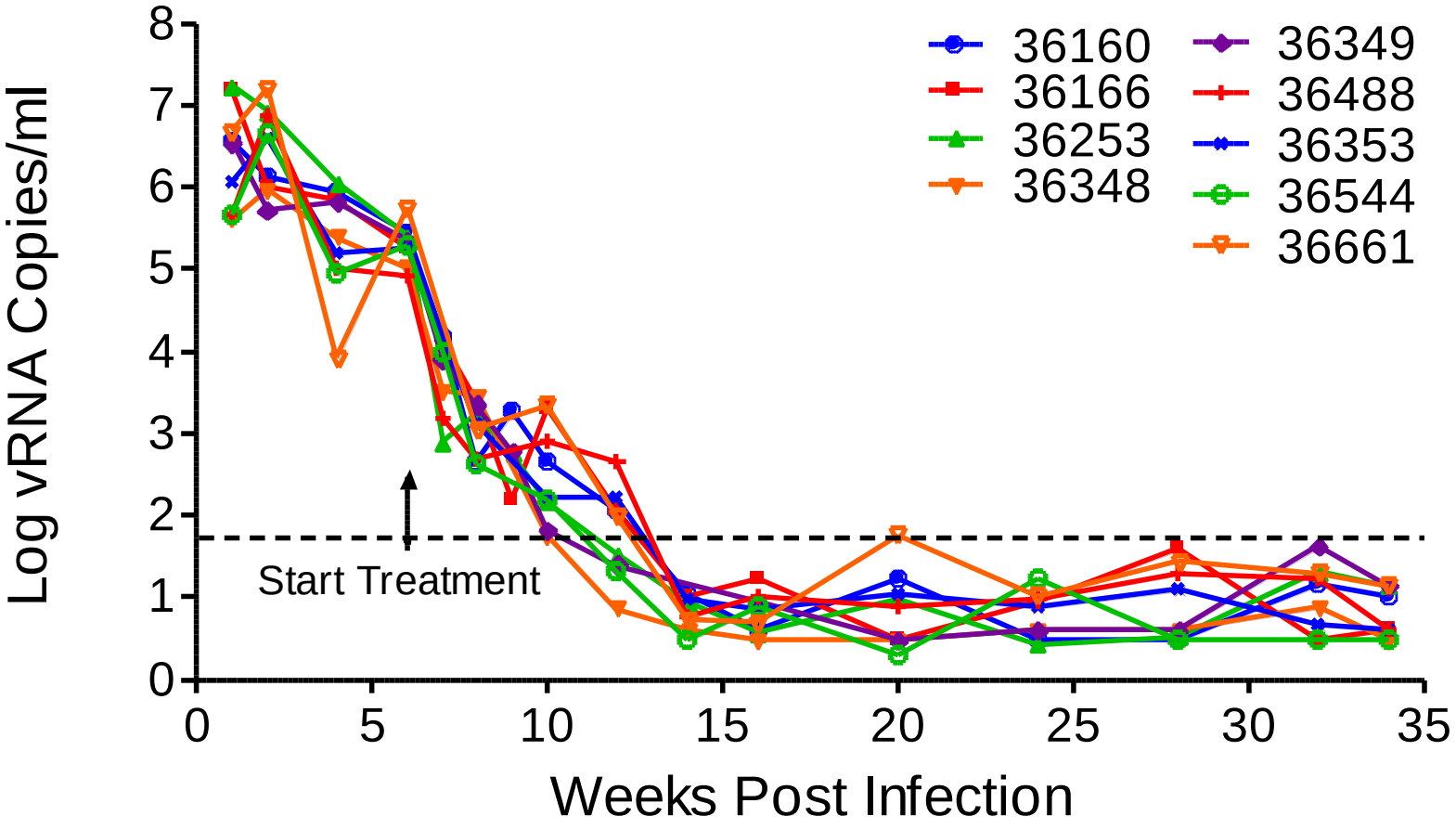
Towards an HIV Cure

Some progress, many questions

Steven G. Deeks
Professor of Medicine
University of California, San Francisco

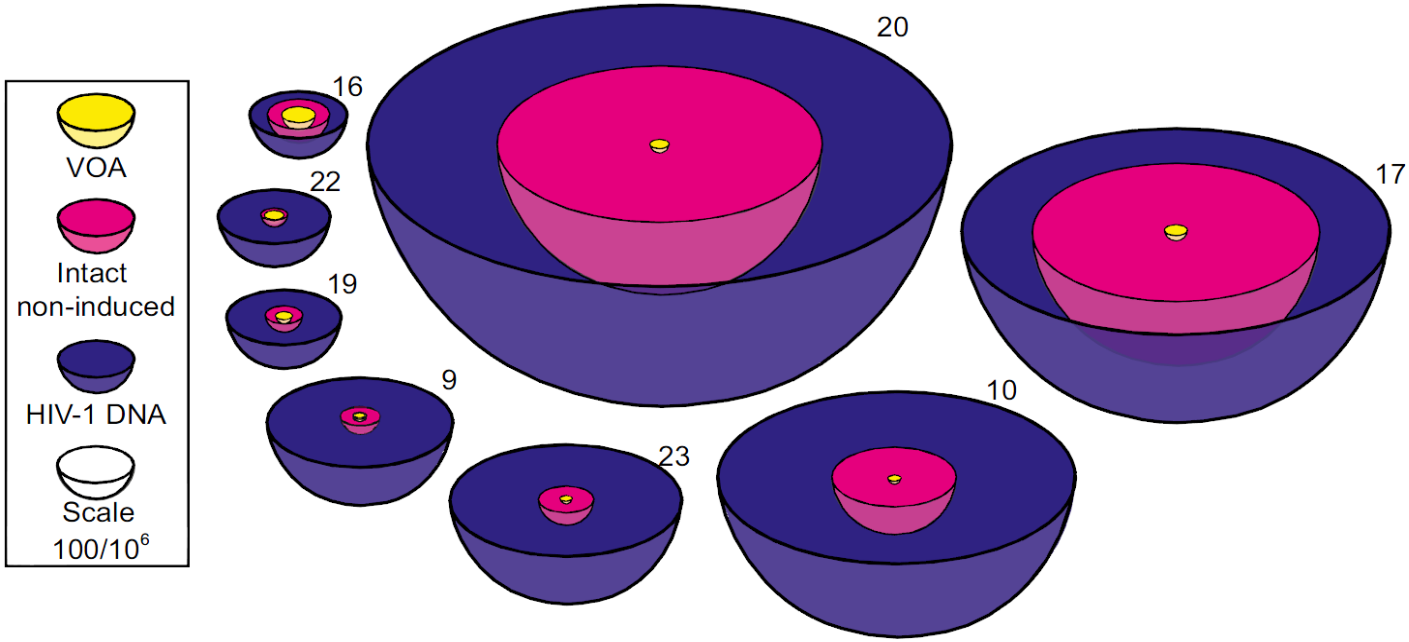
Low-Level Viremia Persists Despite Effective ART



