

HIV Cure

Blood/Plasma Donor Science and HIV Cure Synergies

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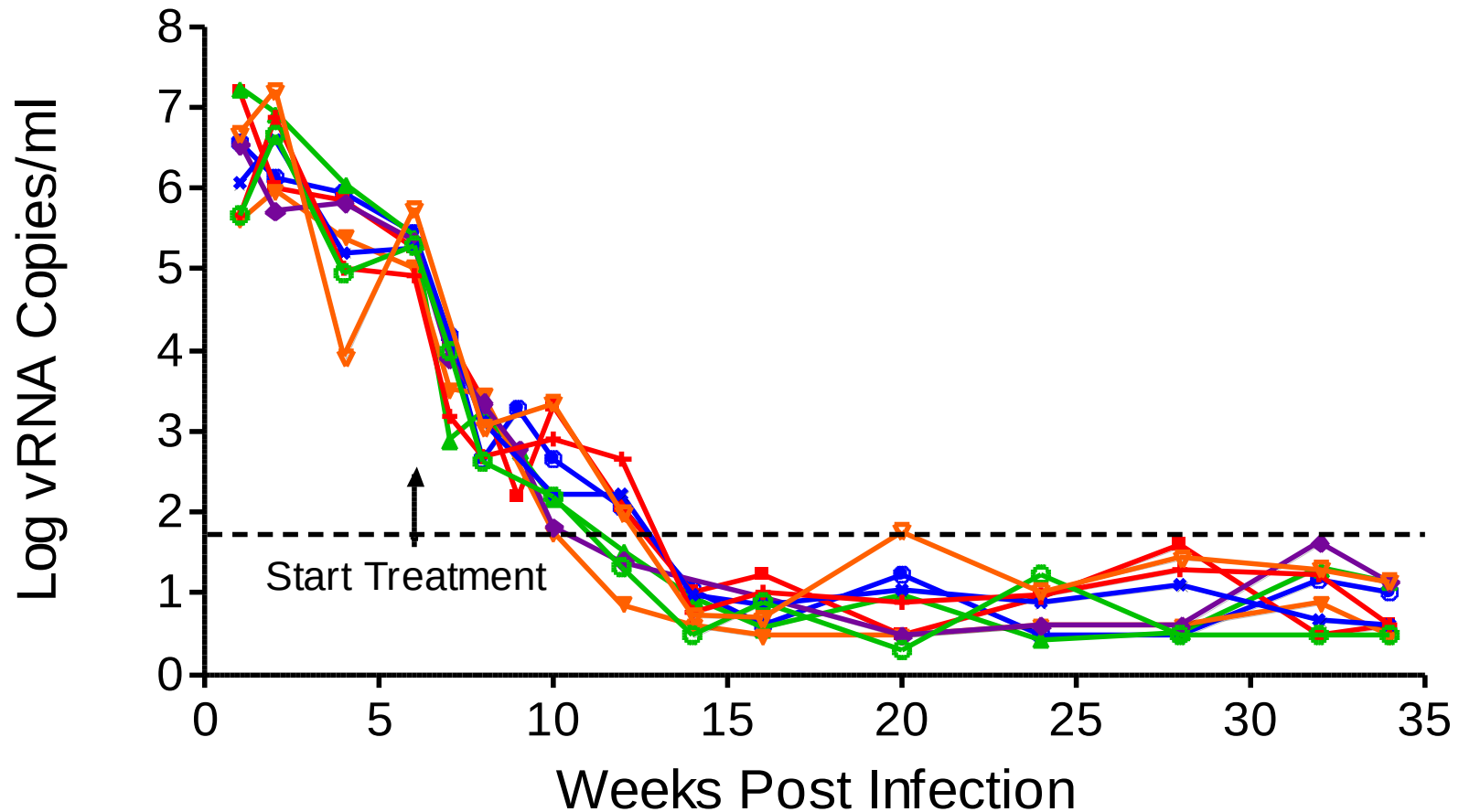
HIV Cure and Blood/Plasma Donor Science

- Pathogenesis
- Assay development
- Donor screening concerns

HIV Cure *Background*

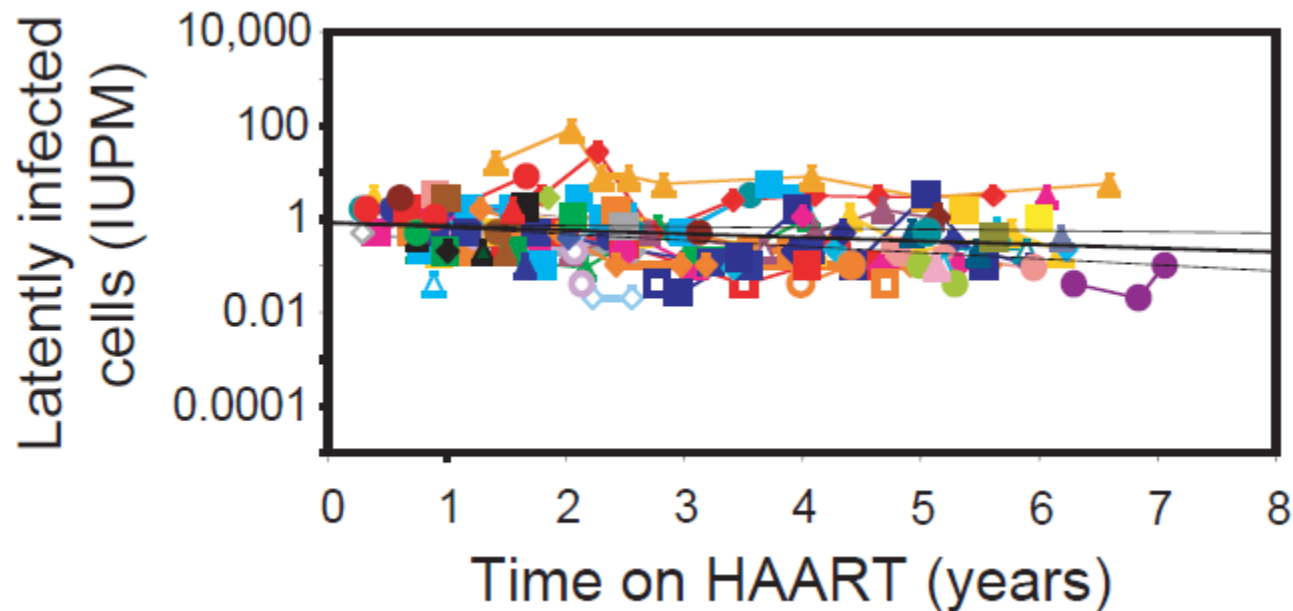
Although ART reduces viremia > 6 to $7 \log_{10}$ some virus indefinitely (0.1 - 3 copies RNA/mL)

Source of the viremia it is not known but is not from an actively replicating population



Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4⁺ T cells

Janet D Siliciano¹, Joleen Kajdas¹, Diana Finzi², Thomas C Quinn^{1,2}, Karen Chadwick³, Joseph B Margolick³, Colin Kovacs⁴, Stephen J Gange⁵ & Robert F Siliciano¹



Why does HIV persist during effective antiretroviral therapy?

- “Latent” infection in cells destined to persist indefinitely (memory CD4+ T cells)
 - Homeostatic T cell proliferation
 - HIV integration in cell growth genes
 - Inflammation/T cell activation
 - Virus production
 - Target cell generation
 - Immune dysfunction (poor clearance)
- HIV “spread” (replication)

How will we cure HIV?

- Gene and cell-based therapy
 - Proof of concept: Berlin Patient
 - Multiple feasible pathways, none yet scalable
- Immunotherapy: remission (elite control, post-treatment control)
 - Cancer model (vaccines, immune-modifying therapy)
- Shock and kill: reservoir reduction
- Early ART: Prevention of latency

HIV Disease Pathogenesis

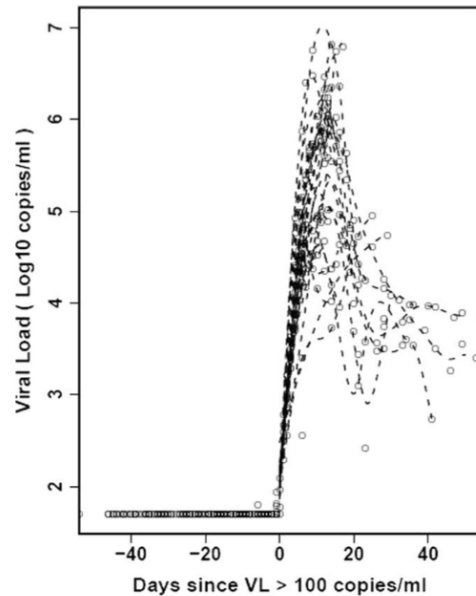
*Leveraging blood/plasma donor
cohorts to investigate
pathogenesis of “hyperacute”
HIV infection*



