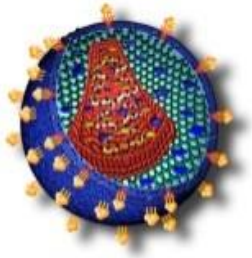
How Does HIV Persist and What Can We Do About It?

John W. Mellors, MD

October 17, 2018



HIV Dynamics and Replication Program

National Cancer Institute at Frederick

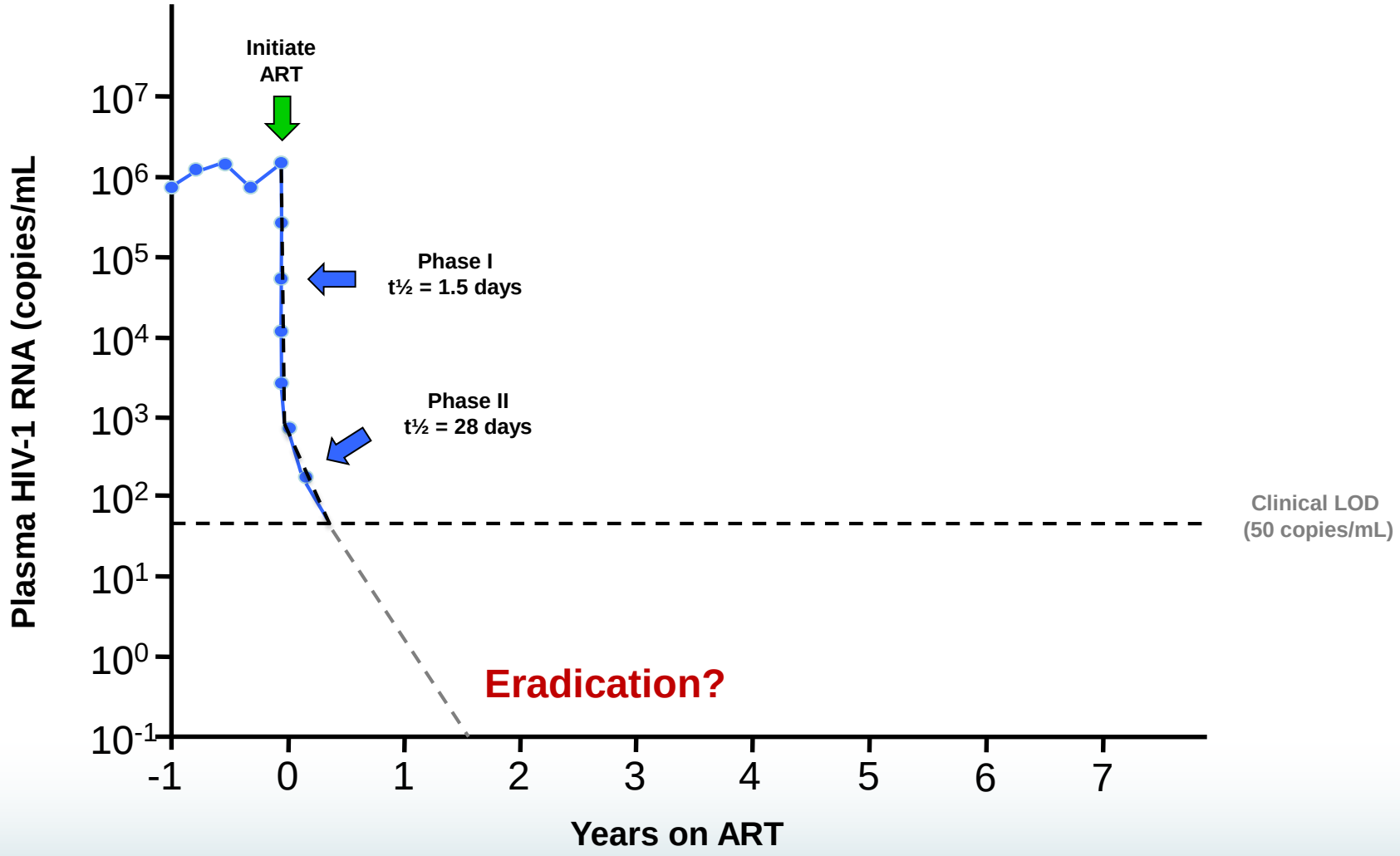
Why Try To Cure HIV?

Which would you rather take?

- No drug toxicity or resistance
- No transmission!
- Life-long ART not required

A Short History of HIV Cure Research

1996-7: HIV Cure Possible?



Perelson et al., Nature 1997

HIV Cure "Impossible": 1997-2009

SCIENCE VOL. 278 * 14 NOVEMBER 1997

Identification of a Reservoir for HIV-1 in Patients on Highly Active Antiretroviral Therapy

Diana Finzi, Monika Hermankova, Theodore Pierson, Lucy M. Carruth, Christopher Buck, Richard E. Chaisson, Thomas C. Quinn, Karen Chadwick, Joseph Margolick, Ronald Brookmeyer, Joel Gallant, Martin Markowitz, David D. Ho, Douglas D. Richman, Robert F. Siliciano*

Recovery of Replication-Competent HIV Despite Prolonged Suppression of Plasma Viremia

Joseph K. Wong,* Marjan Hezareh, Huldrych F. Günthard, Diane V. Havlir, Caroline C. Ignacio, Celsa A. Spina, Douglas D. Richman

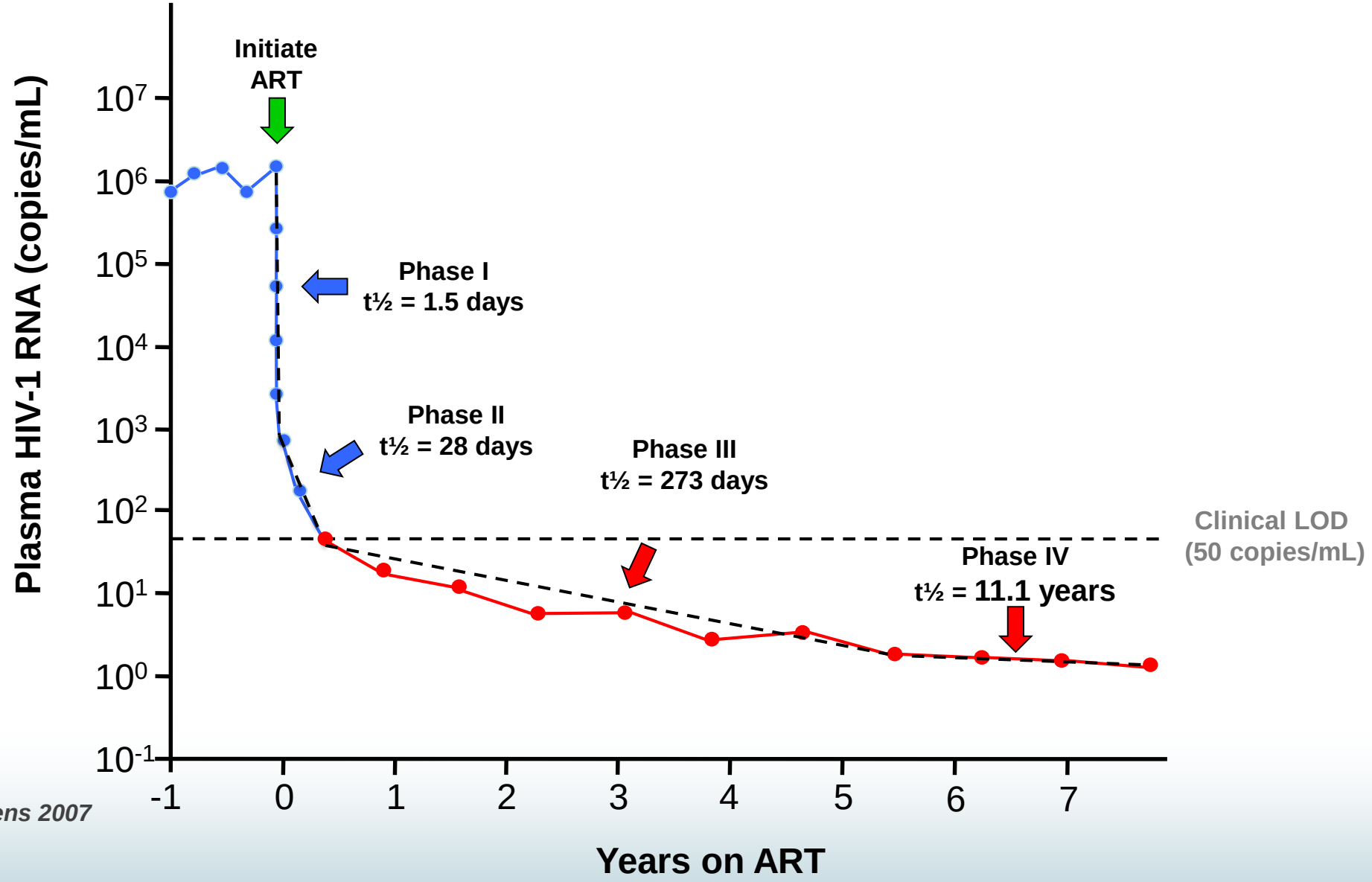
Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 13193–13197, November 1997
Medical Sciences

Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy

TAE-WOOK CHUN*†, LIEVEN STUYVER‡, STEPHANIE B. MIZELL*, LINDA A. EHLER*, JO ANN M. MICAN*, MICHAEL BASELER§, ALUN L. LLOYD¶, MARTIN A. NOWAK¶, AND ANTHONY S. FAUCI*

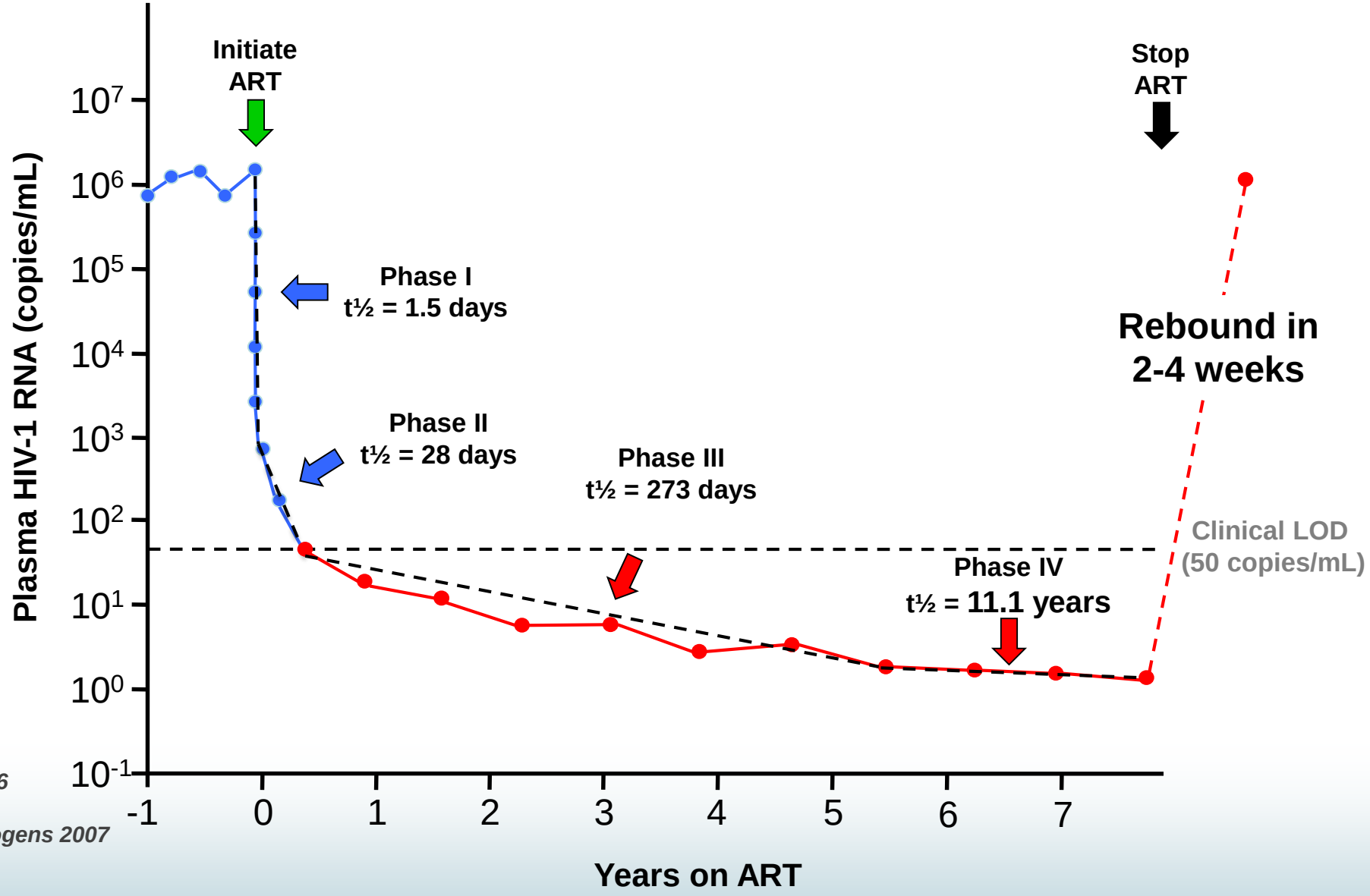
Half-life of latent reservoir ~ 3.7 years (95% CI: 2.3-9.5)

Viremia Persists on ART – Proviruses Not All Latent



Perelson et al., Science 1996
Maldarelli et al., PLoS Pathogens 2007
Palmer et al., PNAS 2008
Riddler et al., JID 2015

Viremia Rebounds Without ART



Perelson et al., Science 1996
Davey et al., PNAS 1999
Maldarelli et al., PLoS Pathogens 2007
Palmer et al., PNAS 2008
Riddler et al., JID 2015

Surprise!

