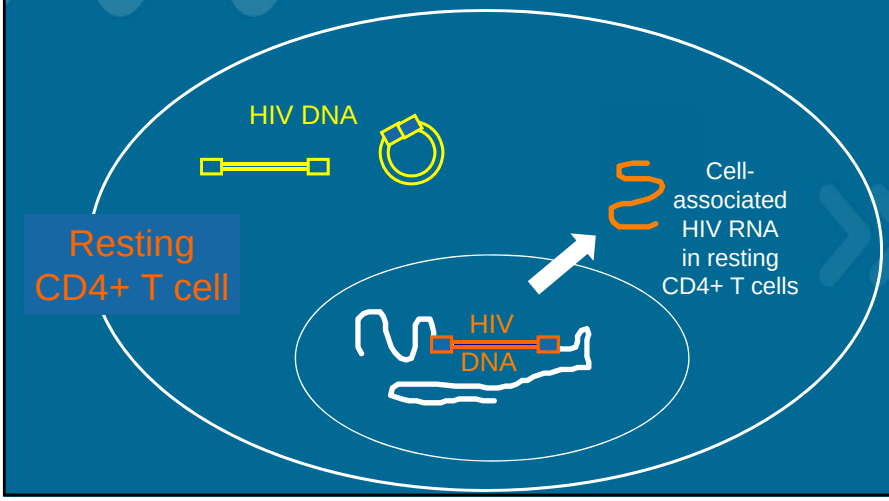


Inhibits HDACs 1, 2, 3, and 8 (class I)
and HDAC 6 (class II)

Archin ARHR 2009
Contreras JBC 2009

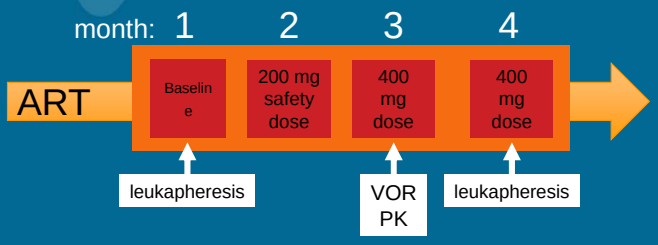
Measures of persistent HIV in fully suppressed patients on ART

Low-level Plasma HIV RNA



Single dose proof-of-concept pilot study with vorinostat

Stable cART >6 months; HIV RNA<50 c/ml; CD4>300 cells/μl



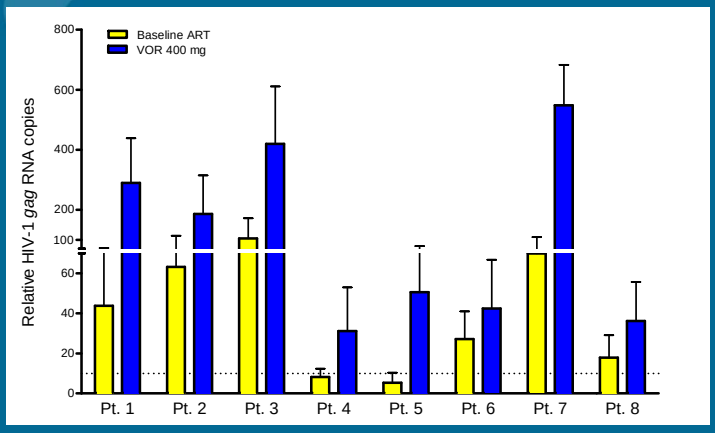
Hypothesis:

- HIV RNA expression in circulating resting CD4 T cells will be increased during the period of VOR intracellular effect
- VOR will disrupt latency in vivo

Archin et al.
nature
International weekly journal of science
25 July 2012

Single 400 mg VOR dose:
Remeasure resting CD4+ T cell HIV RNA expression.
Define potential for VOR to disrupt latency

- Mean 5.2-fold induction (range 1.5- to 10-fold)
- All increases significant ($p < 0.01$)
- No AE > Grade I
- No AE due to VOR



What we have found so far:

- A single dose of VOR induces expression of full-length HIV RNA within latently infected resting CD4+ T cells.
- This is the first direct measurement of disruption of latent HIV infection in vivo
- The optimal dosing schedule of VOR, and its ability to repeatedly and completely perturb latency in all relevant infected cells, must be established
- Separately, the potential for VOR to deplete (some or all) latently infected cells must be established

What if disrupting latency is not enough?