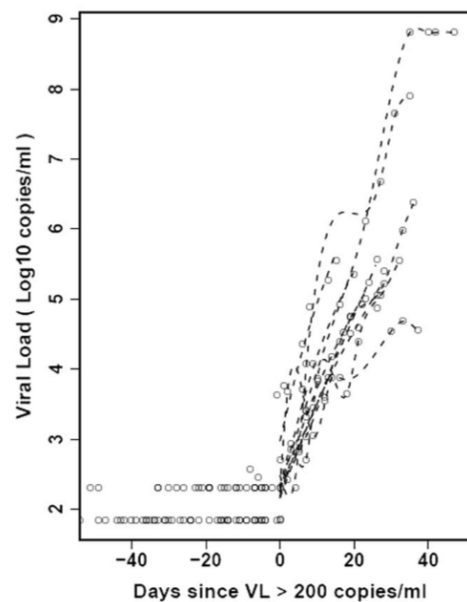
Induction of a Striking Systemic Cytokine Cascade prior to Peak Viremia in Acute Human Immunodeficiency Virus Type 1 Infection, in Contrast to More Modest and Delayed Responses in Acute Hepatitis B and C Virus Infections[▽]

Andrea R. Stacey,^{1†} Philip J. Norris,^{2,3†} Li Qin,^{4,5} Elizabeth A. Haygreen,¹ Elizabeth Taylor,¹ John Heitman,² Mila Lebedeva,² Allan DeCamp,⁴ Dongfeng Li,^{4,6} Douglas Grove,⁴ Steven G. Self,^{4,5} and Persephone Borrow^{1*}

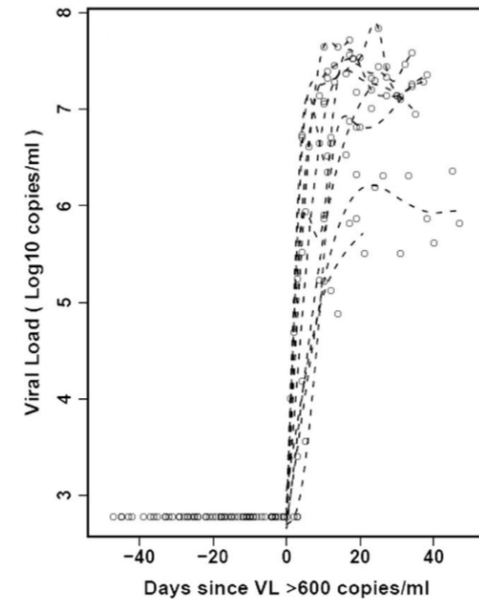
HIV



HBV



HCV

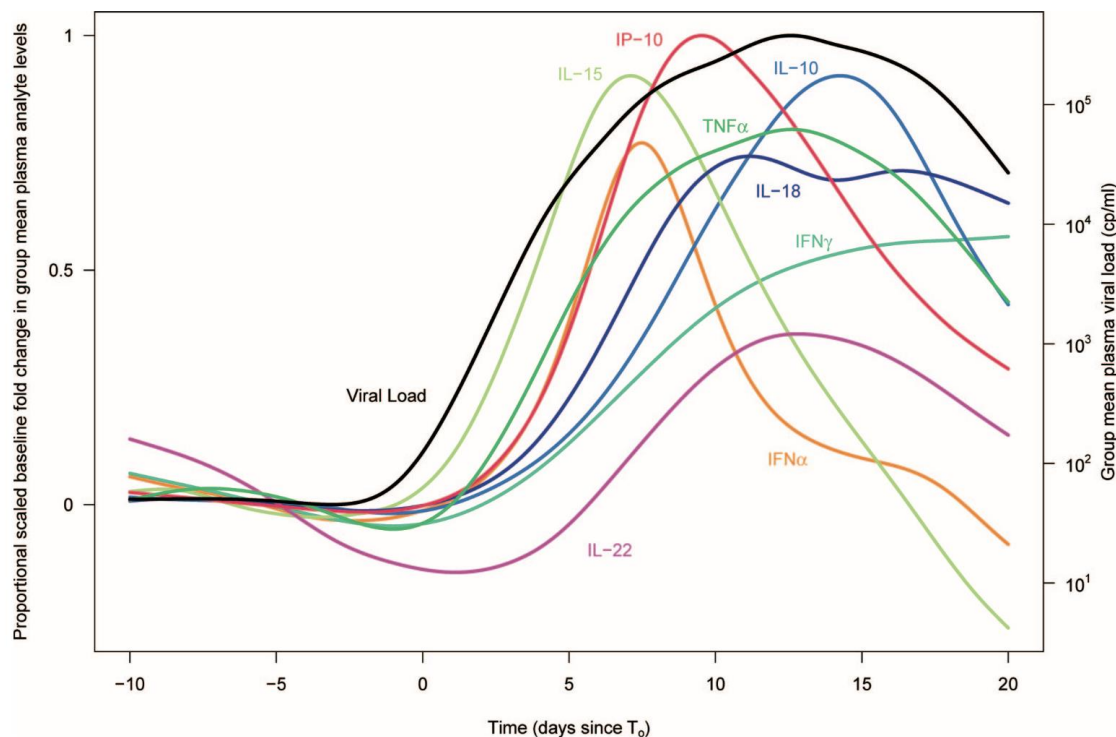


Serial plasma samples during eclipse and exponential virus expansion phase (n=35 HIV, n=10 HBV, n=10 HCV)



Induction of a Striking Systemic Cytokine Cascade prior to Peak Viremia in Acute Human Immunodeficiency Virus Type 1 Infection, in Contrast to More Modest and Delayed Responses in Acute Hepatitis B and C Virus Infections[▽]

Andrea R. Stacey,^{1†} Philip J. Norris,^{2,3†} Li Qin,^{4,5} Elizabeth A. Haygreen,¹ Elizabeth Taylor,¹ John Heitman,² Mila Lebedeva,² Allan DeCamp,⁴ Dongfeng Li,^{4,6} Douglas Grove,⁴ Steven G. Self,^{4,5} and Persephone Borrow^{1*}



A massive inflammatory response with long-term consequences is caused by acute HIV



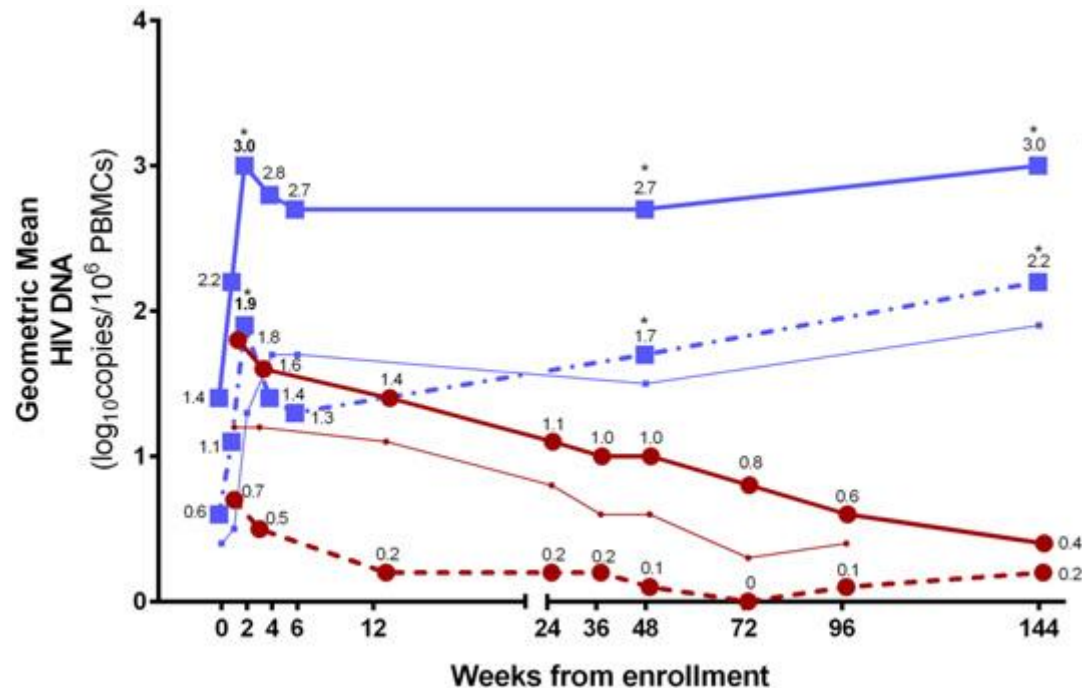
Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection

Eberhard W. Fiebig^{a,b}, David J. Wright^c, Bhupat D. Rawal^d, Patricia E. Garrett^e, Richard T. Schumacher^e, Lorraine Peddada^f, Charles Heldebrant^f, Richard Smith^g, Andrew Conrad^g, Steven H. Kleinman^{c,h} and Michael P. Busch^{a,d,i}