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

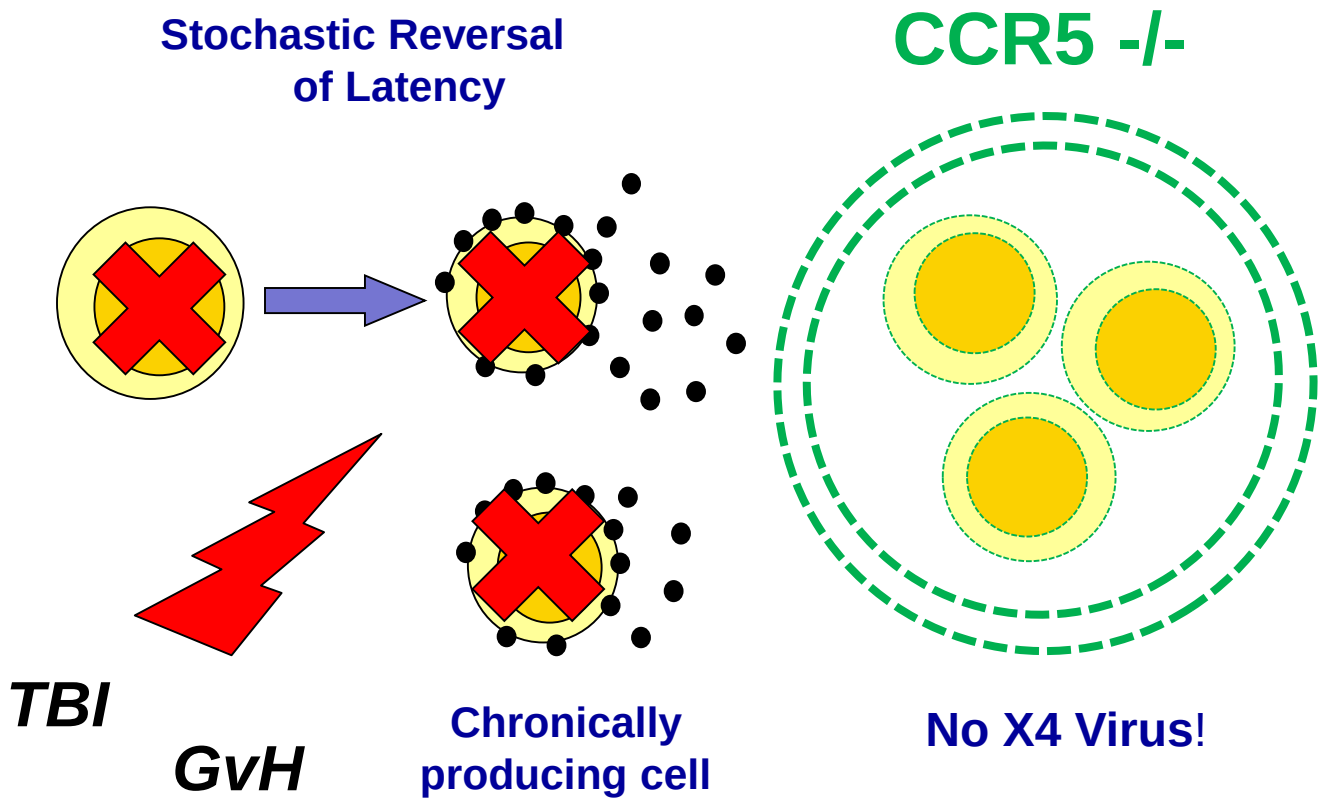
Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

N Engl J Med. 2009; 360:692-8

Timothy Ray Brown, The American in 'Berlin Patient'

No HIV Detectable After Many Years

How was Tim Brown Cured?



Mortality from Allogeneic BMT ~ 25%

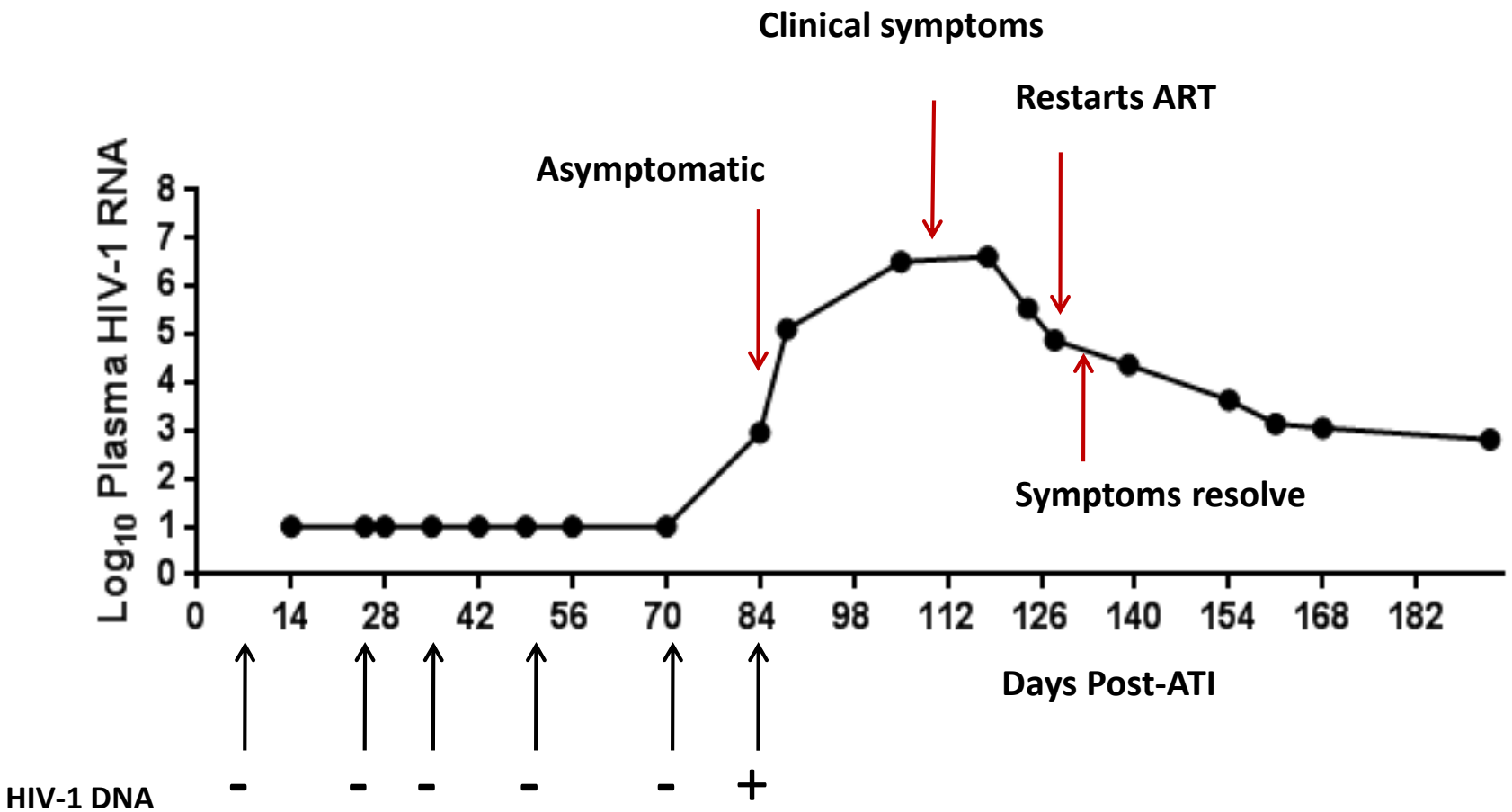
Primarily inspirational!


REALITY
CHECK
AHEAD

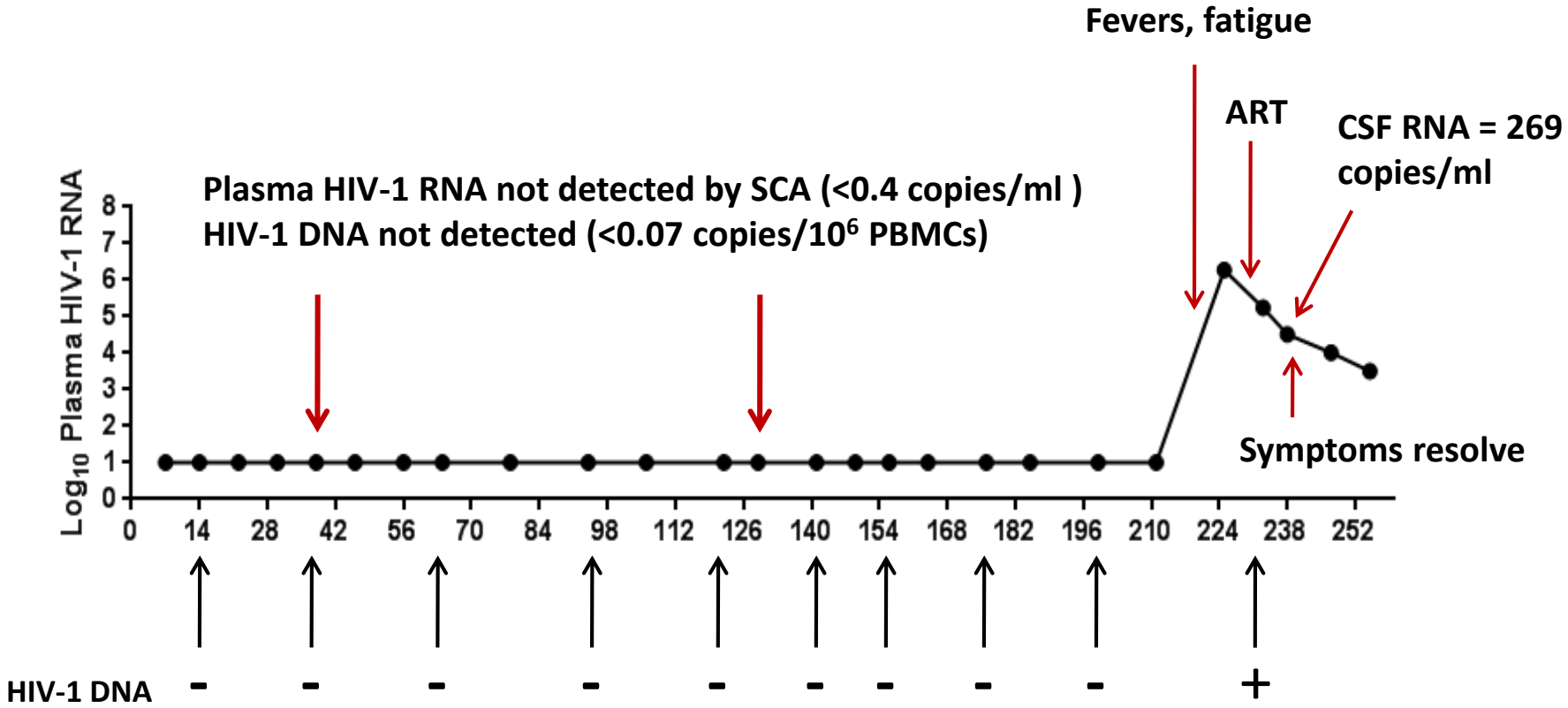
Boston Allotransplants (Henrich et al., Ann Intern Med 2014)

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
Blood Chimerism	**<0.001% host PBMC**	**<0.001% host PBMC**
Post-HSCT HIV-1 DNA	**undetectable**	**undetectable**