Cell PRESS

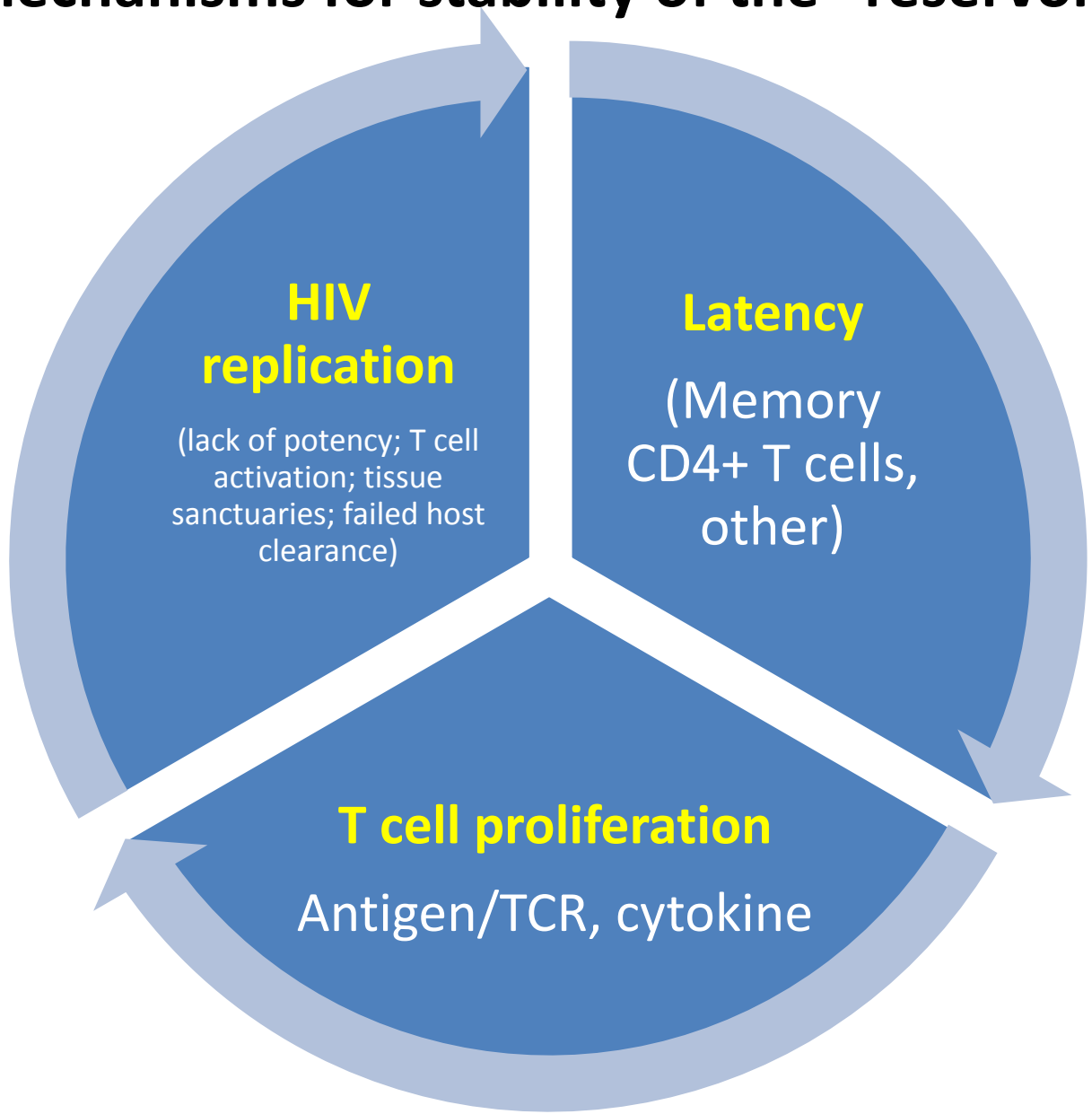
Replication-Competent Noninduced Proviruses in the Latent Reservoir Increase Barrier to HIV-1 Cure

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,*]



- **Most (90%) HIV DNA is defective**
- **Of the apparently replication-competent virus, only a small subset is induced *in vitro***
- **Size of relevant reservoir is not really known**

There are three well-characterized non-mutually exclusive mechanisms for stability of the "reservoir"



Functional Cure

- Long-term health in absence of therapy ("functional cure")
  - Cancer model (remission)
  - Occurs in ~1% of natural infections
- Will there be residual disease?
- Approach: Enhance HIV-specific immunity

Sterilizing Cure

- Complete eradication of all replication competent virus (“sterilizing cure”)
  - Is this remotely possible?
  - Is this necessary?
  - How can this be proven?
- Approach: “Shock and Kill”, gene therapy

How will HIV be eliminated or controlled in absence of ART?