Marker							
Stage	RNA	P24 Antigen	Antibody (EIA)		Western blot	Duration in days (95% CI) ^a	
			NS	S		Individual	Cumulative
I	+	–	–	–	–	5.0 (3.1, 8.1)	5.0 (3.1, 8.1)
II	+	+	–	–	–	5.3 (3.7, 7.7)	10.3 (7.1, 13.5)
III	+	+	–	+	–	3.2 (2.1, 4.8)	13.5 (10.0, 17.0)
IV	+	+/-	–	+	I	5.6 (3.8, 8.1)	19.1 (15.3, 22.9)
V	+	+/-	+/-	+	+ ^b	69.5 (39.7, 121.7)	88.6 (47.4, 129.8)
VI	+	+/-	+	+	+	Open-ended	Open-ended

HIV DNA Set Point is Rapidly Established in Acute HIV Infection and Dramatically Reduced by Early ART☆☆☆

Jintanat Ananworanich ^{a,b,c,*}, Nicolas Chomont ^{d,e,1}, Leigh Ann Eller ^{a,b}, Eugene Kroon ^{c,f}, Sodsai Tovanabutra ^{a,b}, Meera Bose ^{a,b}, Martin Nau ^{a,b}, James L.K. Fletcher ^c, Somporn Tipsuk ^c, Claire Vandergeeten ^{e,1}, Robert J. O'Connell ^d, Suteeraporn Pinyakorn ^{a,b}, Nelson Michael ^a, Nittaya Phanuphak ^c, Merlin L. Robb ^{a,b}, on behalf of the, RV217 and RV254/SEARCH010 study groups:

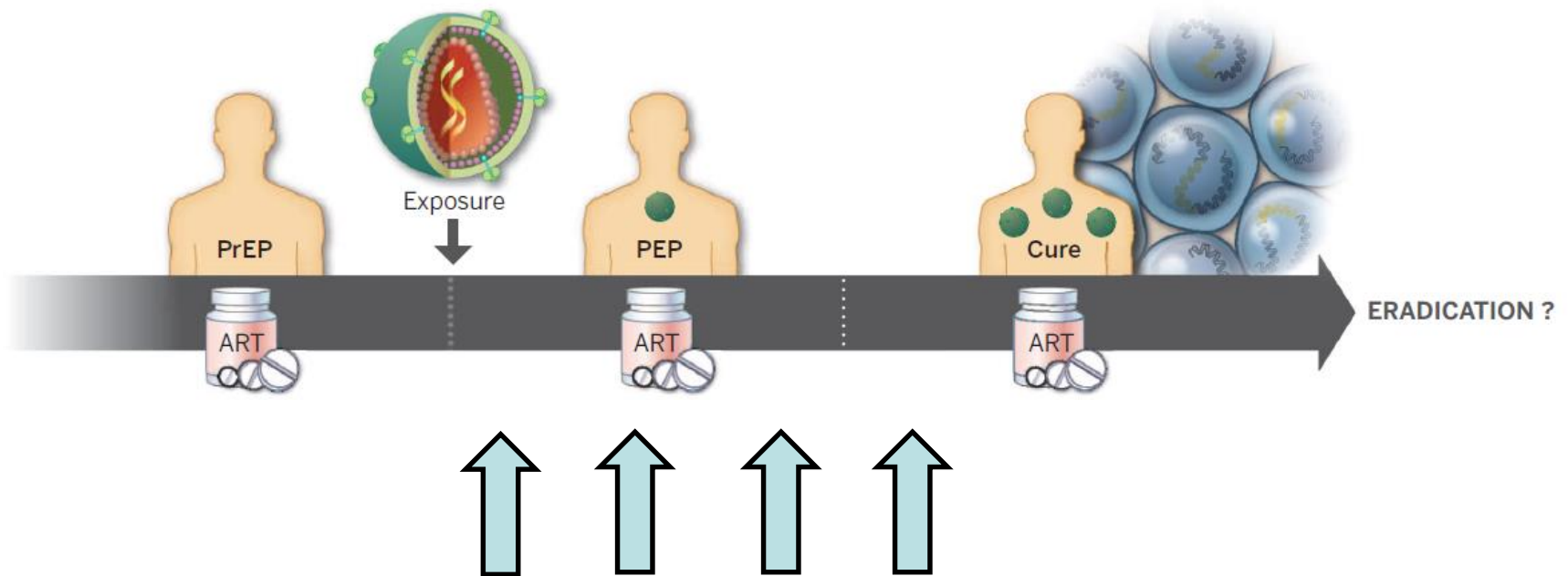


At about the time HIV RNA becomes detectable, the reservoir size begins to increase dramatically, with an apparent 100-fold increase over the next two weeks

Reservoir largely established by week 4 of infection

Can we use ART to prevent latency?

PEP/PrEP/Cure Continuum



Inadvertent transfusion of HIV infected blood

Prevention of HIV transmission with postexposure prophylaxis (TNF/FTC/RTV/DRV/RTG) for 3 months

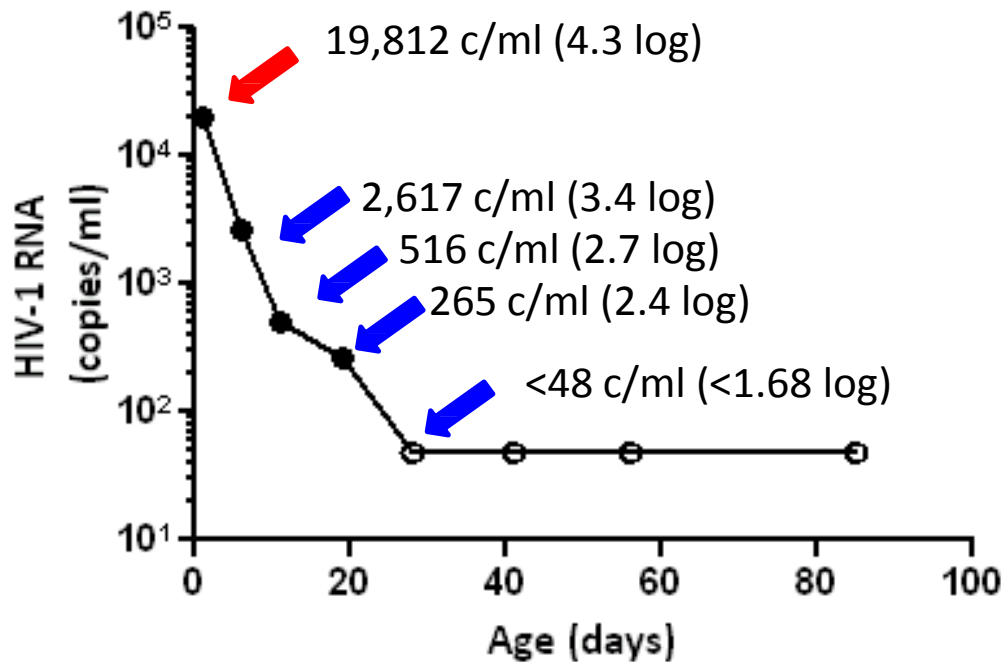
Day posttransfusion	Clinical course	Clinical laboratory testing				
		HIV ab ELISA/WB ^a	Architect HIV-1/2 Ag/Ab Combo ^b	Line immunoassay confirmation ^c	HIV-1 DNA (Blood) ^d	Quantitative HIV-1 RNA PCR ^e
Donor -1		Positive				9740 copies/m
Patient -1		Negative				
0	Transfusion Start ART	Positive				
1					ND	ND
4			463.44	Pos	ND	ND
34					ND	ND
50			132.74	Pos	ND	ND
78	Stop ART				ND	ND
82			33.89	Pos	ND	ND
91						
98					ND	ND
105					ND	ND
112			8.43	Pos	ND	ND
119					ND	ND
126			4.5	Pos	ND	ND
133					ND	ND
140			2.73	Pos	ND	ND
154			1.62	Pos	ND	ND
175			0.69	Neg	ND	ND
240			0.19	Neg	ND	ND