When latency is disrupted, mechanisms to kill virus expressing cells may be needed

- Augment HIV-1 specific immune response with HIV-1 vaccine prior to “kick”
- Improve HIV-1 specific CD8 response through ex vivo manipulation
  - TCR enhancement
- Infuse broadly neutralizing antibody or antibody primed for ADCC
- Wake up “exhausted” HIV-1 specific cells
  - Anti PD1 or Anti PD-L1

Objective

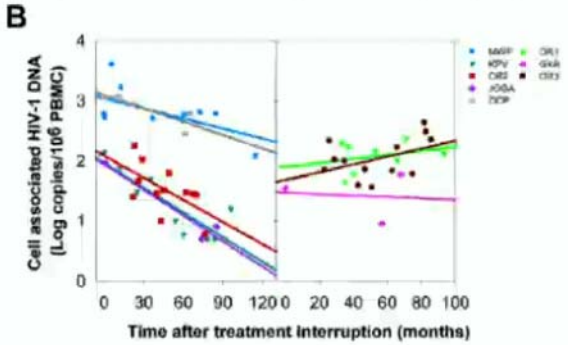
Functional Cure
Control of HIV without ART or deleterious immunologic effects

OPEN ACCESS Freely available online

PLOS | PATHOGENS

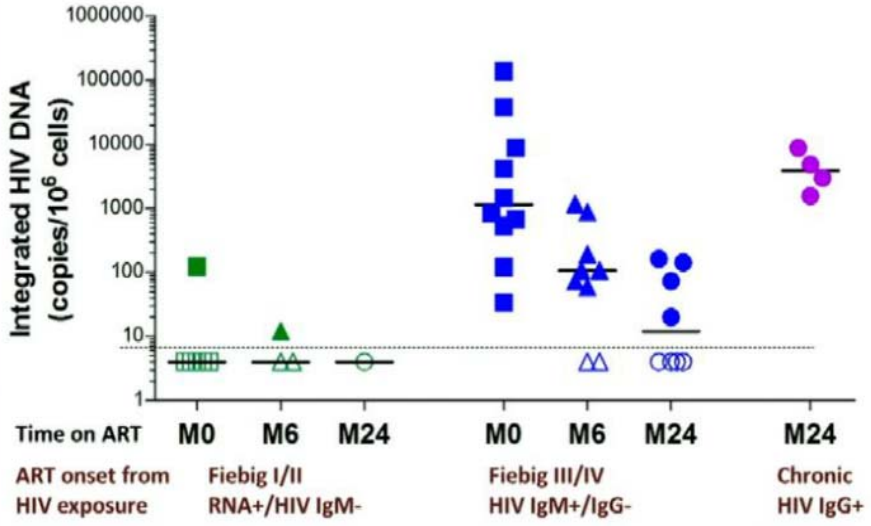
Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1¤], Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5¤], the ANRS VISCONTI Study Group[¤]



RV254/SEARCH 010:

Acutely treated patients have significantly lower integrated HIV DNA in central memory CD4+ T cells



Ananworanich CROI 2013; multiple updates CROI 2014

Strategic Objective

Hybrid
Reduce Functional Reservoirs & Improve Immune Conrol

Immune Control Approaches

- Antibodies
  - Broadly-neutralizing MoAb (promote ADCC?)
  - Ab drug conjugates
  - Bispecific Ab (anti-HIV/anti-CD3)
  - **Reverse immune exhaustion (anti-PD1/L1)***
- Cellular therapies
  - CD8+T-cells with affinity enhanced TCRs or **CARs (scFv)***
  - Activated NK cells
- Therapeutic Vaccines
  - Multiple approaches
  - Induction of de novo responses to epitope escape variants is key

143 **Dendritic Cell-Based HIV Therapeutic Vaccine Increases Residual Viremia in Individuals On ART**
Bernard J. Macatangay[1], Mariam B. Lawani[1], Sharon A. Riddler[1], Nicole D. Wheeler[1], Margaret A. Bedison[1], Charles R. Rinaldo[2], John W. Mellors[1]