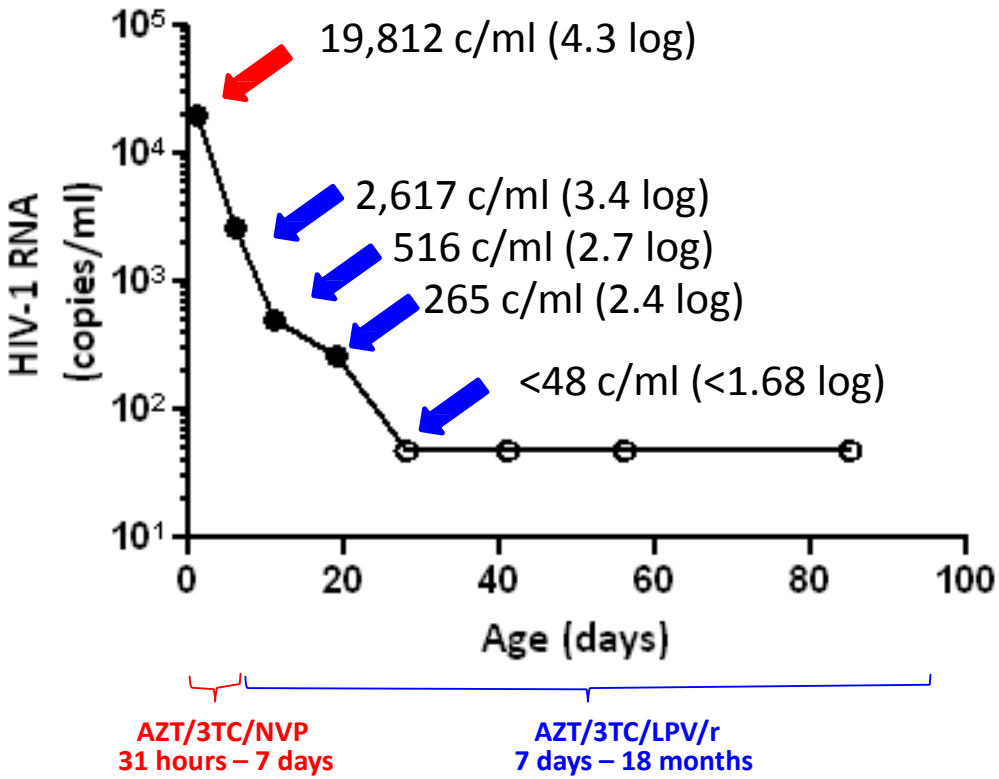
- Prevent latency (early ART)
- Reverse latency (“shock”)
- Clear virus-producing cells (“kill”)
- Modify host enviroment
- Gene therapy/HST

Can we cure HIV with very early therapy?

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.



- **ART started at 31 hours and interrupted at ~18 months**
- **Classic viral decay consistent with infection of infant's T cell population**
- **HIV seronegative; no consistently detectable HIV; no protective HLA alleles**

Science
AAAS

AIDS CONFERENCE

Cure setbacks force HIV researchers to reset sights

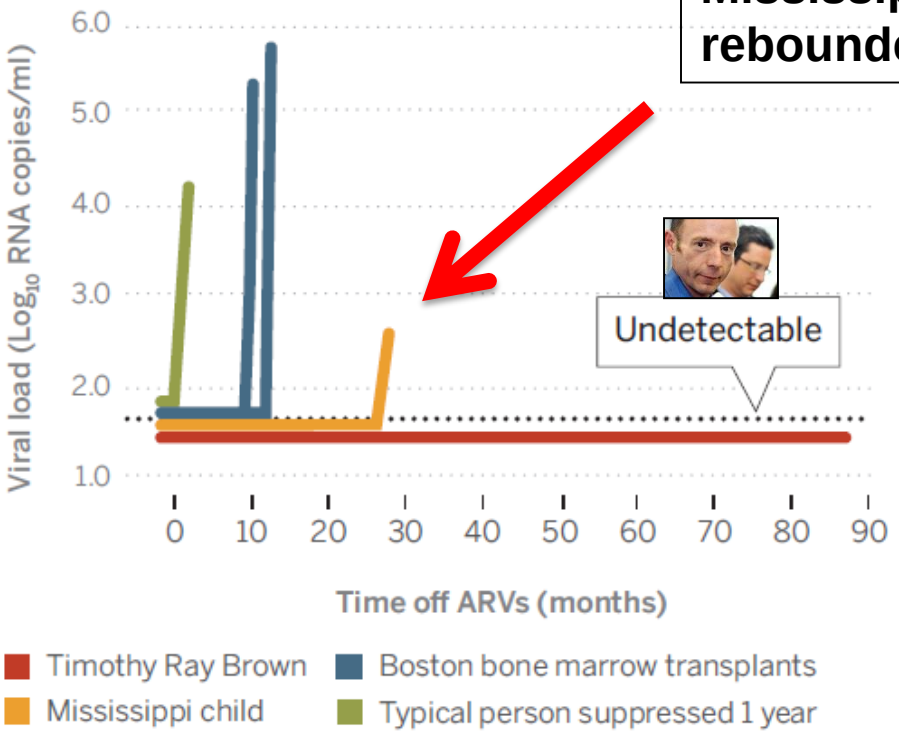
Remission is seen as a more realistic goal

By Jon Cohen, in Melbourne, Australia

ARVs stopped, HIV rebounds

Only one person has been "cured" of HIV.