NEJM



Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

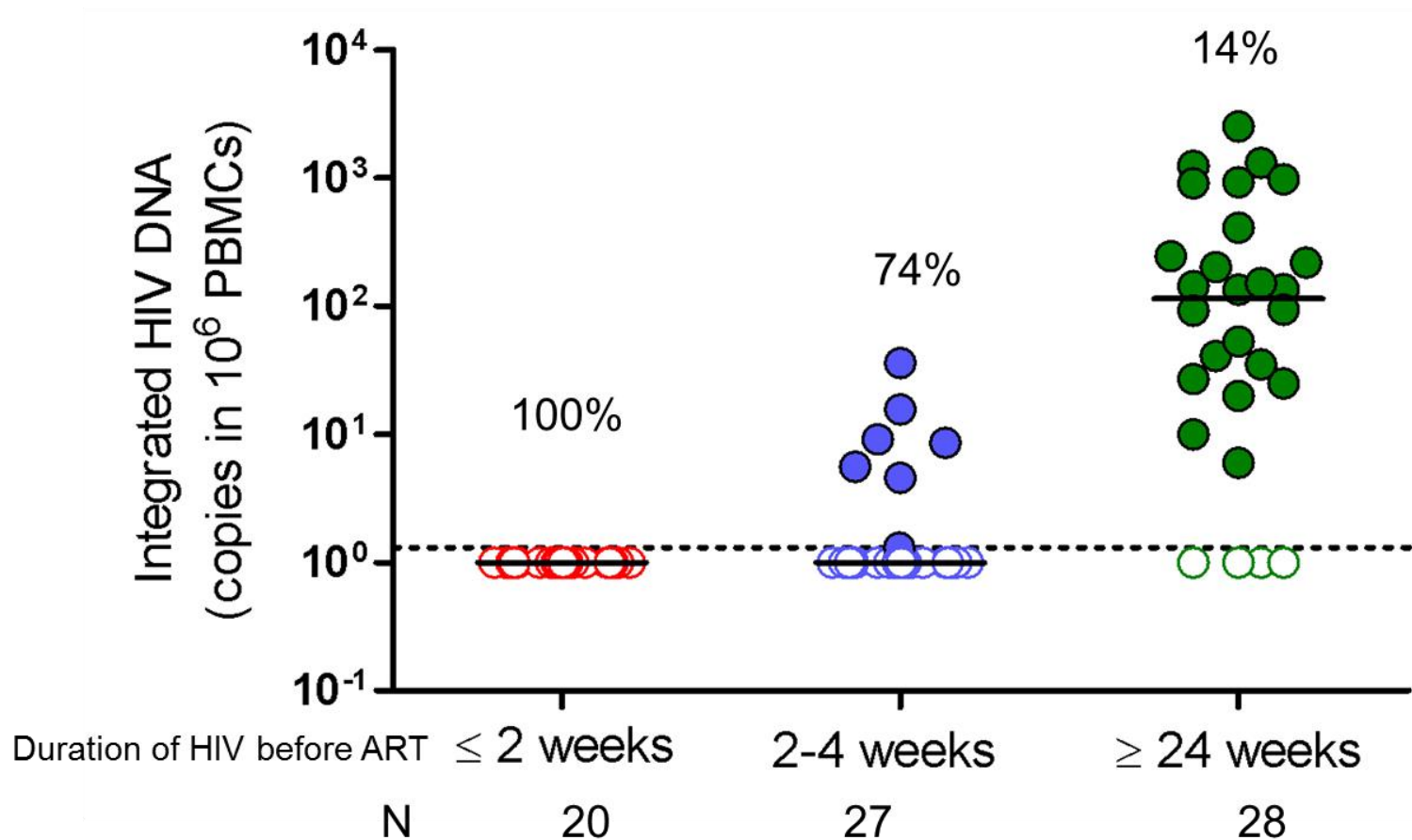


AZT/3TC/NVP
31 hours – 7 days

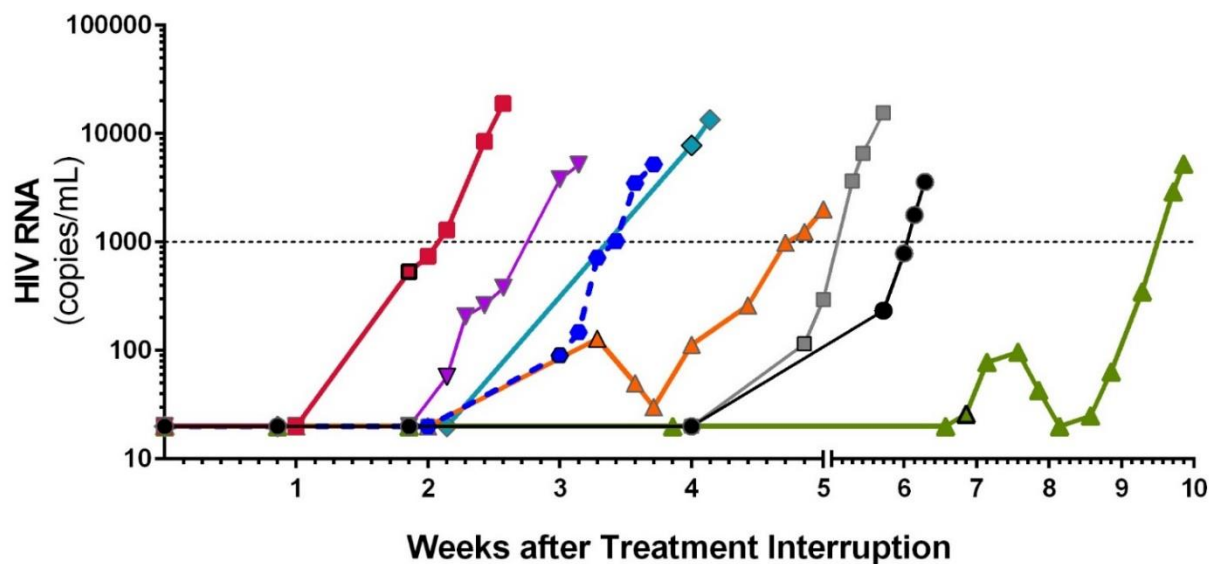
AZT/3TC/LPV/r
7 days – 18 months

ART started at 31 hours and interrupted at ~18 months
HIV seronegative; no consistently detectable HIV after week 4

Very early ART (Fiebig I/II) reduces the reservoir



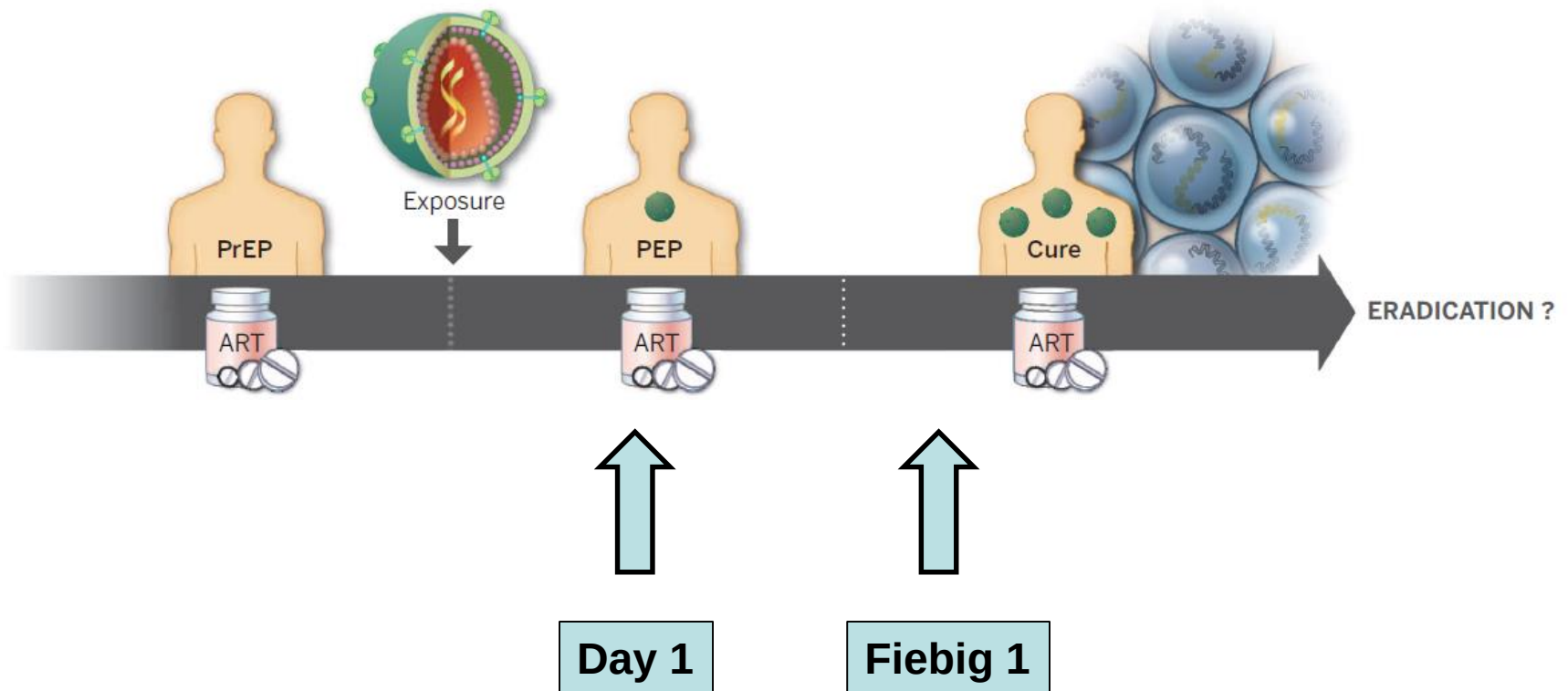
Very early ART reduces the reservoir but is not curative