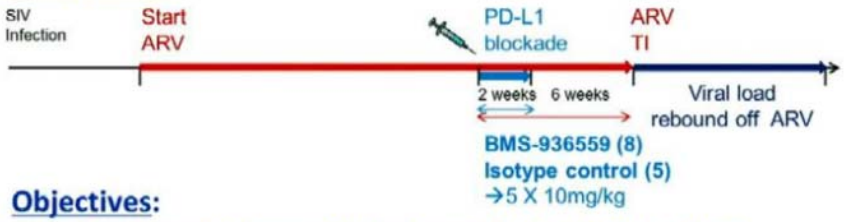
****Successful for cancer therapy***

PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques

Hypothesis:

- **Treatment of ARV-suppressed SIV infected macaques with αPD-L1 should:**
  - restore SIV-specific T cell function. Subsequently, this may:
    - reduce the latent SIV reservoir
    - lead to host control of virus following interruption of ARV

Study design:



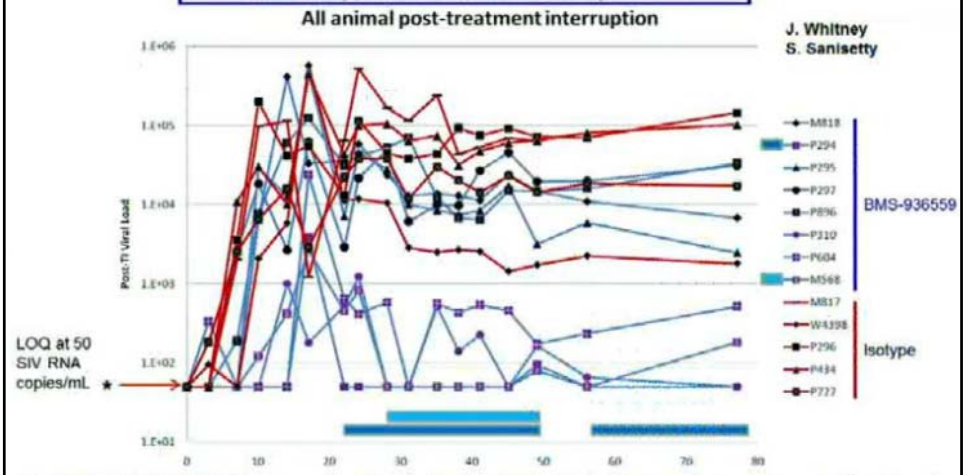
Objectives:

- **Determine whether multiple doses of BMS-936559 affect:**

1. Virus-specific T cell functionality,
2. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
3. Virus recrudescence after cessation of ARV treatment.

318LB Viral Suppression Was Induced by Anti-PD-L1 Following ARV-Interruption in SIV-Infected Monkeys

Stephen W. Mason[1], Srisowmya Sanisetty[2], Christa Osuna-Gutierrez[3], So-Yon Lim[3], Susan Chaniewski[1], Shalyn Campellone[1], Daniel Tenney[1], Scott Balsitis[1], James B. Whitney[3]



- Half of BMS-936559-treated animals had rebound similar to isotype-treated animals
- BMS-936559-responder group remained below 1000 cp/mL for >8 weeks
- Two had undetectable VL for 3-4 weeks

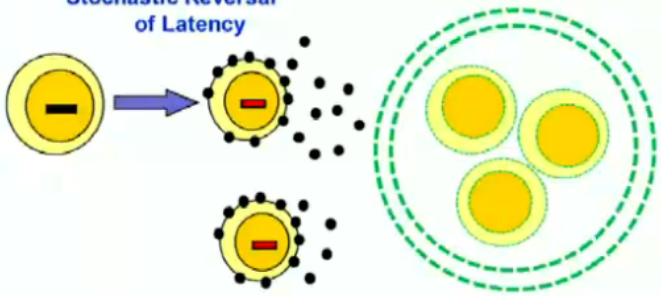
Strategic Objective

Host Modification
Confer resistance of cells to HIV

Host cell modification

KO: CCR5 (Sangamo)
KI: sh5/C46 (Calimmune)

Stochastic Reversal of Latency



Chronically producing cell

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Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