Mississippi Child: HIV rebounded at month 27



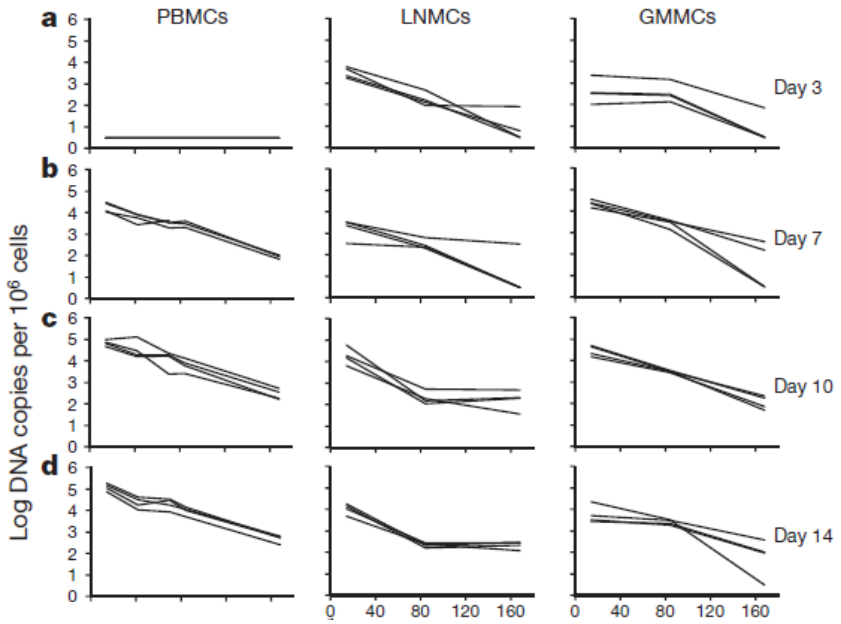
nature

LETTER

doi:10.1038/nature13594

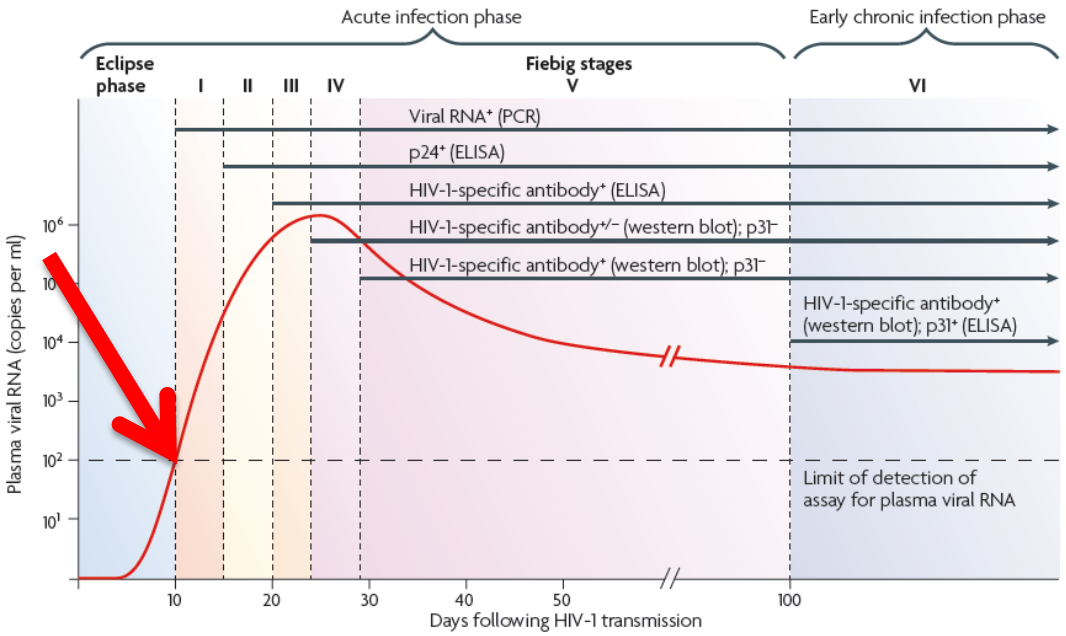
Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys

James B. Whitney[1,2], Alison L. Hill[3], Srisowmya Sanisetty[1], Pablo Penaloza-MacMaster[1], Jinyan Liu[1], Mayuri Shetty[1], Lily Parenteau[1], Crystal Cabral[1], Jennifer Shields[1], Stephen Blackmore[1], Jeffrey Y. Smith[1], Amanda L. Brinkman[1], Lauren E. Peter[1], Sheeba I. Mathew[1], Kaitlin M. Smith[1], Erica N. Borducchi[1], Daniel I. S. Rosenbloom[3], Mark G. Lewis[4], Jillian Hattersley[5], Bei Li[5], Joseph Hesselgesser[5], Romas Geleziunas[5], Merlin L. Robb[6], Jerome H. Kim[6], Nelson L. Michael[6] & Dan H. Barouch[1,2]



- **ART at day 3 prevents seeding in blood, but not lymph node/gut**
- **Virus rebound delayed but not prevented by early ART**
- **Caveats: large bolus, short-term non-optimized ART**
- ***A delay in starting ART for a few days results in > 1 log_{10} increase in reservoir size (Okoye/Picker)***

Is early ART doomed to fail?