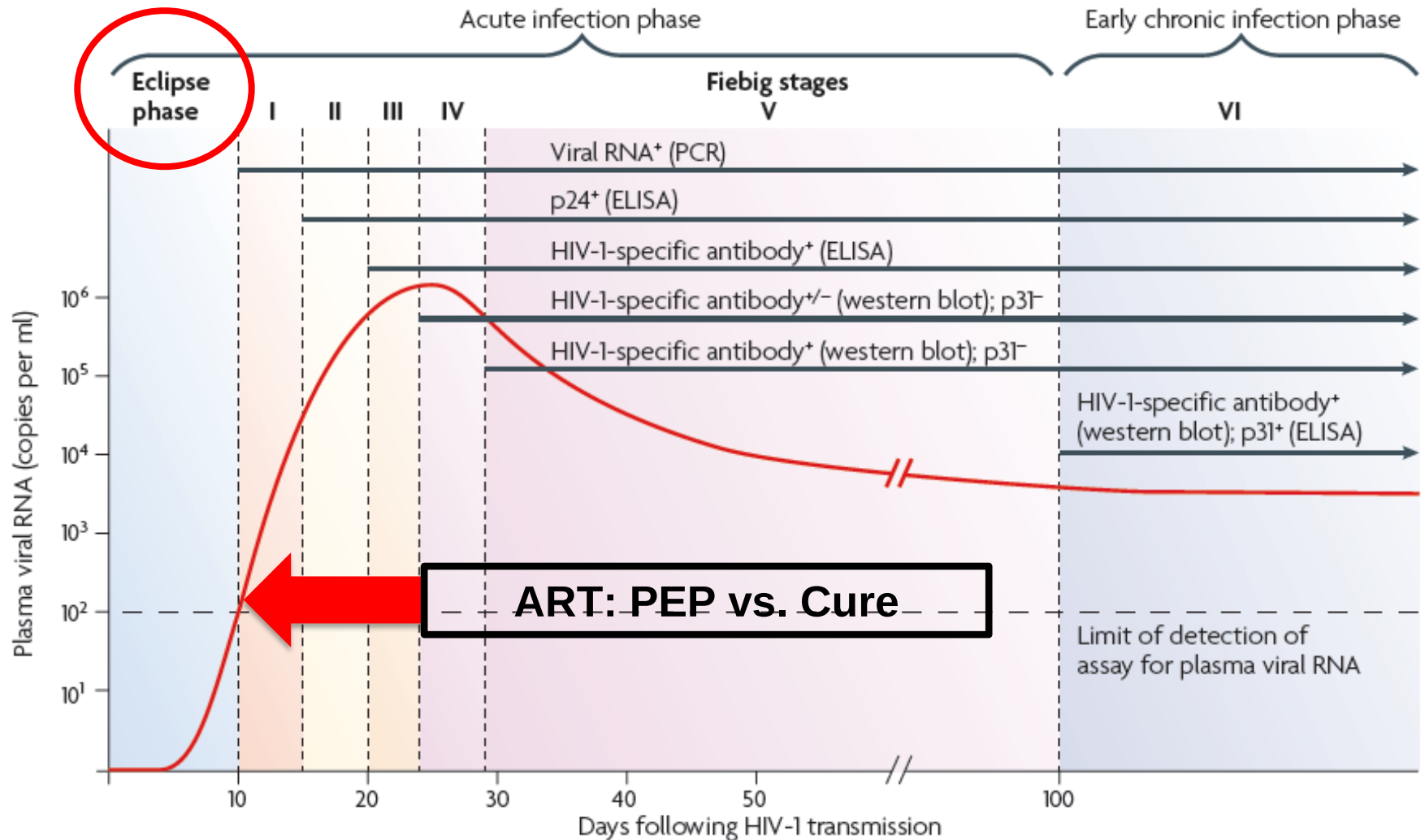
N=8; ART in Fiebig I for >96 weeks; VL<50 c/ml;
CD4>400 cells/ul

Can we use ART to prevent latency?

PEP/PrEP/Cure Continuum



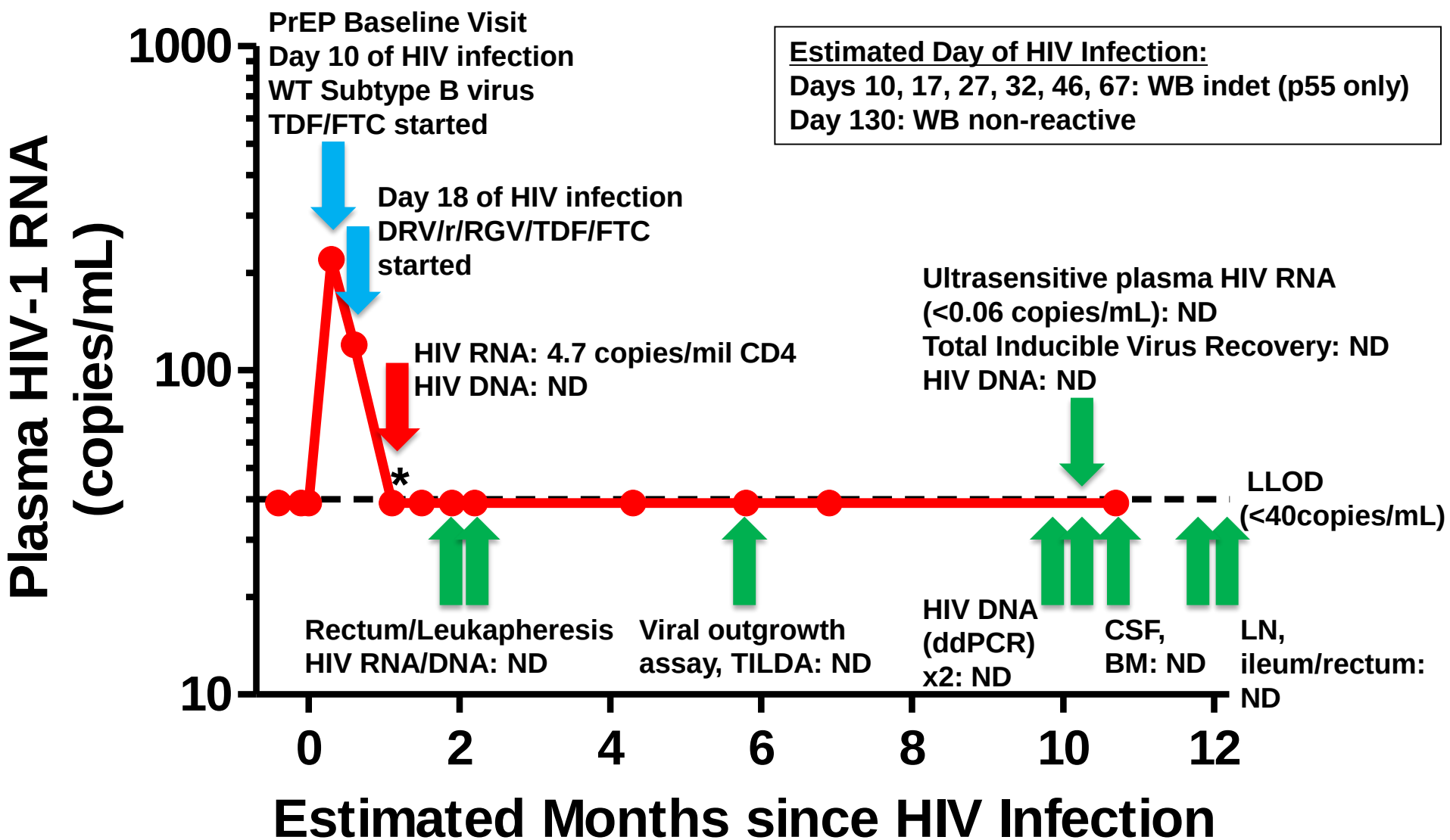
Can very early ART (Fiebig 0) prevent latency and result in a “cure”?