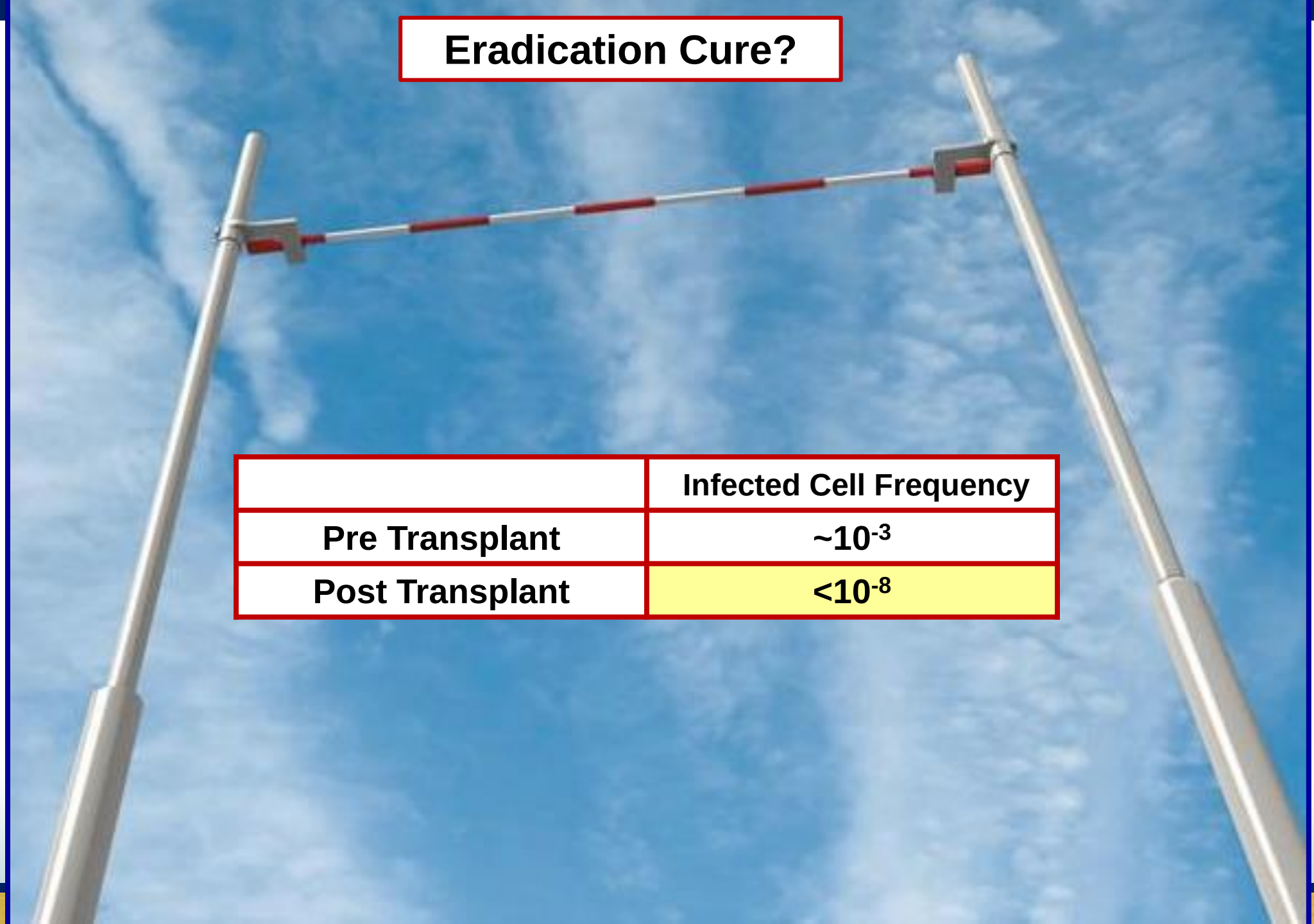
ATI: Patient A



ATI: Patient B



Eradication Cure?



	Infected Cell Frequency
Pre Transplant	~10^{-3}
Post Transplant	<10^{-8}

No other Cures from Allo-transplants with CCR5$^{-/-}$ donors

Table 1. Men with Human Immunodeficiency Virus Type 1 (HIV-1) Infection Who Received an Allogeneic Transplant from a Stem-Cell Donor Who Was Homozygous for the *CCR5* delta32/delta32 Mutation.*

Location of Transplantation	Age of Patient	Type of Cancer	Type of Graft	Outcome after Transplantation
	yr			
Berlin†	40	Acute myeloid leukemia	HLA-matched unrelated	Alive after 7 yr, no viral rebound, no ART
Utrecht, the Netherlands‡	53	Myelodysplastic syndrome	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo
Münster, Germany§	51	Non-Hodgkin's lymphoma	HLA-mismatched unrelated	Died from infection after 4 mo
Essen, Germany¶	30	Non-Hodgkin's lymphoma	HLA-matched unrelated	CXCR4-tropic HIV-1 rebound, died from relapse of non-Hodgkin's lymphoma after 12 mo
Minneapolis§	12	Acute lymphoblastic leukemia	Umbilical-cord blood	Died from GVHD after 3 mo
Santiago, Chile§	46	Non-Hodgkin's lymphoma	HLA-matched related	Died from pneumonia shortly afterward
Barcelona§	37	Non-Hodgkin's lymphoma	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of non-Hodgkin's lymphoma after 3 mo

100% Mortality

Hütter, NEJM 2015

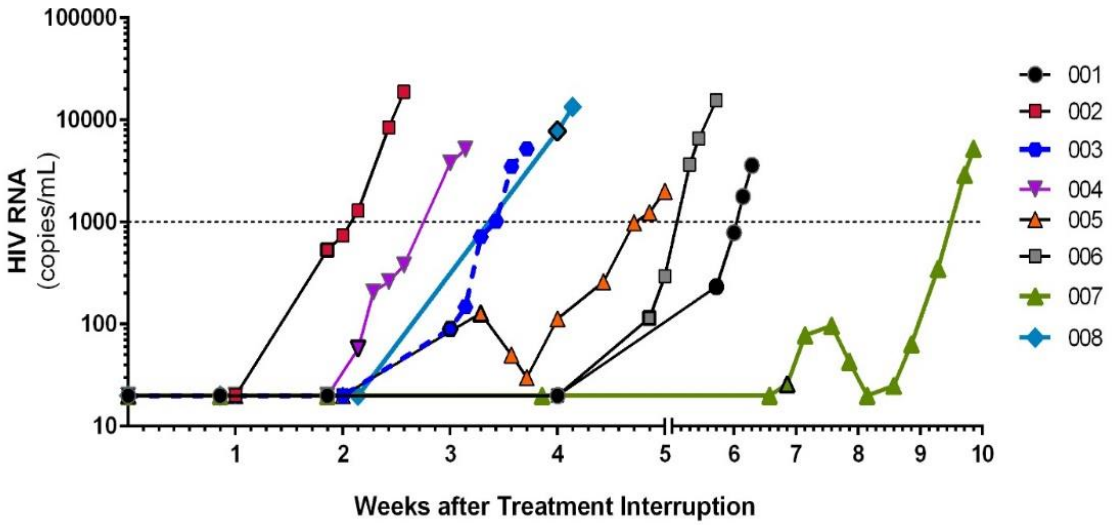
Early ART Is Not Early Enough

RV411: Time to VL Rebound in Fiebig I Treated Individuals

7 men and 1 woman
median age 29 yrs
ART in Fiebig I for median of 2.8 yrs
VL < 20, no blips
Median CD4 577 cells/mm^3

ATI for up to 24 weeks
(VL q 3-7 days)

ART resumed with VL > 1000

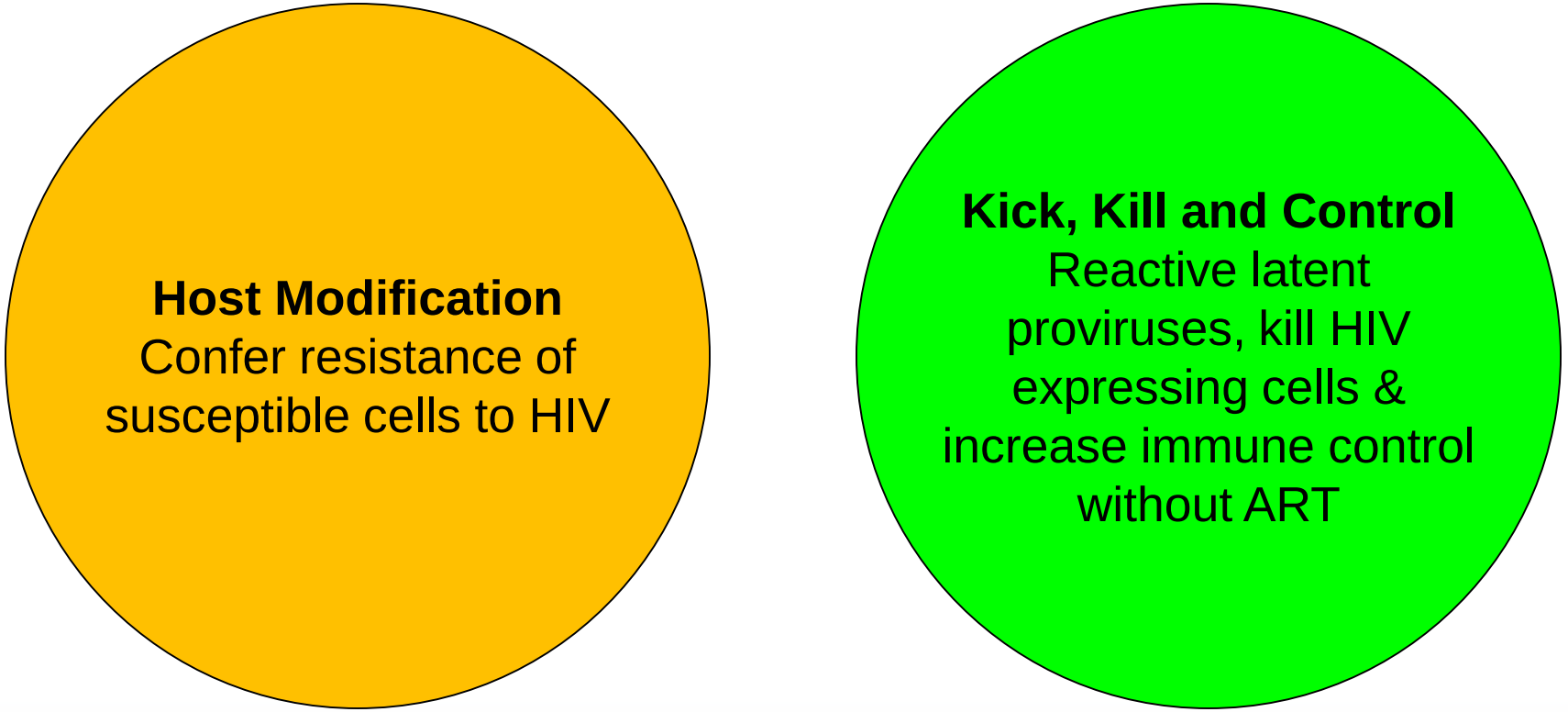


Time to viral load rebound >20 copies/ml
Median 26 days
Range 13 to 48 days

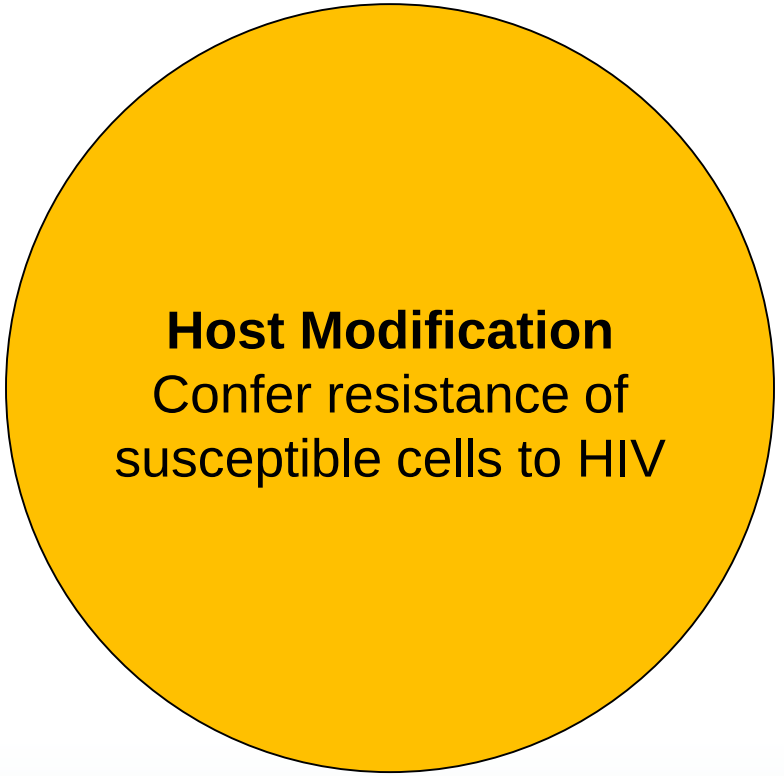
Colby, Ananworanich, et al, Nat Med 2018