<u>Hatano:</u> ART during "hyperacute" (end of eclipse period) in PrEP failures prevents detectable seeding of HIV in blood and tissues

OPEN ACCESS Freely available online

PLOS | PATHOGENS

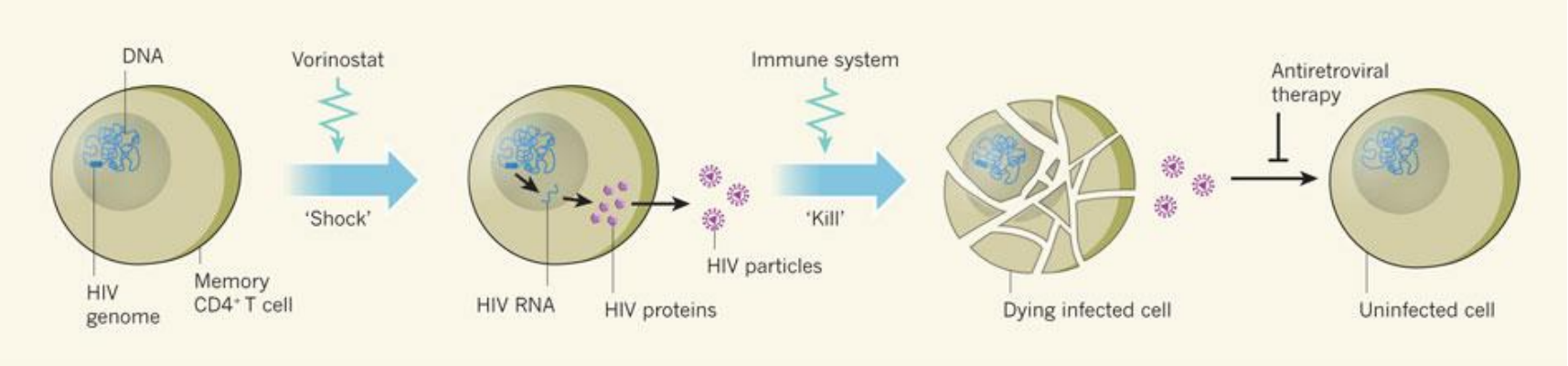
Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

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[¶]

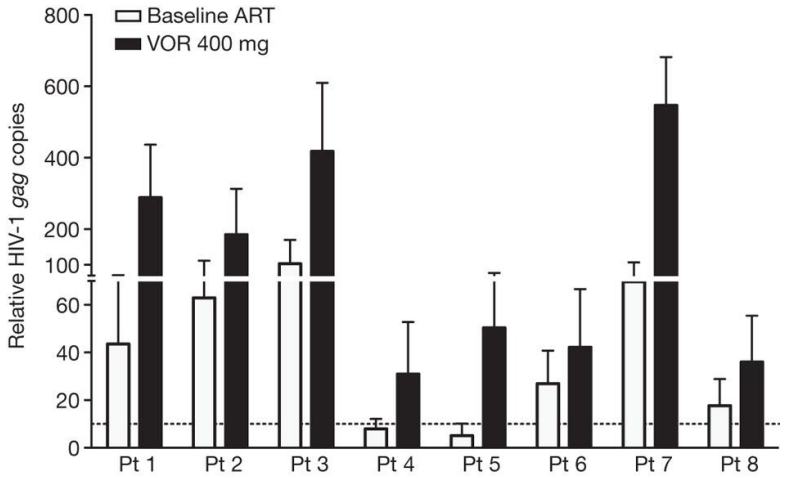
- **14 subjects who started therapy early (but not Fiebig I/II), remained on therapy for years, and had no rebound after stopping therapy**
- **Lack CTL and protective HLA alleles**
- **Low reservoir of replication-competent virus**
- **HIV DNA declines in absence of ART (n=4)**
- **Very low T cell activation**