Lack of Detectable HIV DNA in a PrEP Study Participant Treated After “Eclipse” Phase

- PrEP Demo Project: Pre-exposure prophylaxis program in at-risk MSM
- HIV-uninfected at 2 pre-enrollment visits
 - 21 and 13 days prior to PrEP baseline
 - Pooled RNA neg, 4th gen EIA neg, rapid Ab neg
- Fiebig 0/1 Phase at PrEP baseline
 - RNA 220 copies/mL, 4th gen EIA neg, rapid Ab neg
 - *Estimated ~10 days after HIV infection*
- Received PrEP (TDF/FTC) for 7 days and then conventional ART

Lack of Detectable HIV DNA in a PrEP Study Participant Treated Immediately After “Eclipse” Phase



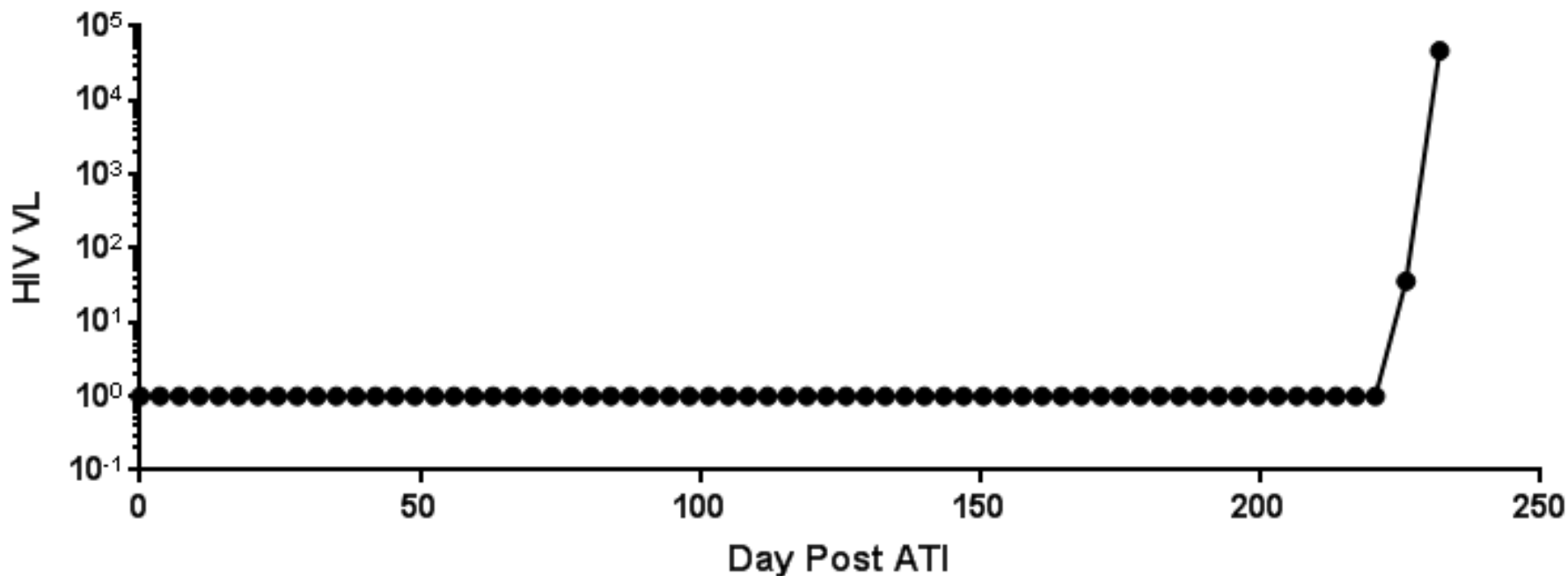
Lack of Detectable HIV DNA in a PrEP Study

Participant: Treatment Interruption

- Month 36: Stopped ART
- Frequency clinical viral load monitoring

Lack of Detectable HIV DNA in a PrEP Study

Participant: Treatment Interruption

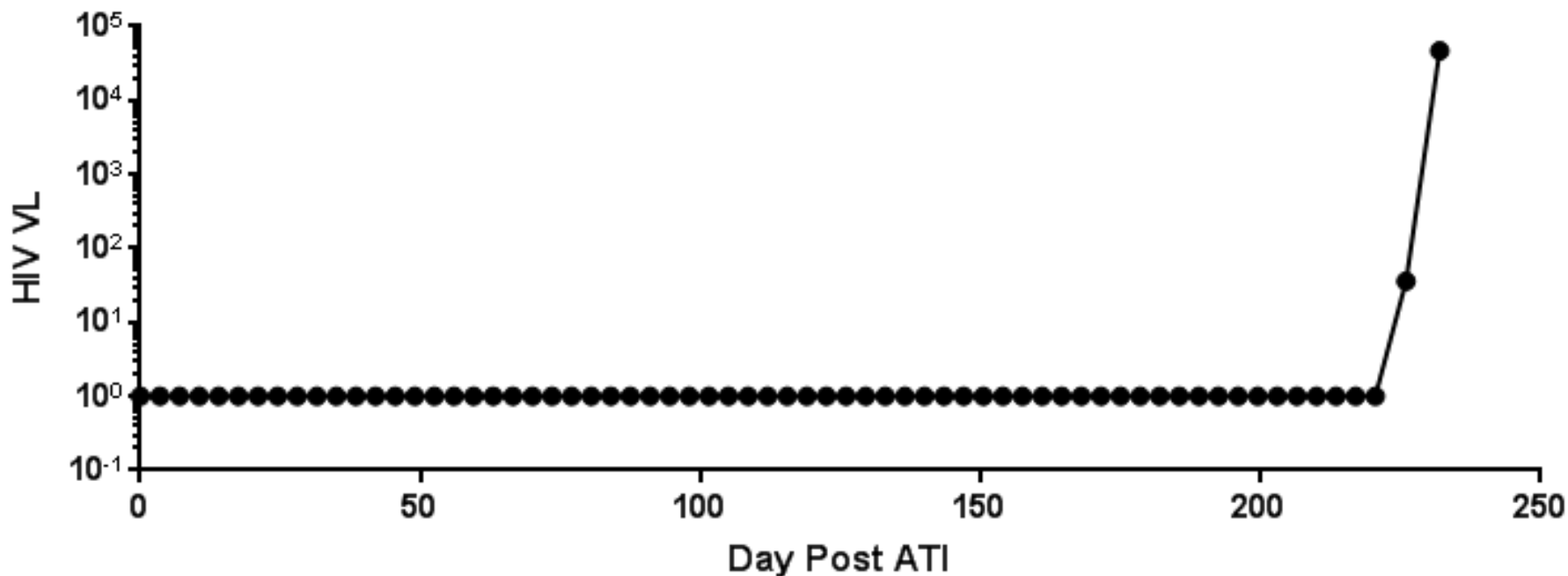


HIV Diagnostics

Blood donor diagnostics are being repurposed for HIV cure studies

Lack of Detectable HIV DNA in a PrEP Study

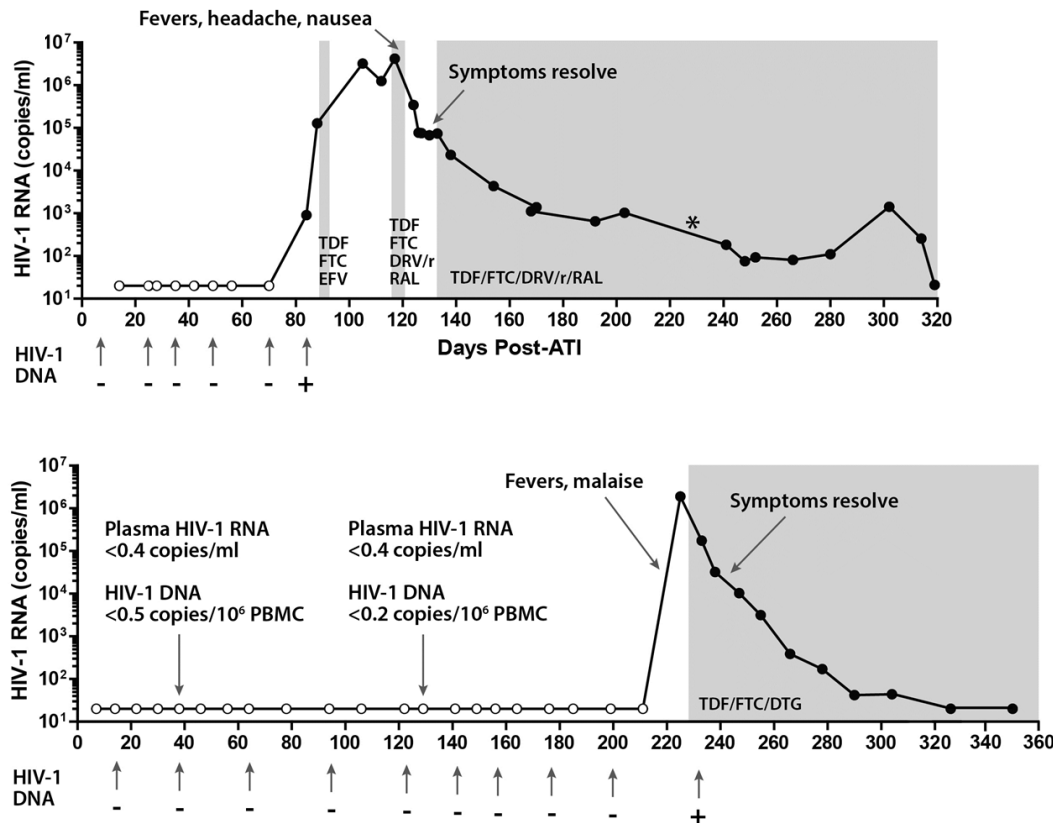
Participant: Treatment Interruption



Antiretroviral-Free HIV-1 Remission and Viral Rebound After Allogeneic Stem Cell Transplantation