Therapeutic Approaches

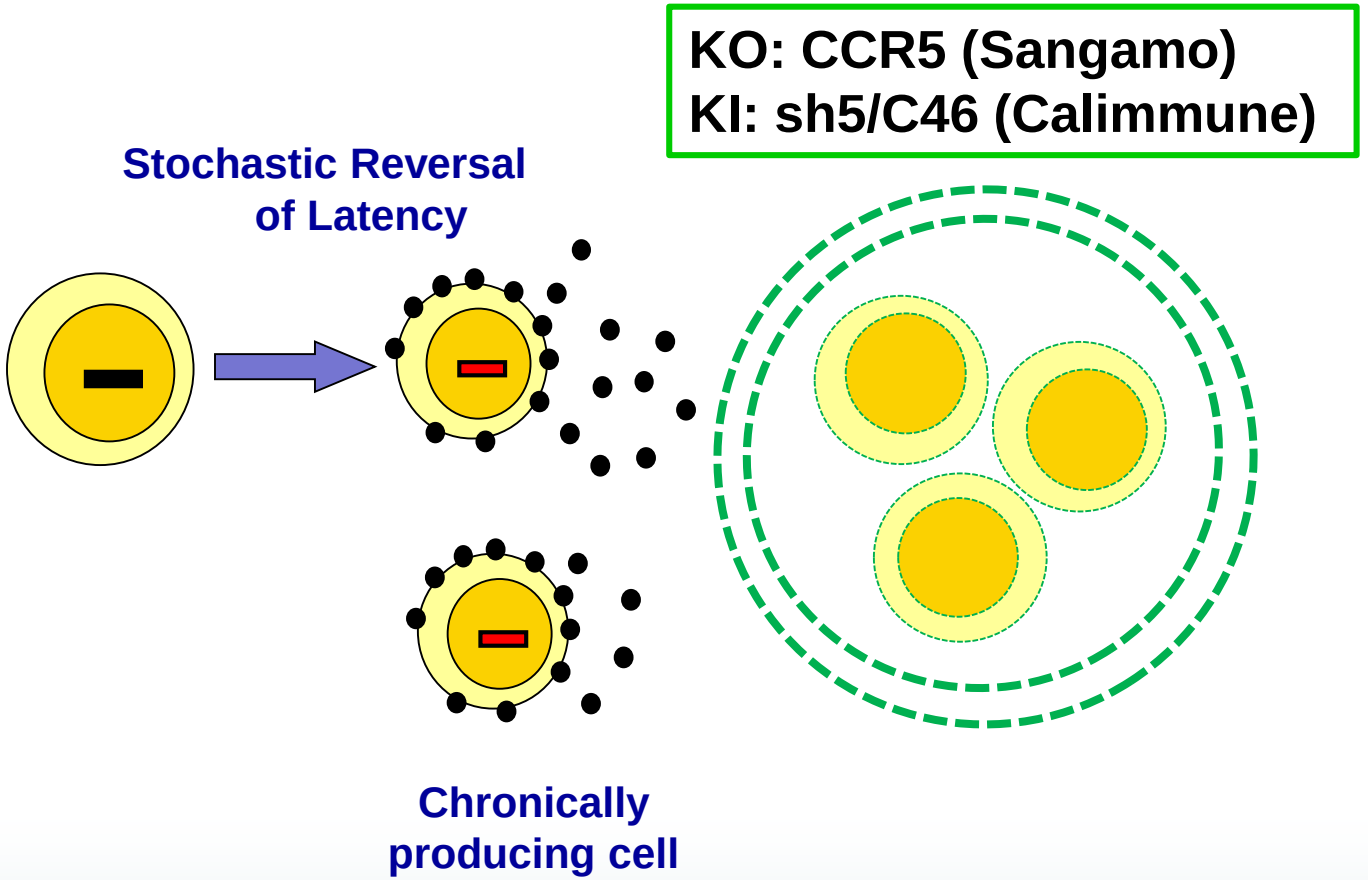
Which Cure Strategy?



Which Cure Strategy?



Host cell modification



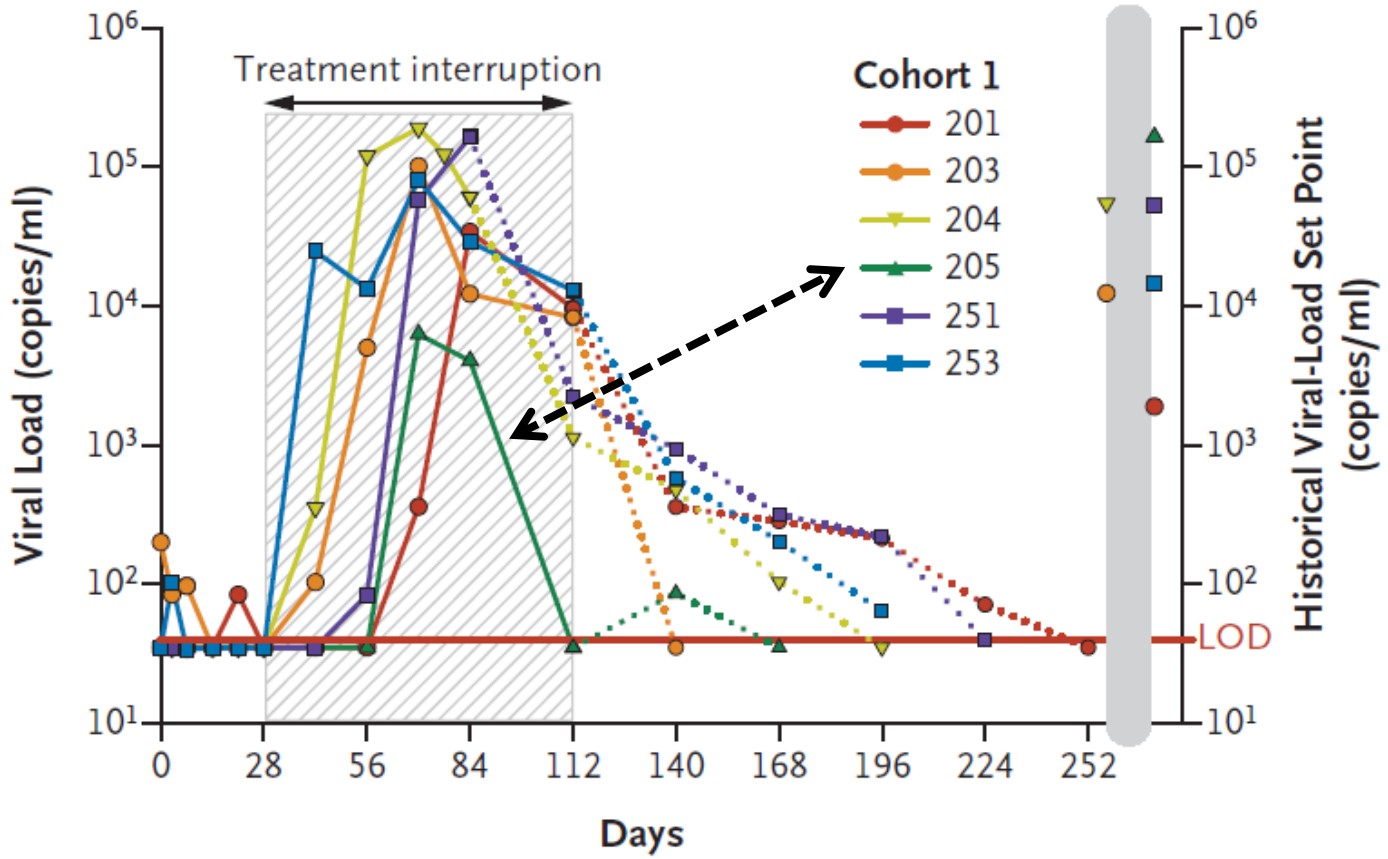
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

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

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

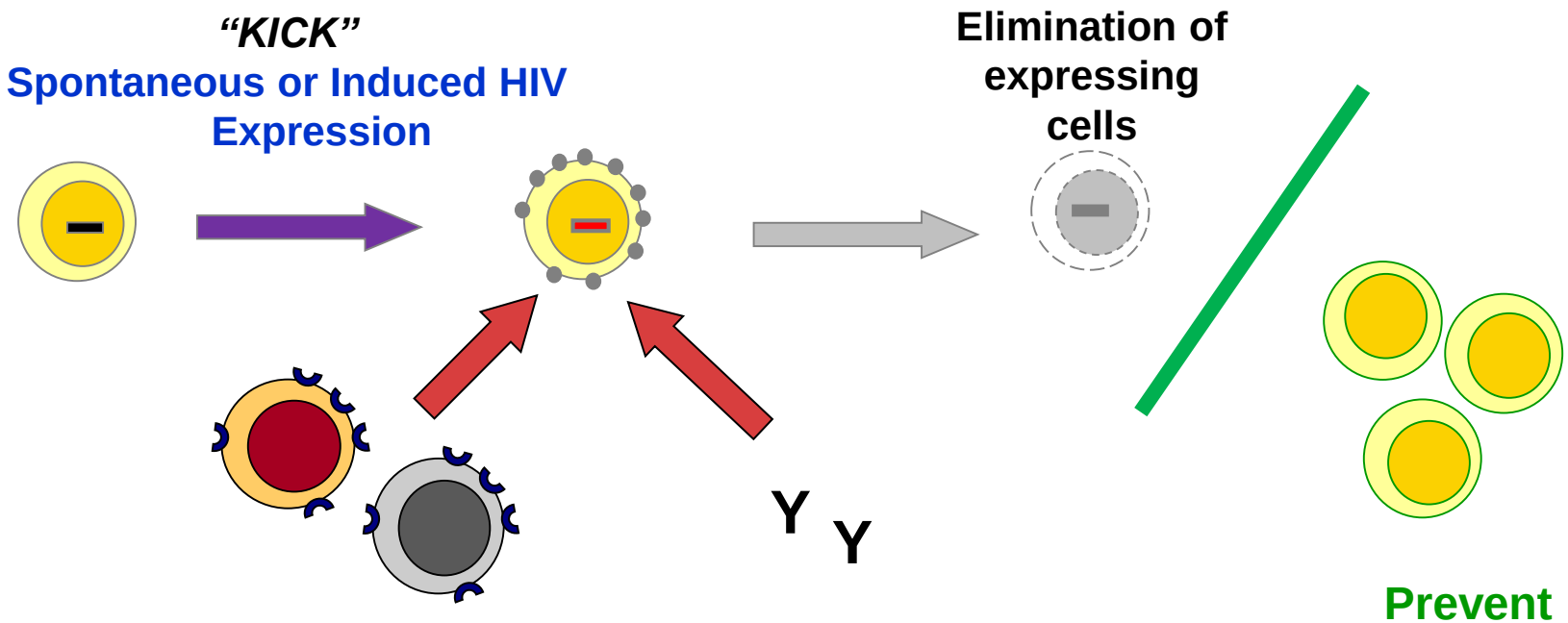
- CCR5-modified CD4 T cells at 1 week post infusion constituted 13.9% of circulating CD4 T cells
- Modified cells had an estimated mean half-life of 48 weeks
- After ART interruption, decline in circulating CCR5-modified cells (−1.81 cells per day) was significantly less than the decline in unmodified cells (−7.25 cells per day) ($P = 0.02$)
- HIV RNA became undetectable in one of four patients who could be evaluated



- Challenges moving forward:
  - Is cytoreductive therapy needed? Acceptable?
  - Is there X4 escape?
  - Scalability? Cost?

Which Cure Strategy?

“Kick, Kill & Control” HIV Cure Strategy



“KICK” Candidates (LRAs)

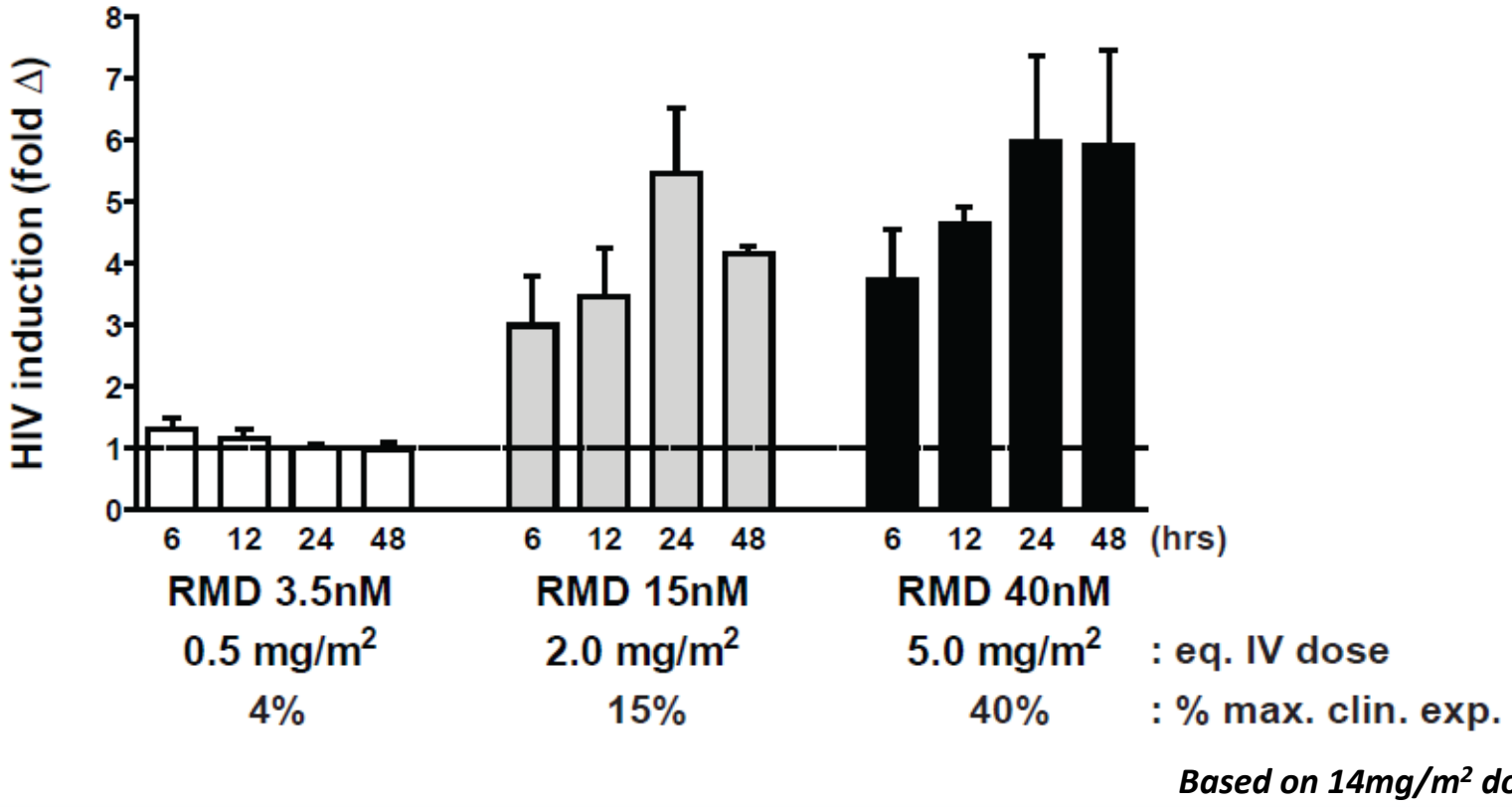
- PKC agonists
  - most potent activators but toxicity of concern
- Brd4 inhibitors
  - JQ1 and analogs
- TLR agonists
  - TLR-4, 7
- Cytkokines
  - IL-15
- SMAC mimetics (non-canonical NFkB)
  - AZD5582
- HDACi
  - Vorinostat, panobinostat, **romidepsin**

ACTG A5315:
A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

Deborah McMahon, MD, for the A5315 Team

University of Pittsburgh

RMD Activates Intracellular HIV Expression Ex Vivo at Concentrations Expected from Doses of 2 and 5 mg/m^2



Based on 14mg/m^2 dose

Ex vivo HIV-1 induction from resting CD4 cells from donors on ART

Wei DG, et al. (2014) PLoS Pathog 10(4): e1004071. https://doi.org/10.1371/journal.ppat.1004071

A5315 Study Design

- **Study intervention**: Participants randomized 4:1 to receive i.v. RMD (12 participants/cohort) or **placebo** (0.9% saline) (3 participants/cohort).