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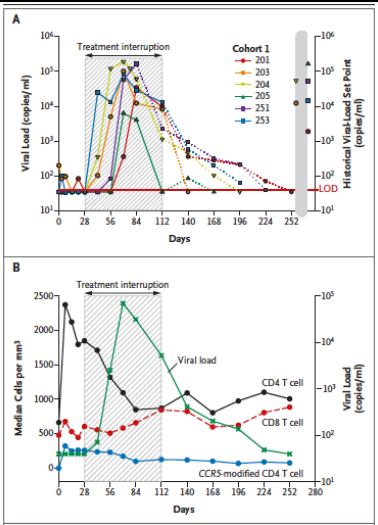
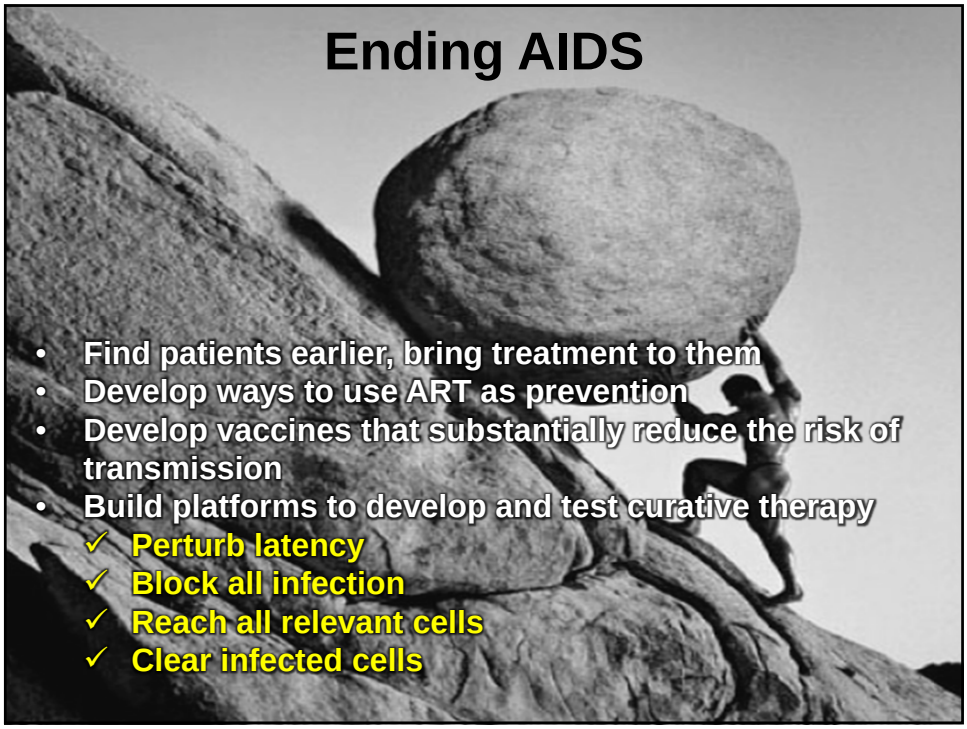


Figure 3. Changes in Viremia during Treatment Interruption.

Panel A depicts HIV viral loads (HIV RNA) for the six patients in cohort 1. SB-728-T was infused on day 0. A 12-week (84-day) treatment interruption (shaded area) was initiated on day 28 and terminated on day 112. The treatment interruption was terminated prematurely, on day 84 (week 8 of the interruption period), in Patients 204 and 251. The dotted lines indicate reinstitution of highly active antiretroviral therapy. The historical HIV-RNA set point for each patient is also shown. The limit of detection (LOD) for the viral-load assay is plotted at 50 copies. Patient 205 was heterozygous for *CCR5* delta32. Panel B shows the median CD4 T-cell, CD8 T-cell, and *CCR5*-modified T-cell counts in cohort 1 during the treatment interruption, as well as the viral load.


Ending AIDS
• Find patients earlier, bring treatment to them
• Develop ways to use ART as prevention
• Develop vaccines that substantially reduce the risk of transmission
• Build platforms to develop and test curative therapy
✓ Perturb latency
✓ Block all infection
✓ Reach all relevant cells
✓ Clear infected cells