Report of 2 Cases

Timothy J. Henrich, MD; Emily Hanhauser, BS; Francisco M. Marty, MD; Michael N. Sirignano, BS; Sheila Keating, PhD; Tzong-Hae Lee, MD, PhD; Yvonne P. Robles, BA; Benjamin T. Davis, MD; Jonathan Z. Li, MD; Andrea Helsey, BS; Allison L. Hill, PhD; Michael P. Busch, MD, PhD; Philippe Armand, MD, PhD; Robert J. Soiffer, MD; Marcus Altfield, MD, PhD; and Daniel R. Kurtzkes, MD



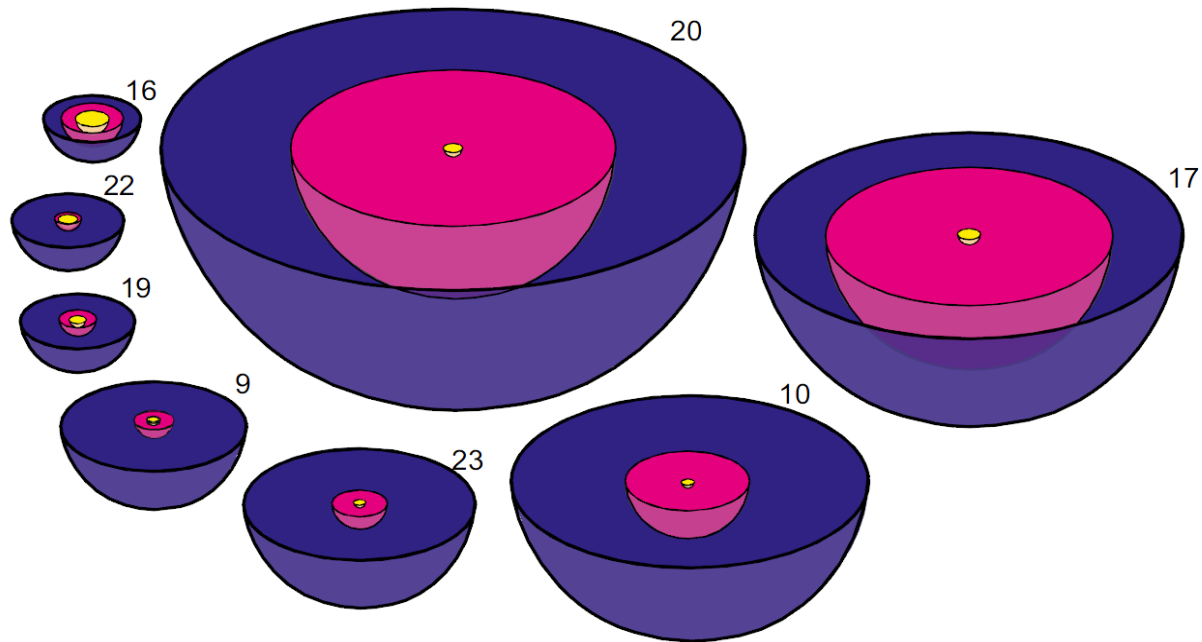
- A single cell containing latent HIV can reignite viral replication at any time
- The impact on the health of the “cured” person and his or her partner can be profound

HIV Diagnostics: Unmet Needs 1

- Point-of-care (or home) HIV RNA test
- Sensitivity: ~ 200 to 1000 copies RNA/mL
- NIAD Symposium: Technologies for HIV Self-Testing: Detection of Acute or Rebound Viremia (June 19, 2017)

Replication-Competent Noninduced Proviruses in the Latent Reservoir Increase Barrier to HIV-1 Cure

Ya-Chi Ho,¹ Liang Shan,^{1,5} Nina N. Hosmane,¹ Jeffrey Wang,² Sarah B. Laskey,¹ Daniel I.S. Rosenbloom,³ Jun Lai,¹ Joel N. Blankson,¹ Janet D. Siliciano,¹ and Robert F. Siliciano^{1,4,*}



- Purple: Most (90%) HIV DNA is defective
- Red: Of the apparently replication-competent virus, most can not be induced to replicate *in vitro*
- Yellow: Only a small subset of virus replicates when stimulated

Size of relevant reservoir is not really known



Evidence for Persistent Low-Level Viremia in Individuals Who Control Human Immunodeficiency Virus in the Absence of Antiretroviral Therapy[▽]

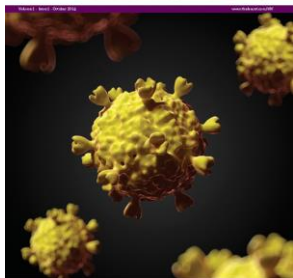
Hiroyu Hatano,^{1*} Eric L. Delwart,^{1,2} Philip J. Norris,^{1,2} Tzong-Hae Lee,² Joan Dunn-Williams,² Peter W. Hunt,¹ Rebecca Hoh,¹ Susan L. Stramer,³ Jeffrey M. Linnen,⁴ Joseph M. McCune,¹ Jeffrey N. Martin,¹ Michael P. Busch,^{1,5} and Steven G. Deeks¹



Evidence of persistent low-level viremia in long-term HAART-suppressed, HIV-infected individuals

Hiroyu Hatano^a, Eric L. Delwart^{b,c}, Philip J. Norris^{a,b,c}, Tzong-Hae Lee^b, Torsten B. Neilands^d, Colleen F. Kelley^e, Peter W. Hunt^a, Rebecca Hoh^a, Jeffrey M. Linnen^f, Jeffrey N. Martin^a, Michael P. Busch^{b,c} and Steven G. Deeks^a

THE LANCET HIV

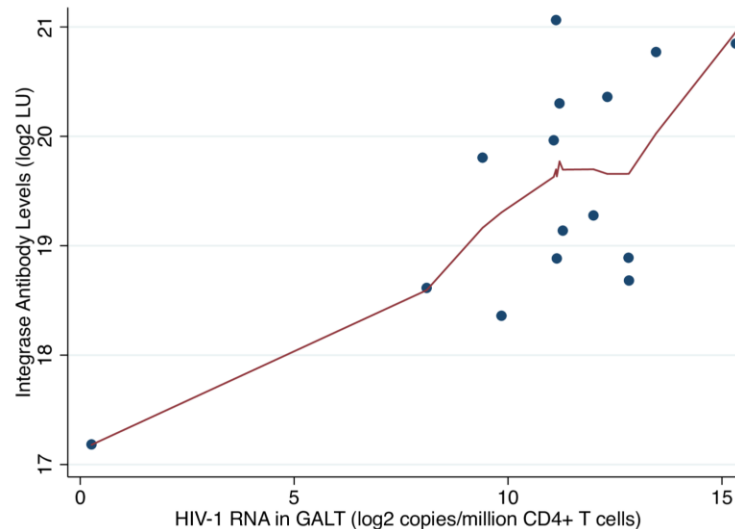


Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial

Thomas A Rasmussen, Martin Tolstrup, Christel R Brinkmann, Rikke Olesen, Christian Erikstrup, Ajantha Solomon, Anni Winckelmann, Sarah Palmer, Charles Dinarello, Maria Buzon, Mathias Lichterfeld, Sharon R Lewin, Lars Østergaard, Ole S Søgaard

PLOS ONE Anti-HIV Antibody Responses and the HIV Reservoir Size during Antiretroviral Therapy

Sulggi A. Lee^{1aa*}, Peter Bacchetti¹, Nicolas Chomont², Remi Fromentin², Sharon R. Lewin^{3,4}, Una O'Doherty⁵, Sarah Palmer⁶, Douglas D. Richman⁷, Janet D. Siliciano⁸, Steven A. Yukl^{1,9}, Steven G. Deeks¹, Peter D. Burbelo^{10ab}



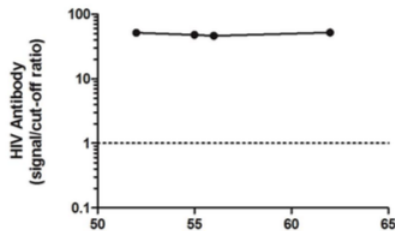
HIV antibody responses to gp120, integrase and protease (but not other proteins) associated with reservoir (RNA, DNA) in tissues



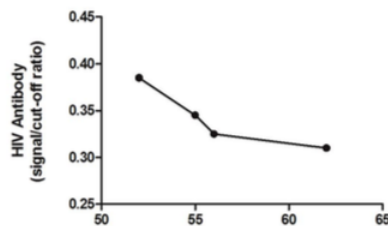
Challenges in Detecting HIV Persistence during Potentially Curative Interventions: A Study of the Berlin Patient