  - Cohort 1: 12 participants (0.5 mg/m2 RMD in 0.9% saline) - completed
  - Cohort 2: 12 participants (2.0 mg/m2 RMD in 0.9% saline) - completed
  - Cohort 3: 12 participants (5.0 mg/m2 RMD in 0.9% saline) - completed

Ongoing, fully enrolled, not presented today:

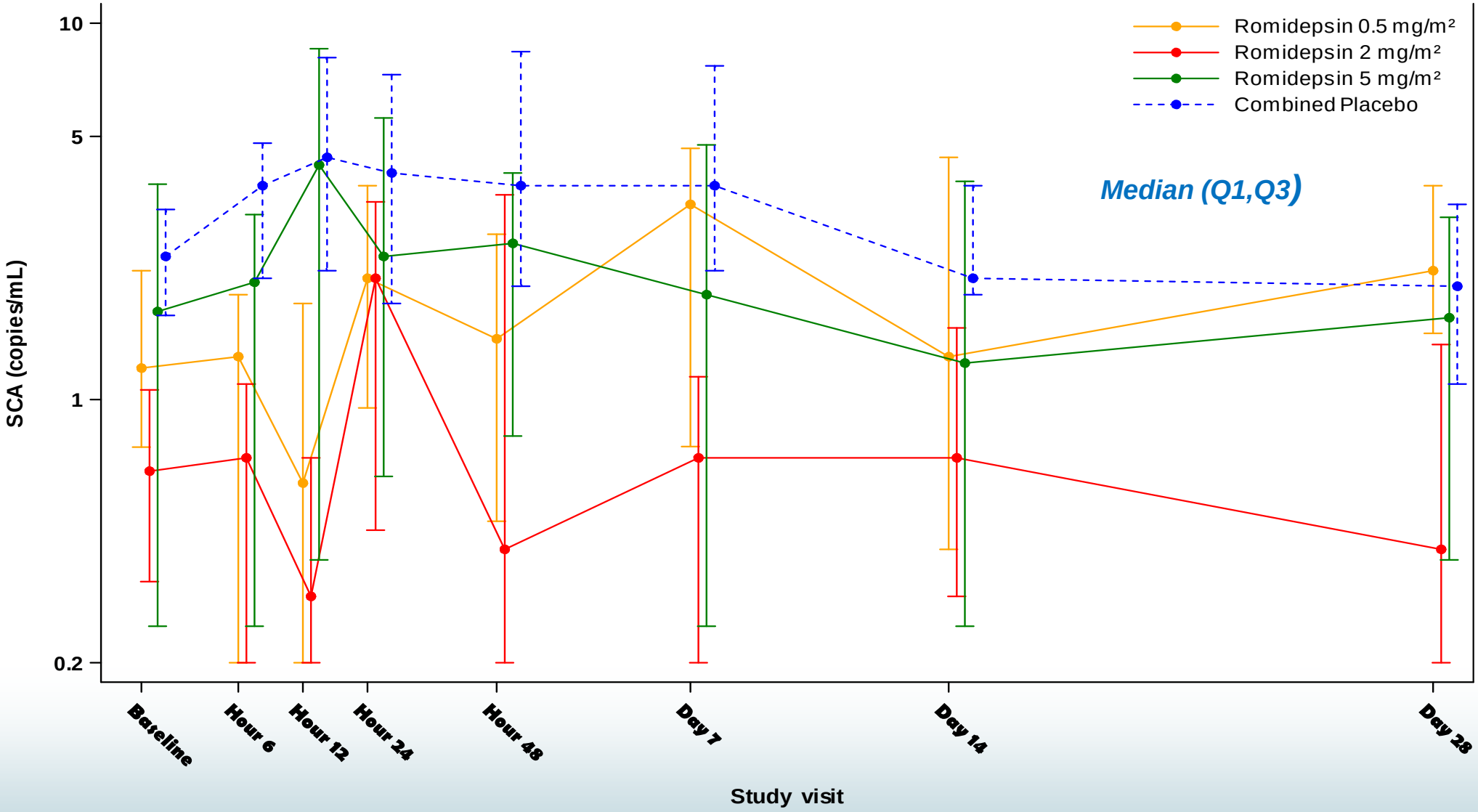
- Cohort 4: 12 participants (5.0 mg/m2 RMD in 0.9% saline q14d x 4 doses)

Dose-Dependent Romidepsin Concentrations (ng/mL) Median (Q1,Q3)

Time Post-Infusion	Romidepsin Dose		
	0.5 mg/m^2	2 mg/m^2	5 mg/m^2
Hour 4	**12 (6.6, 16.7)**	**75.2 (54.1, 84.0)**	**89 (53.3, 127.5)**
Hour 6	**3.2 (-,-)***	**2.7 (1.7, 4.2)**	**2.6 (2.0, 5.0)**