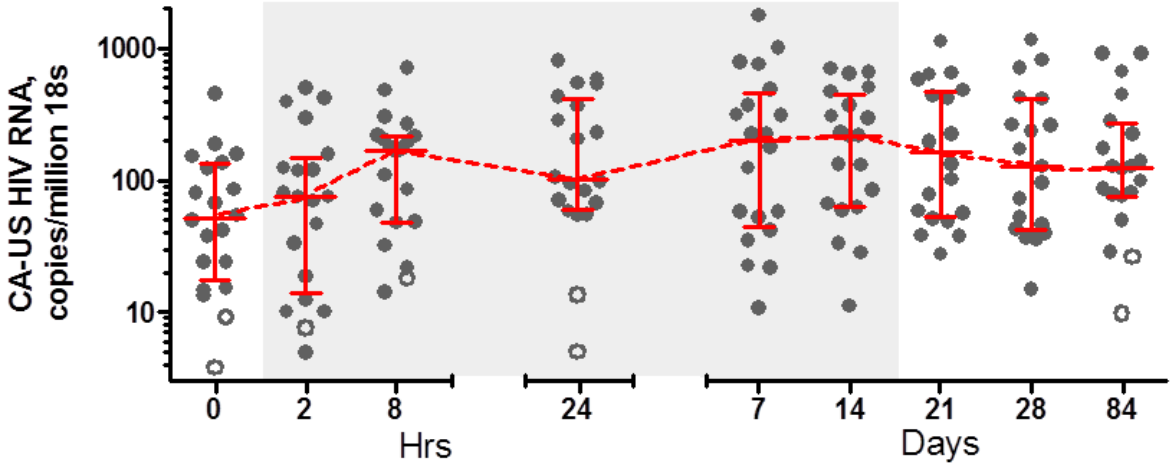
Shock and Kill

Shock and Kill

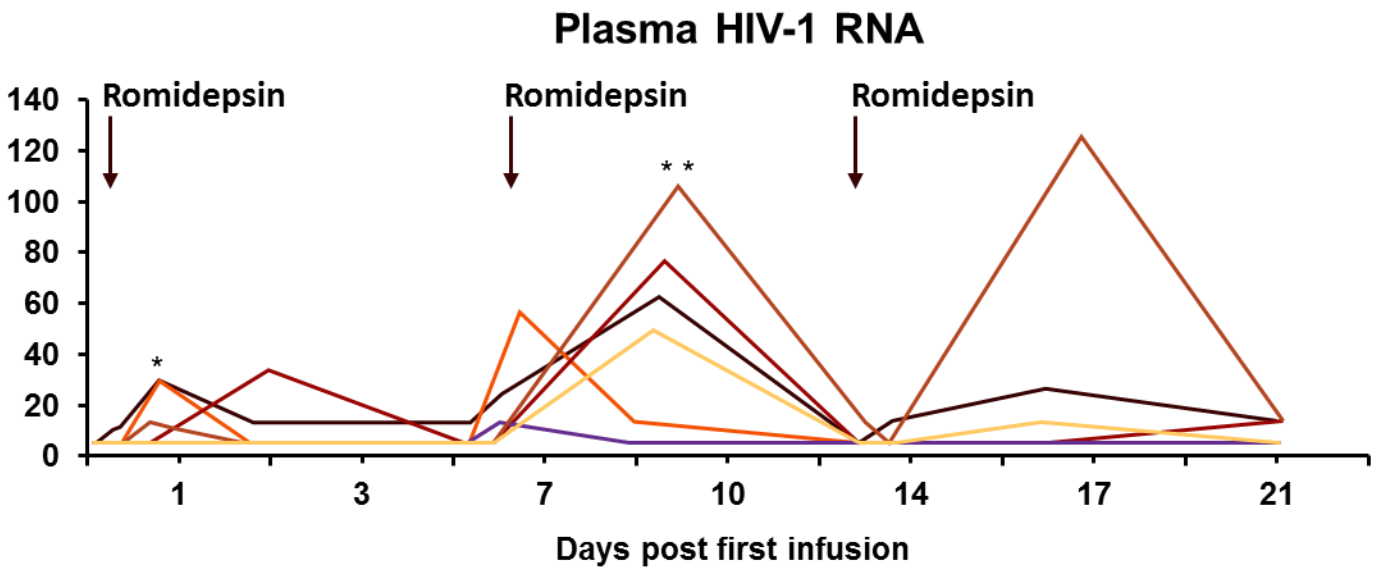


Vorinostat (SAHA) increases RNA production during ART but does not cause virus production (Margolis/Lewin)



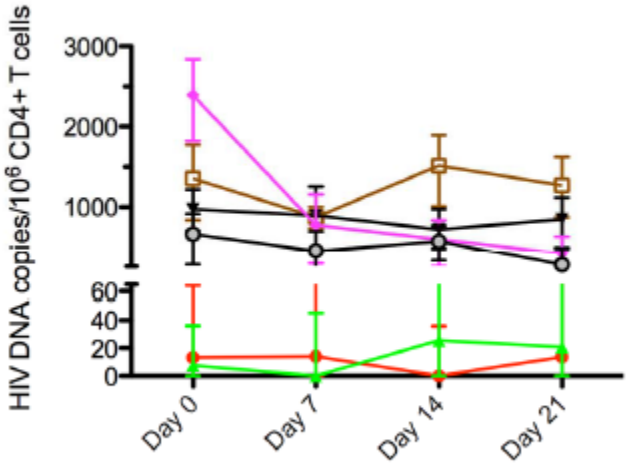


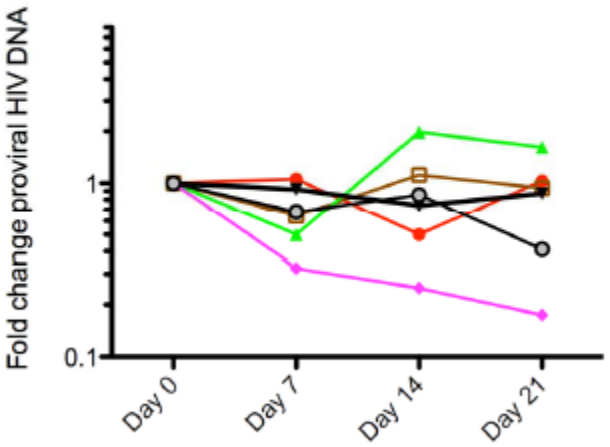
Romidepsin stimulates virus production



Søgaard and colleagues; AIDS 2014 (abstract TUAA0106LB)

Despite clear efficacy as a “shock”, romidepsin does not affect the reservoir size





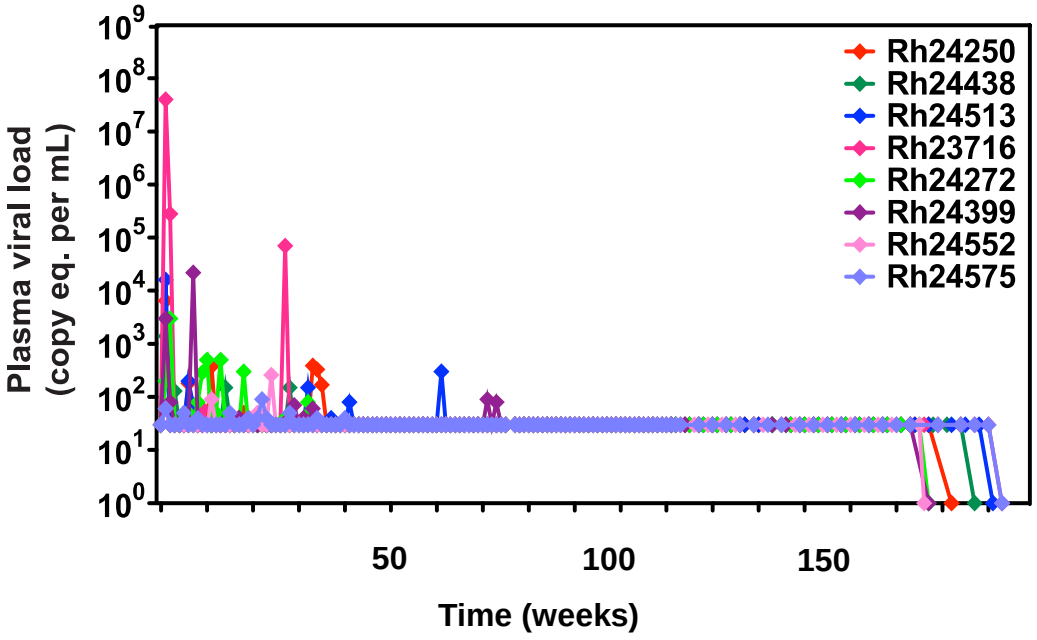
Søgaard and colleagues; AIDS 2014 (abstract TUAA0106LB)