Steven A. Yukl^{1,9}, Eli Boritz^{2,9}, Michael Busch³, Christopher Bentsen⁴, Tae-Wook Chun⁵, Daniel Douek², Evelyn Eisele⁶, Ashley Haase⁷, Ya-Chi Ho⁶, Gero Hütter⁸, J. Shawn Justement⁵, Sheila Keating³, Tzong-Hae Lee³, Peilin Li¹, Danielle Murray⁵, Sarah Palmer⁹, Christopher Pilcher¹⁰, Satish Pillai¹, Richard W. Price¹¹, Meghan Rothenberger⁷, Timothy Schacker⁷, Janet Siliciano⁶, Robert Siliciano^{6,12}, Elizabeth Sinclair¹⁰, Matt Strain¹³, Joseph Wong¹, Douglas Richman¹³, Steven G. Deeks¹⁰

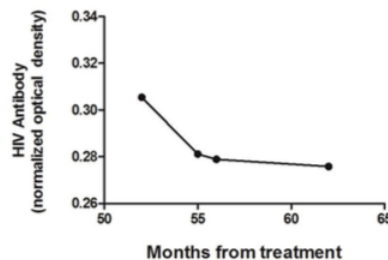
A. HIV Antibody (Standard)



B. HIV Antibody (Detuned)



C. Limiting Antigen Avidity



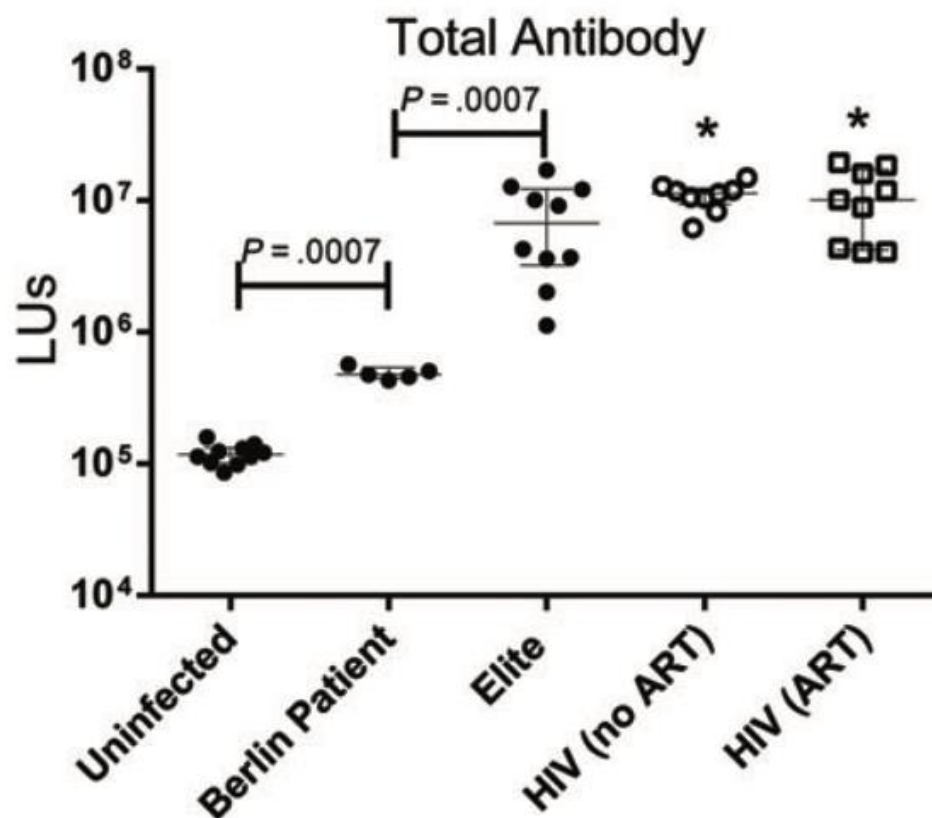
HIV antibodies are waning slowly in the “Berlin Patient” but have been stable in controllers and near-cured states (Boston Patients)

HIV Diagnostics: Unmet Needs 2

- High throughput quantitative measure of the total body (not blood) reservoir of replication-competent HIV
- Assays developed for blood screening are highly sensitive and specific and are now being re-purposed for cure research (RAVEN)
- Antibody responses to HIV are promising (Keating/Busch, JID 2017)

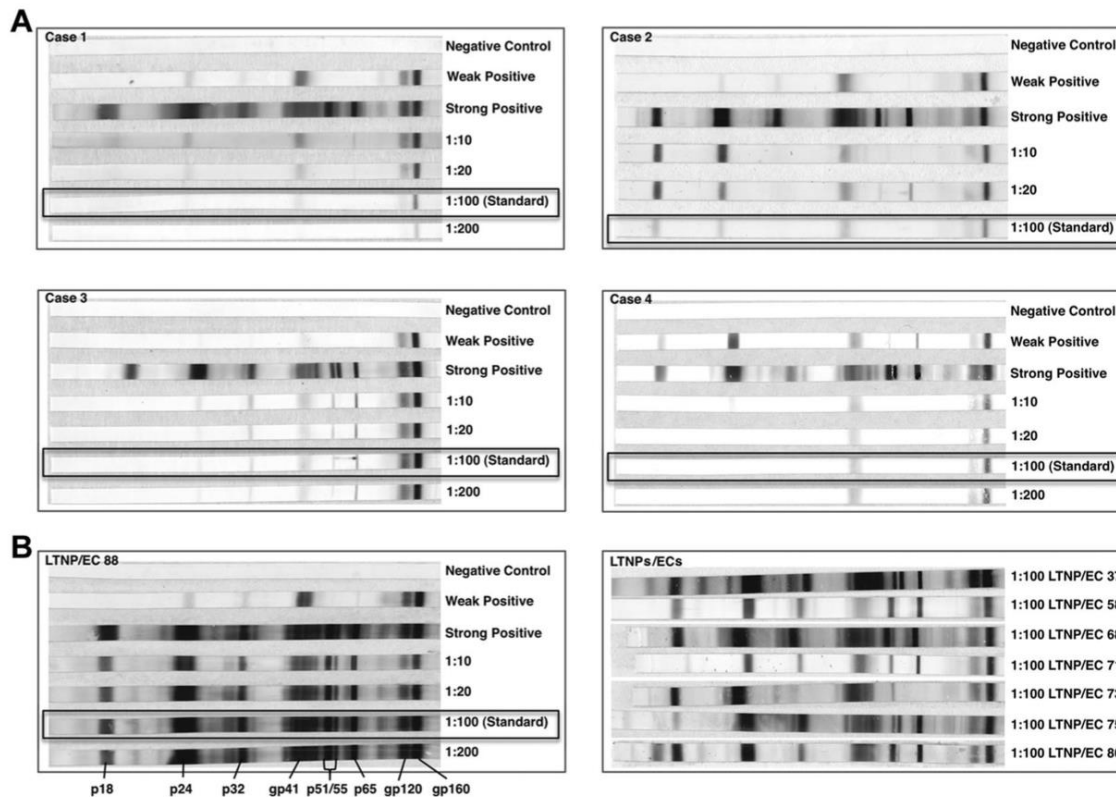
HIV Antibody Characterization as a Method to Quantify Reservoir Size During Curative Interventions

Peter D. Burbelo,¹ Ahmad Bayat,² Craig S. Rhodes,³ Rebecca Hoh,⁴ Jeffrey N. Martin,^{4,5} Rémi Fromentin,⁶ Nicolas Chomont,⁶ Gero Hütter,⁷ Joseph A. Kovacs,⁸ and Steven G. Deeks⁴



Comprehensive analysis of unique cases with extraordinary control over HIV replication

Daniel Mendoza,¹ Sarah A. Johnson,¹ Bennett A. Peterson,¹ Ven Natarajan,² Maria Salgado,^{3,4} Robin L. Dewar,² Peter D. Burbelo,⁵ Nicole A. Doria-Rose,¹ Erin H. Graf,⁶ Jamieson H. Greenwald,¹ Jessica N. Hodge,¹ William L. Thompson,¹ Nancy A. Coglianor,¹ Cheryl L. Chairez,¹ Catherine A. Rehm,¹ Sara Jones,² Claire W. Hallahan,⁷ Joseph A. Kovacs,⁸ Irini Sereti,¹ Omar Sued,⁹ Sheila A. Peel,¹⁰ Robert J. O'Connell,¹⁰ Una O'Doherty,⁶ Tae-Wook Chun,¹ Mark Connors,¹ and Stephen A. Migueles¹



Extraordinary “elite” controllers: rare individuals with low antibodies and HIV DNA

HIV Diagnostics: Unmet Needs 3

- Should a cure emerge will current diagnostic tests be sufficient to protect blood supply
- Potent remission (no cure) might be associated with no detectable virus and declining antibody levels

State of the ART: 2017

- HIV Cure: Massive international effort now underway to develop a curative intervention
 - Complete eradication (cure)
 - Control (remission)
- Early ART reduces reservoir size (by several orders of magnitude) but is unlikely to be curative
- A reproducible, sensitive and specific measurement of the reservoir may be the field's greatest need (industry)

Acknowledgements



amfAR Institute
FOR HIV CURE RESEARCH

Delaney AIDS Research Enterprise
DARE
to find a cure