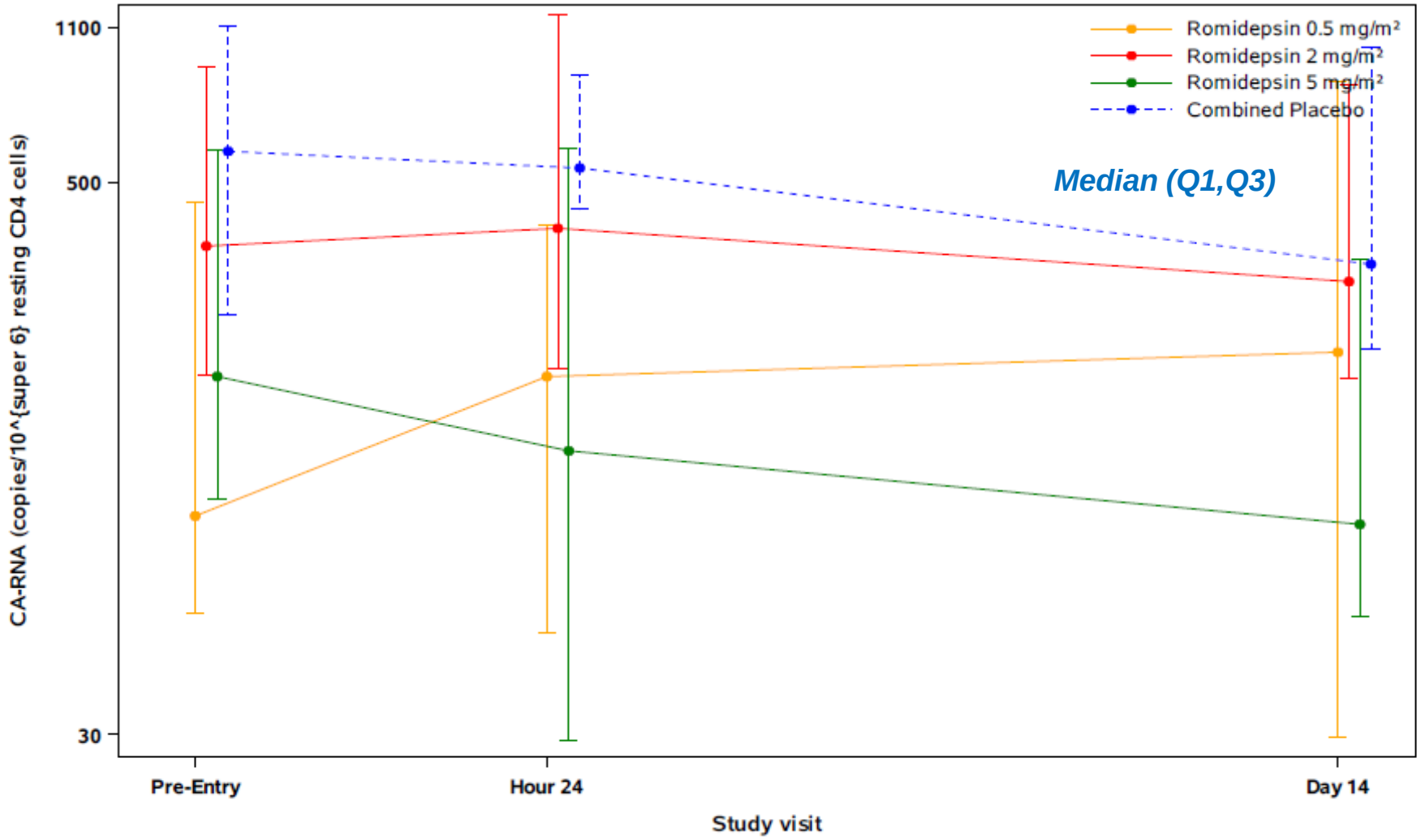
*N=1 detectable; Q1,Q3 not available

Plasma Viremia by SCA Cohorts 1-3



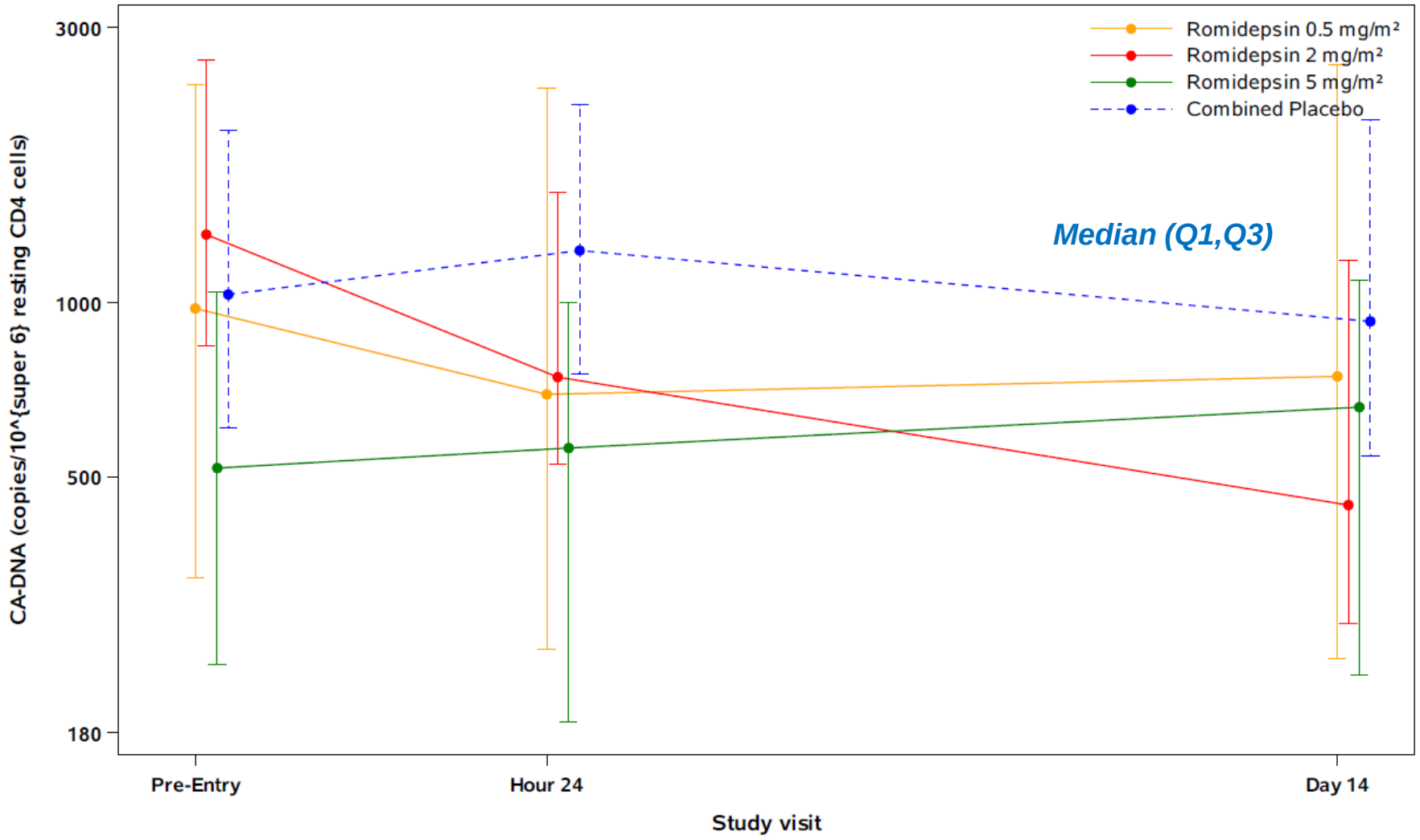
CA-HIV RNA Cohorts 1-3

Copies/10^6 resting CD4+ cells



CA-HIV DNA Cohorts 1-3

Copies/10^6 resting CD4+ cells



Dose-Dependent Increase in CD4+ T-cell Activation

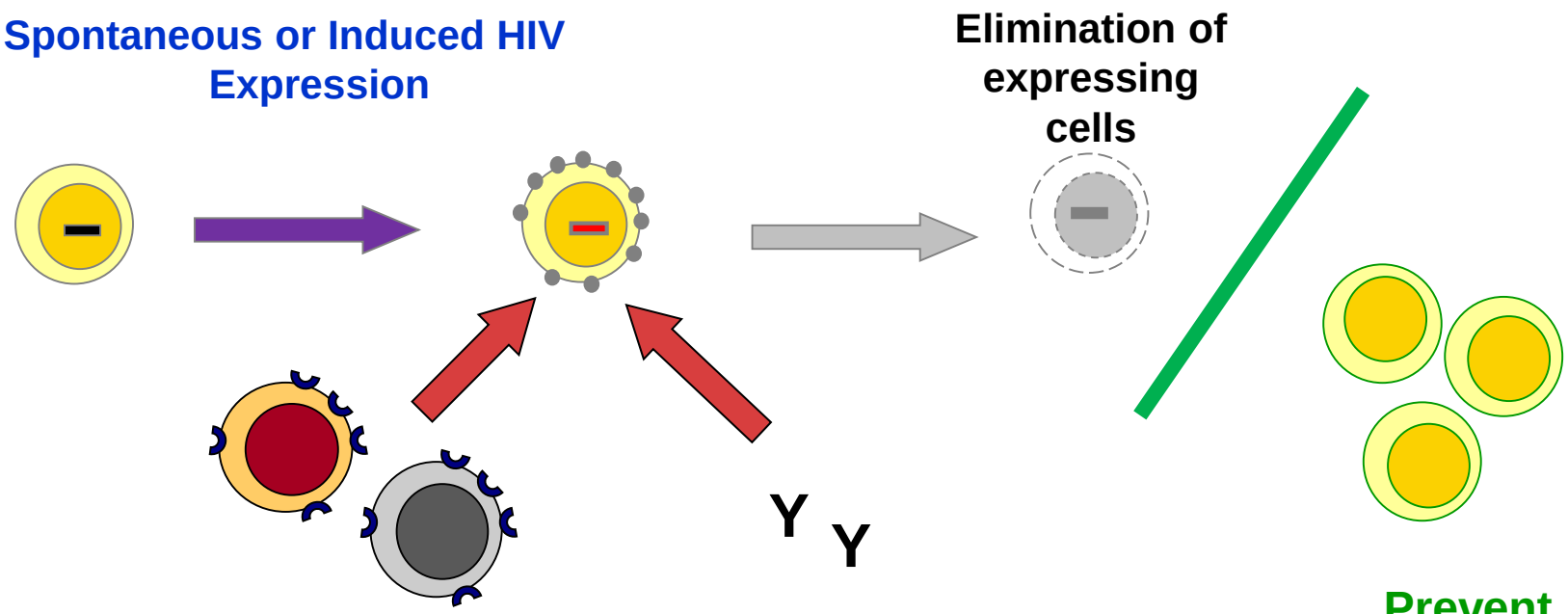
CD4+ CD38+ HLA-DR+ (median % change from pre-dose)				
Time point	Romidepsin Dose			P-value*
	0.5 mg/m²	**2 mg/m²**	**5 mg/m²**	
Day 2	**0.3%**	**0.5%**	**0.8%**	**0.07**
Day 7	**-0.1%**	**1.6%**	**1.7%**	**0.008**
Day 28	**0.4%**	**0.9%**	**3.1%**	**0.022**

*Jonckheere-Terpstra Test for trend

Summary

- Single dose RMD was safe and generally well-tolerated
  - Administered at doses below the MTD
- RMD exposures were dose-dependent
  - At levels a/w with proviral activation ex vivo in infected donor cells
- No increase in viremia post-infusion by SCA or Abbott M2000
  - At 24 and 48 hours or at day 7
- No change in HIV CA-RNA or CA-DNA in resting $CD4^+$ cells pre-infusion to 24 hours post-infection
  - Disconnect between ex vivo and in vivo responses
- **Multi-dose study completed (4 x 5 mg/M^2); CROI 2019**

“Kill and Control”

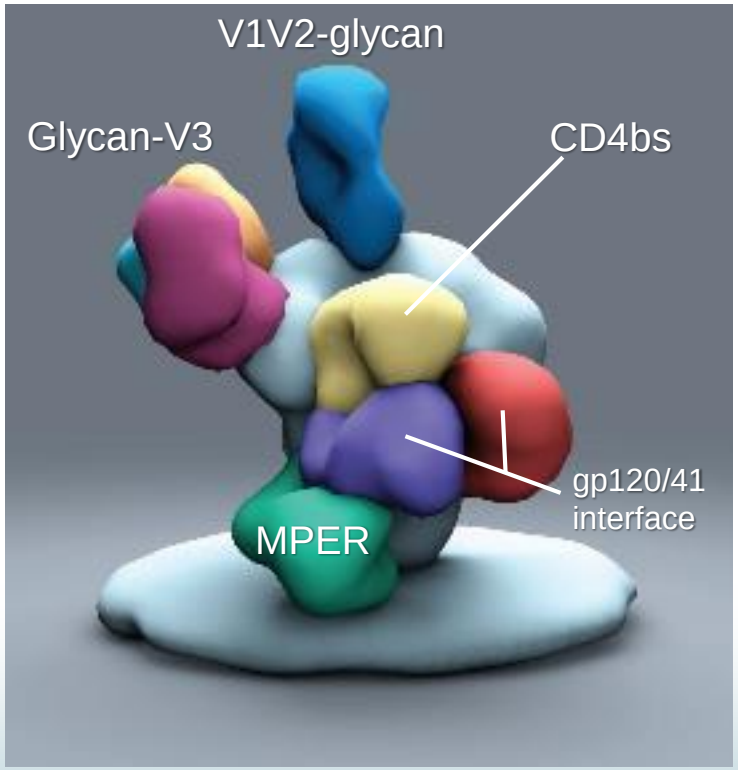


VRC-01 (A5342)

bnMAb Binding Sites

V1V2 Glycan:
PG9, PG16
PGT141-145
CAP256-VRC26.25
PGDM1400

N332 Glycan Supersite:
PGT128, DH542,
PGT121, 10-1074

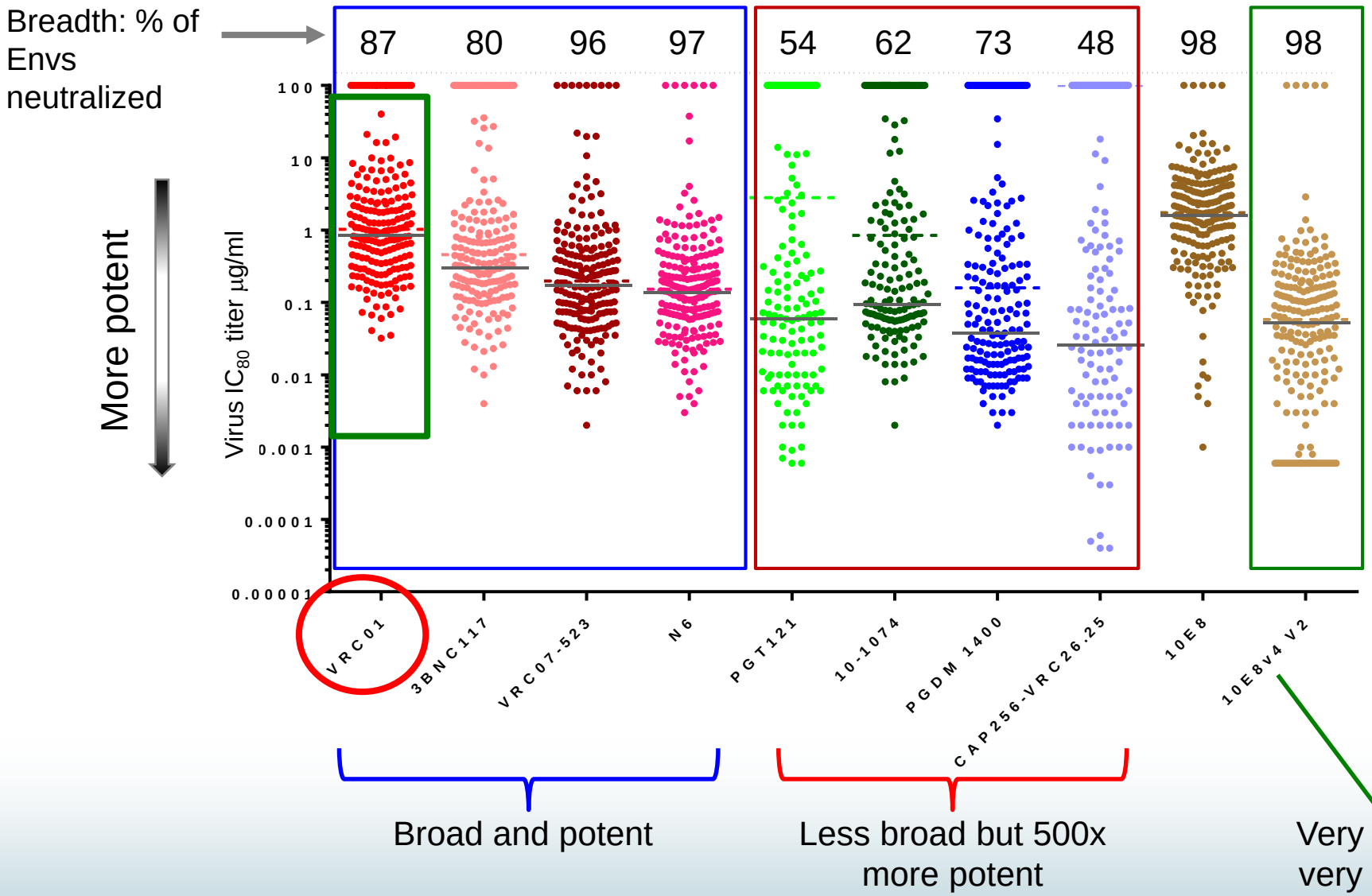


CD4 Binding Site:
PG04, CH31, 12A12, VRC13,
VRC01, VRC01LS,
VRC07-523LS, 3BNC117, N6

gp41 MPER:
2F5, 4E10, 10e8

gp120/41 interface
8ANC195
PGT151
35022

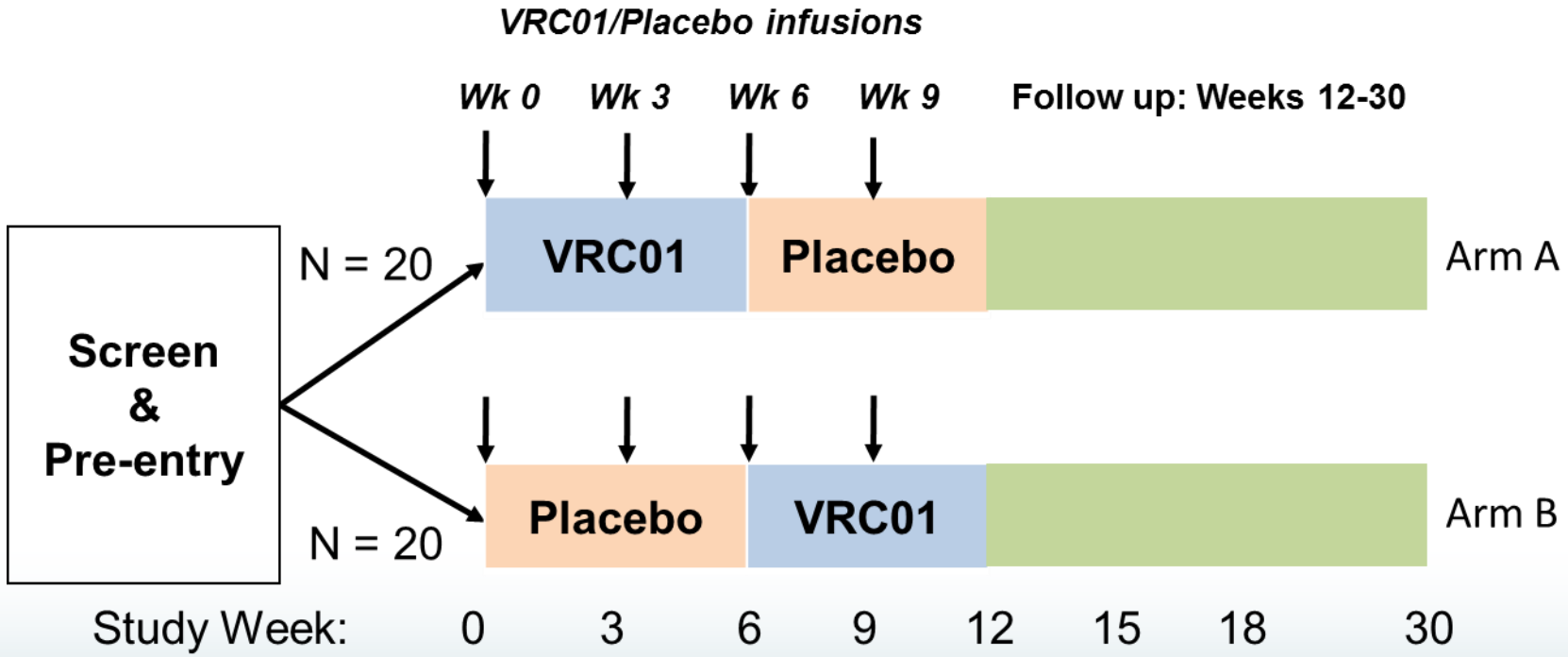
Antibody Potency/Breadth



Panel of 206 HIV Env pseudoviruses from all major clades

A5342/VRC01 Study

- Double-blind, randomized, placebo-controlled, Phase I study
- 40 participants (20 per arm)
- VRC01 40 mg/kg IV at Day 0 & 21 (Arm A) or Day 42 & 63 (Arm B)