Can we enhanced killing of HIV-infected cells *in vivo*?

nature International weekly journal of science

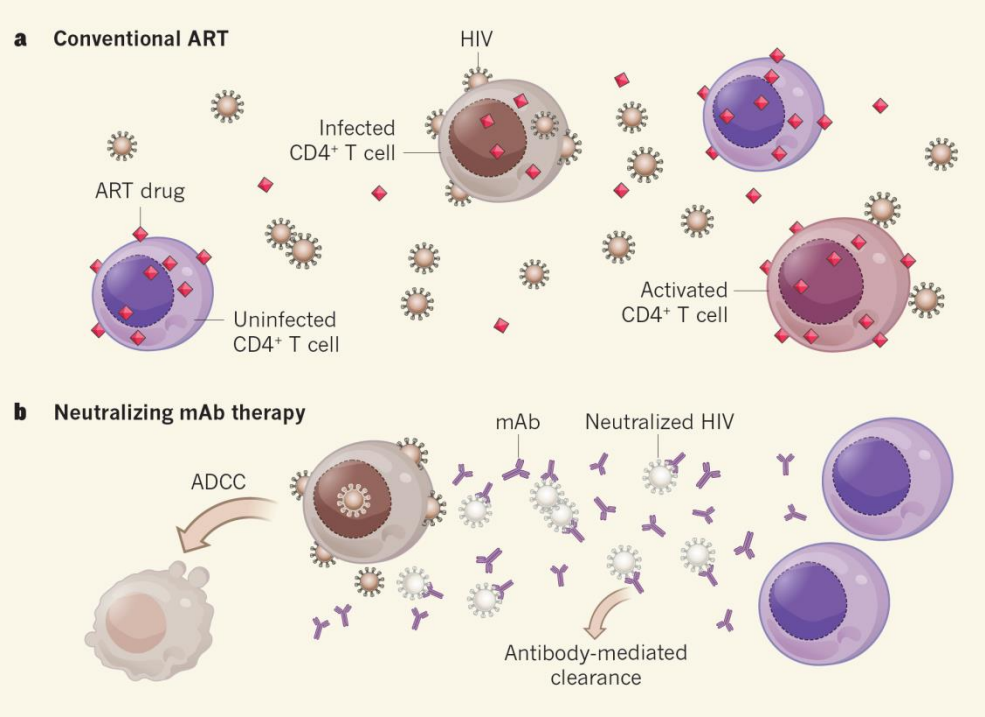
Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]



- **CMV as SIV vaccine vector causes high levels of tissue-based effector CD8+ T cells that target novel epitopes**
- **These cells prevent/clear latency during early infection, resulting in cure (as shown by challenge studies)**

HIV antibodies and cure



Broadly neutralizing antibodies inhibit HIV replication in macaques, and can be optimized (if needed) to enhance clearance of virus-producing cells (ADCC)

Can we cure HIV infection with immune-based therapeutics?

Immune activation

T cell proliferation

Negative regulators

Enhanced clearance

Delaney AIDS Research Enterprise
DARE
to find a cure

Cell proliferation maintains the reservoir during ART

PNAS

PNAS PLUS

The HIV-1 reservoir in eight patients on long-term suppressive antiretroviral therapy is stable with few genetic changes over time

Lina Josefsson[a,b,1], Susanne von Stockenstrom[a,b], Nuno R. Faria[c], Elizabeth Sinclair[d], Peter Bacchetti[e], Maudi Killian[d], Lorrie Epling[d], Alice Tan[d], Terence Ho[d], Philippe Lemey[c], Wei Shao[f], Peter W. Hunt[d], Ma Somsouk[d], Will Wylie[g], Daniel C. Douek[g], Lisa Loeb[d], Jeff Custer[d], Rebecca Hoh[d], Lauren Poole[d], Steven G. Deeks[d], Frederick Hecht[d,2], and Sarah Palmer[a,b,h,i,2]

Science

AAAS

Proliferation of cells with HIV integrated into cancer genes contributes to persistent infection

Thor A. Wagner,[1,2*] Sherry McLaughlin,[1,2*] Kavita Garg,[3] Charles Y. K. Cheung,[3] Brendan B. Larsen,[2] Sheila Styrchak,[1] Hannah C. Huang,[1] Paul T. Edlefsen,[2,3] James I. Mullins,[2*] Lisa M. Frenkel[1,2*†]

Science

AAAS

Specific HIV integration sites are linked to clonal expansion and persistence of infected cells

F. Maldarelli,[1*] X. Wu,[2*] L. Su,[2] F. R. Simonetti,[1,3] W. Shao,[2] S. Hill,[1] J. Spindler,[1] A. L. Ferris,[1] J. W. Mellors,[4] M. F. Kearney,[1] J. M. Coffin,[5] S. H. Hughes[1†]