Summary of Virologic Outcomes

Parameter Median (Q1, Q3)	Arm A	Arm B	p-value*	Arms A and B Combined		Change from Pre- to Post-VRC01	p-value**
	Change from baseline to Week 6			Pre-VRC01 values	Post-VRC01 values		
Cell-associated HIV RNA/DNA ratio^	1.12 (0.92, 2.15)	0.83 (0.57, 2.37)	0.16	0.04 (0.02 0.08)	0.05 (0.02, 0.08)	1.24 (0.61, 2.15)	0.29
Cell-associated HIV RNA (log_{10} cps/10^6 CD4 cells)	0.08 (-0.23, 0.32)	-0.08 (-0.26, 0.29)	0.39	1.55 (0.99, 1.99)	1.48 (0.99, 2.10)	0.09 (-0.23, 0.32)	0.64
Cell-associated HIV DNA (log_{10} cps/10^6 CD4 cells)	-0.06 (-0.13, 0.06)	-0.01 (-0.08, 0.13)	0.30	2.93 (2.43, 3.15)	2.92 (2.51, 3.11)	-0.05 (-0.12, 0.06)	0.19
Stimulated Virus Production from total CD4+T-cells (log_{10} cps/ml)	-0.13 (-0.51, 0.92)	0.12 (-0.52, 0.30)	0.91	2.99 (2.06, 3.37)	2.66 (2.28, 3.41)	-0.10 (-0.51, 0.44)	0.85
	Week 6		p-value***				p-value****
Plasma HIV RNA ≥1 cp/ml by single copy assay (%)	8/19 (42%)	7/19 (37%)	1.0	16/38 (42%)	14/38 (37%)		0.59

Conclusions

- In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were safe and well tolerated.
- Two high-dose infusions of VRC01 did **not** affect virologic outcomes including:
  - Residual plasma viremia
  - Cell-associated HIV RNA/DNA levels
  - Total stimulated virus production from CD4+T-cells
- Potential mechanisms being evaluated to explain the lack of response include
  - viral envelope resistance to VRC01
  - inherent inability of VRC01 to clear virus particles or env-expressing cells
  - poor penetration of VRC01 to sites of virus expression

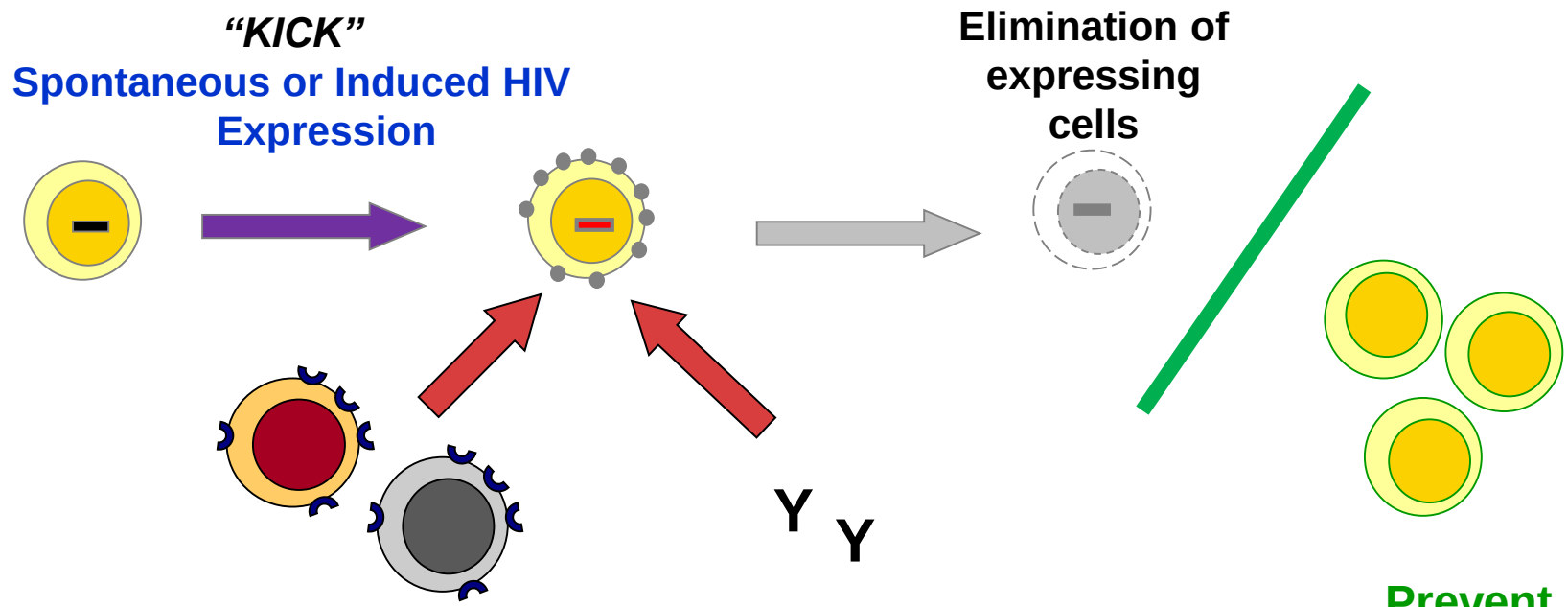
Other “Kill & Control” Candidates

- Immune Checkpoint Blocking Antibodies (ICBs)
  - Anti-PD-1/PD-L1, LAG-3, 2B4, CD160, TIM-3, others
  - A5326: anti-PD-L1 (Gay, et al. 2017)
  - ACTG 5370: anti-PD-1
  - Safety concerns
- Cellular therapies
  - CD8+T-cells with chimeric antigen receptors (CARs)
  - Activated NK cells
- Therapeutic Vaccines
  - Multiple approaches
  - CMV vector; VSV vector; Ad26/MVA vectors; Dendritic cell
  - Convserved antigens

Apologies, too many references to cite!

“Kick, Kill & Control” Strategy: Promising Macaque Studies

TLR-7 Agonist GS-9620



Stimulate & recruit CD8+ CTLs, NKs, Monocytes
“Kill & Control”

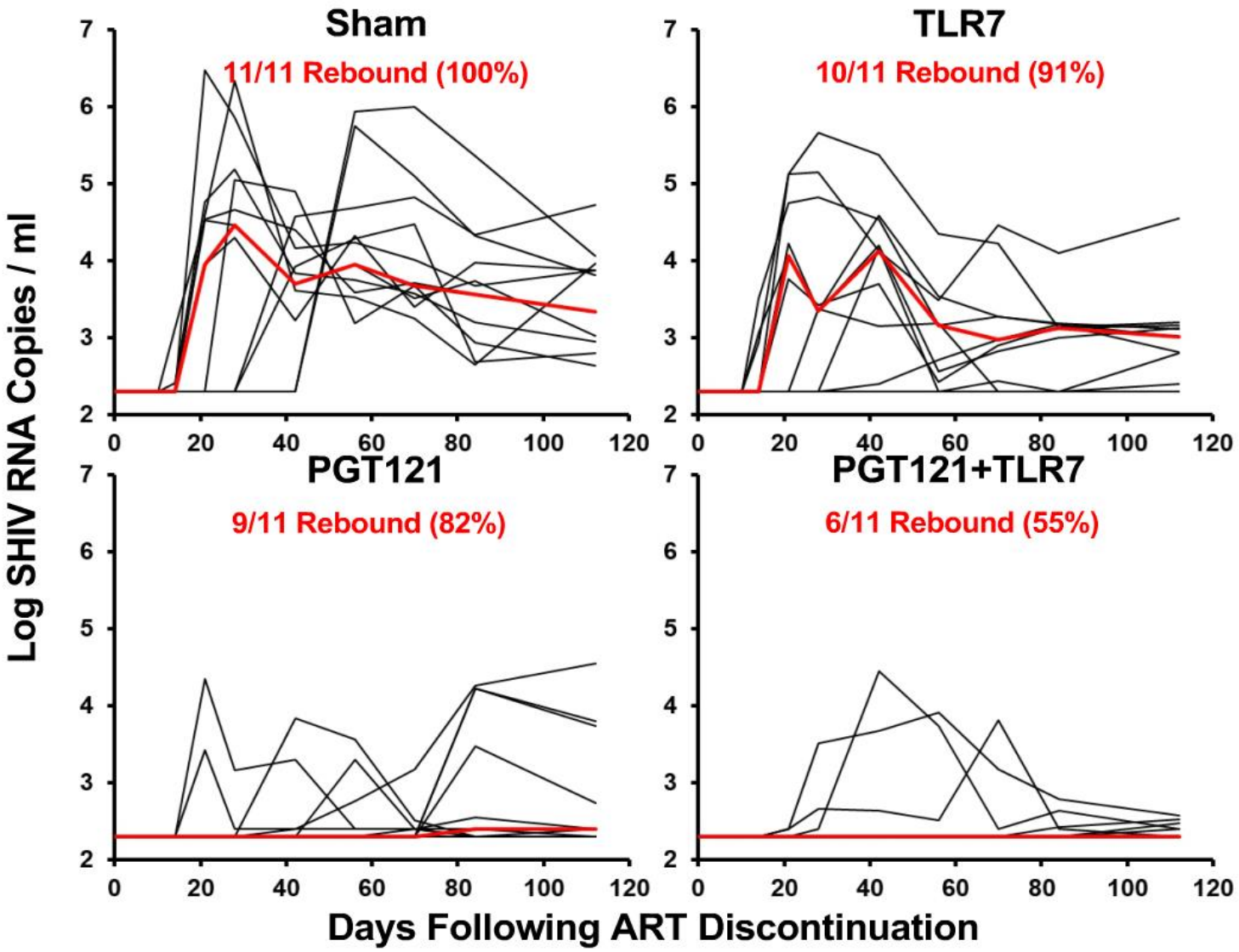
Effector molecules targeted to cells expressing HIV envelope
“Kill & Control”

Prevent Infection of CD4+T-cells

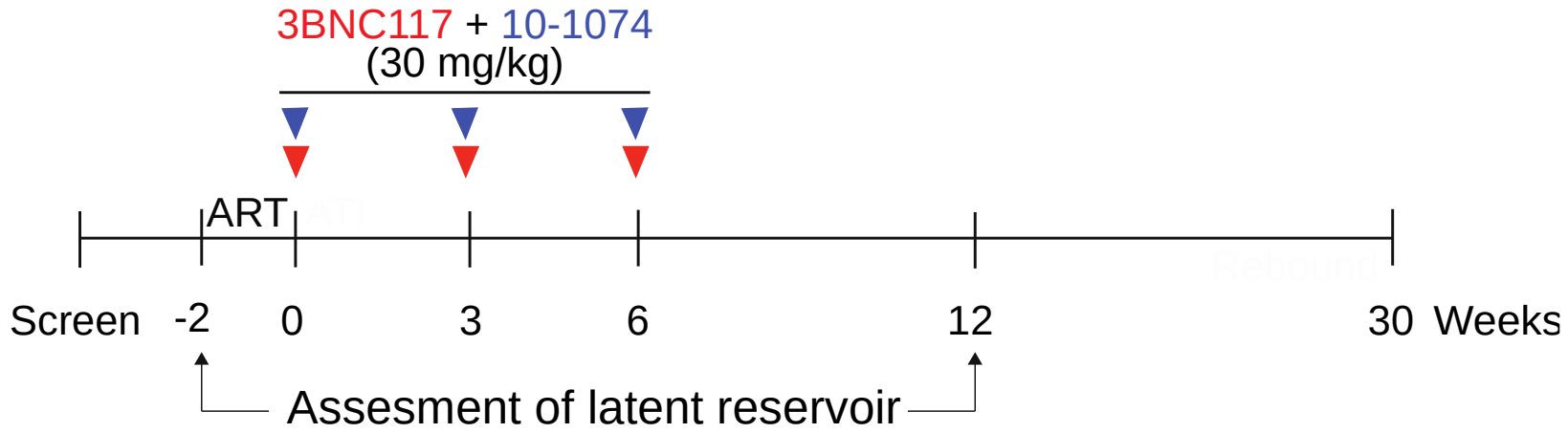
TLR-7 Agonist GS-9620 + PGT-121

Borducchi EN...Barouch DH. Nature 2018

SHIV RNA Following ART Discontinuation



3BNC117 plus 10-1074 Combination ATI Study



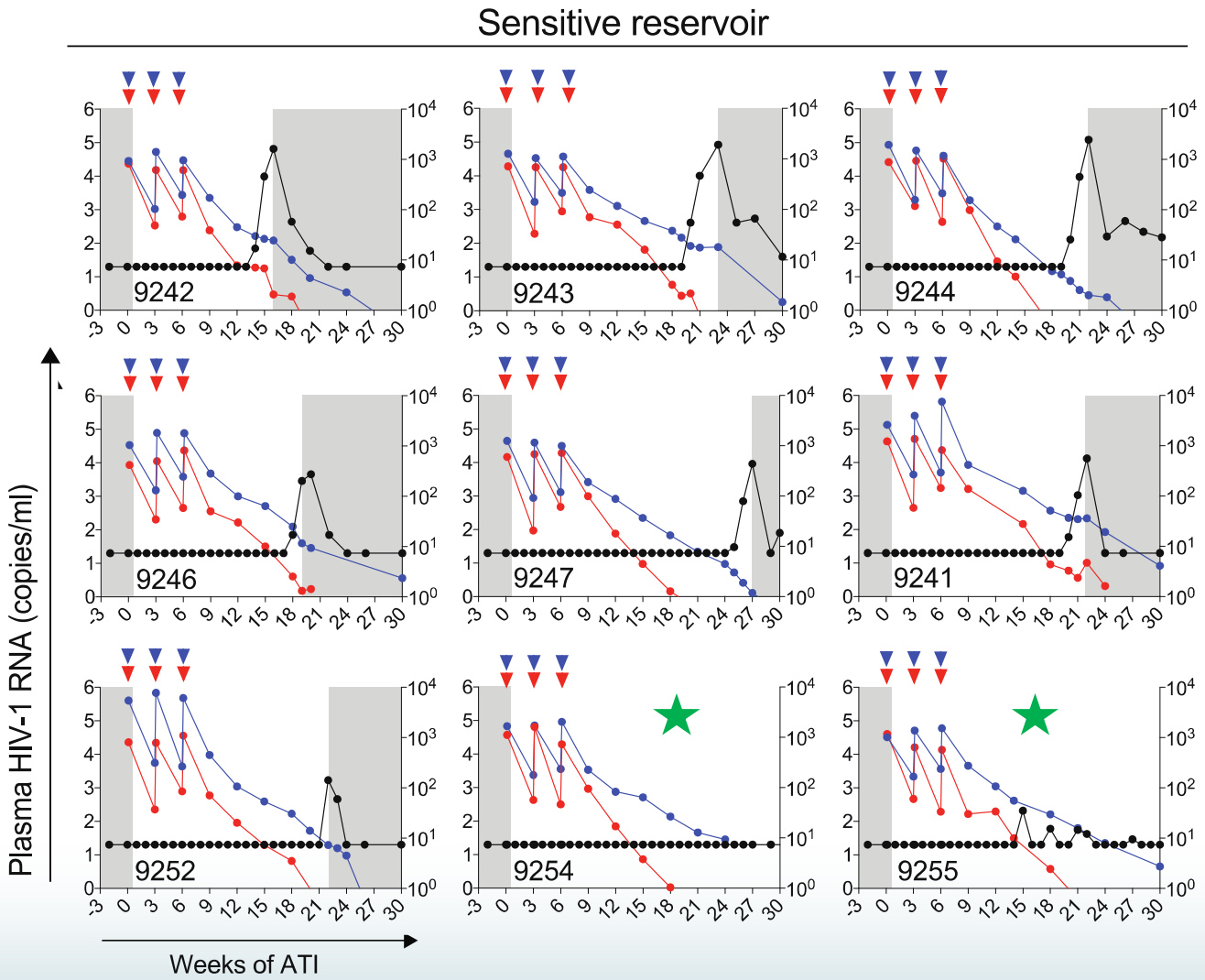
Bulk culture	+					
Q2VOA		+			+	
Near full length seq.		+			+	
Plasma SGA						+
Rebound outgrowth						+

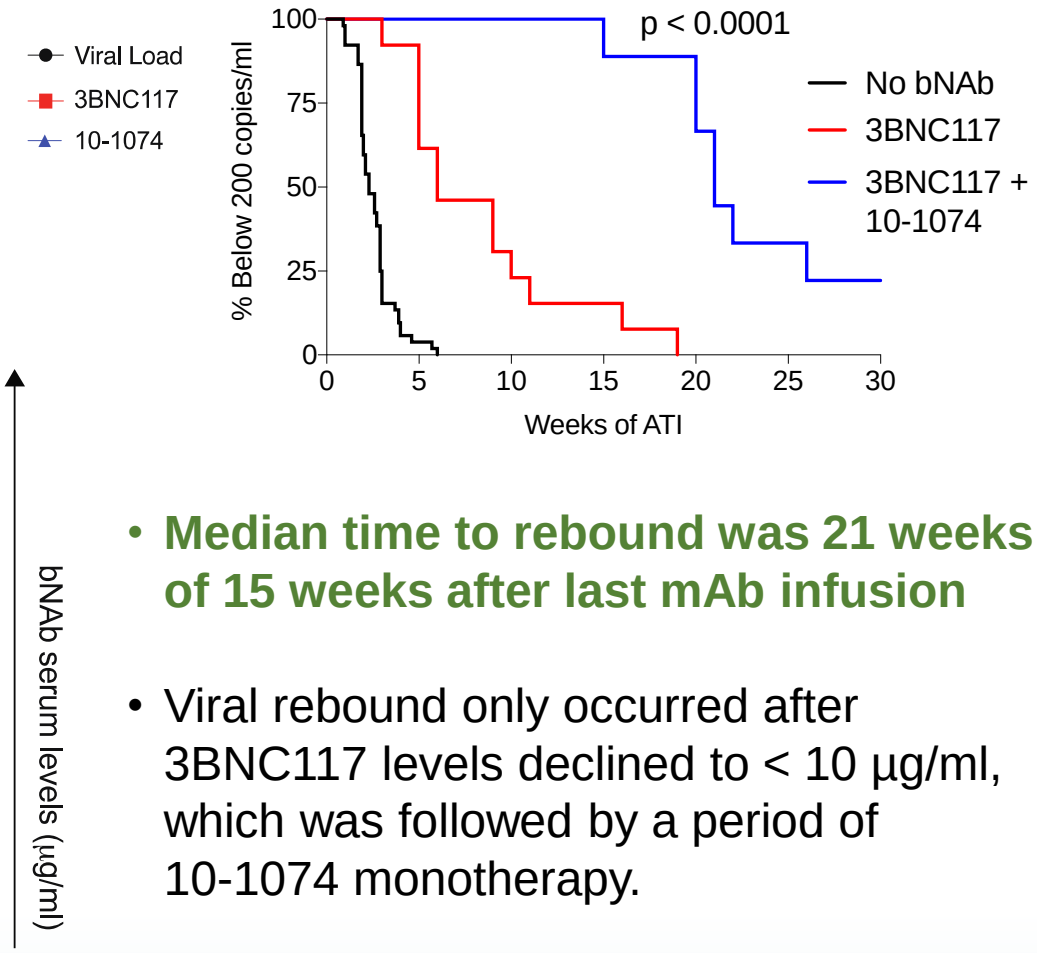
Inclusion:

- On ART > 24 months, with HIV-1 VL < 50 copies/ml x 18 months and < 20 copies/ml at screen
- Current CD4 count > 500 cells/ul
- CD4 count nadir > 200/ul

Mendoza P…Nussenzweig MC. Nature 2018

Sensitivity to Both Antibodies at Baseline





- **Median time to rebound was 21 weeks of 15 weeks after last mAb infusion**
- Viral rebound only occurred after 3BNC117 levels declined to < 10 µg/ml, which was followed by a period of 10-1074 monotherapy.

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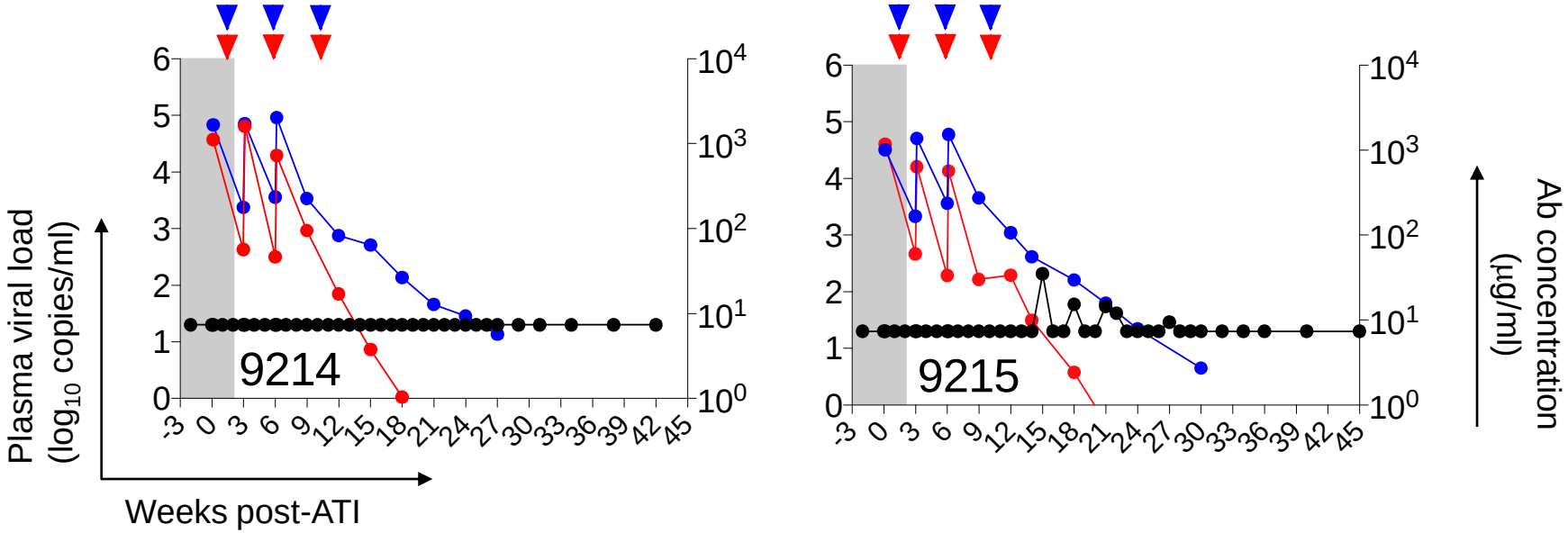
Post-treatment Controllers



Initial Viral Load 860,000
IUPM 12 weeks = $0.68/10^6$
HLA A*01, A*29, B*38, B*44
No ART detected in blood

Initial Viral Load 85,000
IUPM 12 weeks = $1.4/10^6$
HLA-A*03 A*25 **HLA-**B*18 B*44
No ART detected in blood

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Key Upcoming Human Studies

- Higher dose cohorts of GS-9620 TLR-7 agonist in HIV-1 infection
  - 8, 10, 12 mg doses q2wks
- bnMAb with greater potency, longer-half life, better effector function
  - Combinations: PGT121 or 10-1074 (V3) + VRC07-523LS or 3NC117 or N6 (CD4bs)
  - Do they affect the reservoir? Time to Rebound?
- Human Therapeutic Vaccines:
  - RV405: Ad26/MVA vaccination in F1-4
  - **DC-03: Dendritic cell, HIV conserved peptide in F1-2**
  - **DC-04: Dendritic cell, HIV conserved peptide vs. whole virus in F6**
  - PennVax: HIV gag/pol or gag/pol/env with IL-12 DNA vaccine
  - A5369: HIV gag conserved element DNA vaccine
- **“Kitchen Sink”**
  - Vaccine + TLR + 2 or 3 bnMAb

How does the future look for HIV cure?

There are always unrealistic optimists and skeptics

Remember, 1 pill a day to treat HIV was a once fantasy!

Lab Collaborators

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- Nathan Enick
- Elias Halvas
- Jana Jacobs
- Kevin Joseph
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leidos

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GILEAD

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Sites (CRS)

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UNC Chapel Hill
Massachusetts Gen Hospital
The Ohio State University
Penn Therapeutics
The Ponce de Leon Center
UCLA Care Center
UCSF
Univ Colorado Hospital
Univ Pittsburgh
Univ Rochester
Univ Washington

Study Participants

Industry Partners

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Others

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CRS Lab Staff
Pitt ISL Staff
Pitt VSL Staff
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Questions?


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STUDY VOLUNTEERS!

What's Ahead?