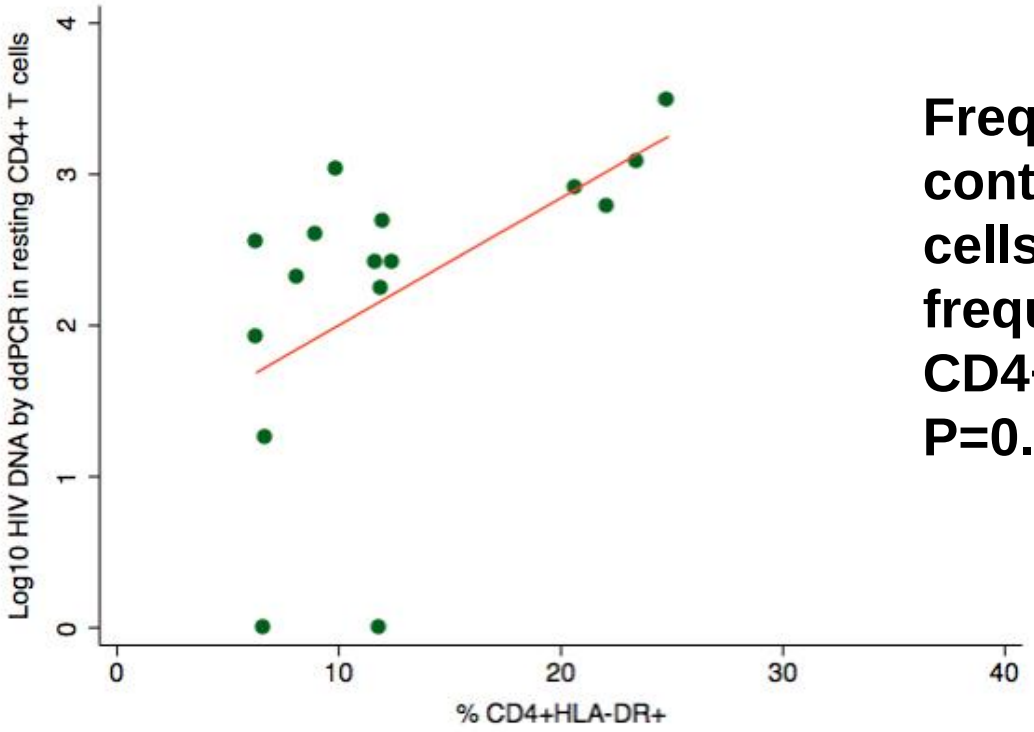
- **Up to 50% of infected cell population (blood) is clonal in nature**
- **Integration sites enriched for genes associated with cell growth/cancer**
- **Latency reversal/T cell activation may stimulate cell proliferation, thus maintaining if not increasing reservoir size**

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Comparative Analysis of Measures of Viral Reservoirs in HIV-1 Eradication Studies

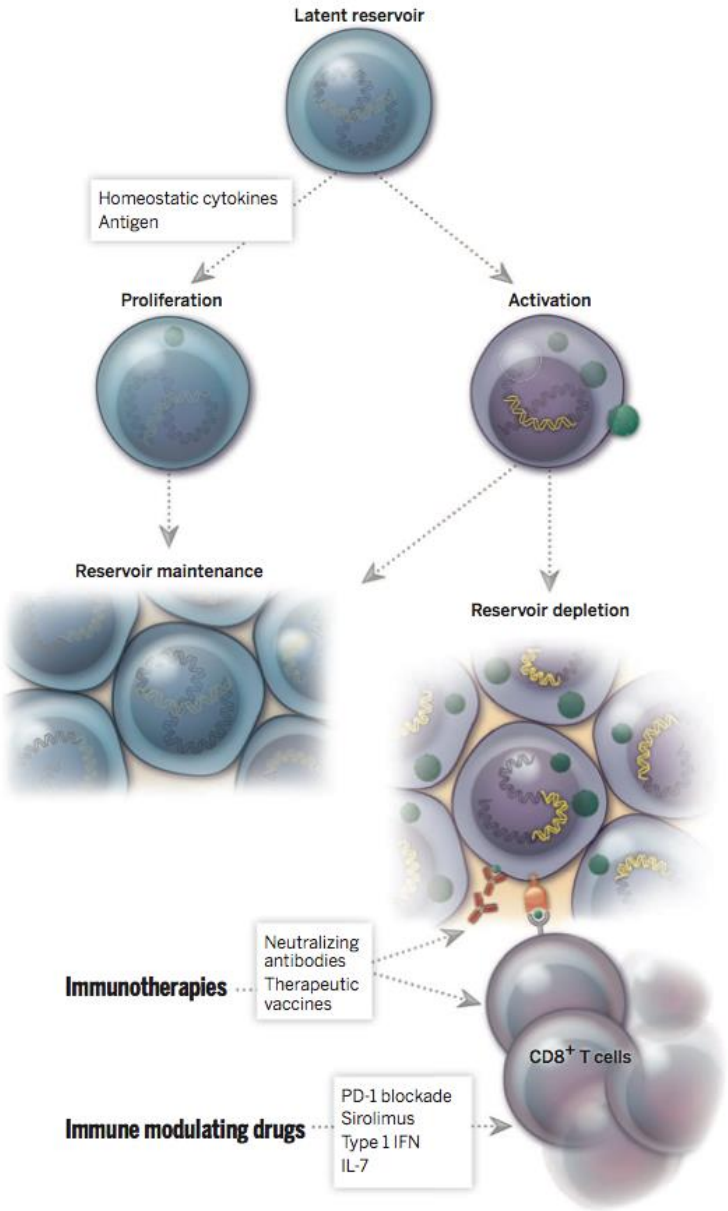
Susanne Eriksson[1☯], Erin H. Graf[2☯], Viktor Dahl[1☯], Matthew C. Strain[3☯], Steven A. Yukl[4,5☯], Elena S. Lysenko[2], Ronald J. Bosch[6], Jun Lai[7], Stanley Chioma[7], Fatemeh Emad[7], Mohamed Abdel-Mohsen[5], Rebecca Hoh[5], Frederick Hecht[5], Peter Hunt[5], Ma Somsouk[5], Joseph Wong[4,5], Rowena Johnston[8], Robert F. Siliciano[7,9], Douglas D. Richman[3], Una O'Doherty[2], Sarah Palmer[1], Steven G. Deeks[5], Janet D. Siliciano[7]*

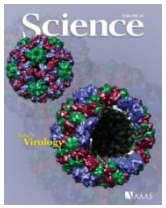


Frequency of HIV DNA-containing resting memory cells correlates with frequency of HLA-DR+ CD4+ T cells (rho=0.65, P=0.006)

ARCHE amfAR Research Consortium on HIV Eradication

Delaney AIDS Research Enterprise DARE to find a cure





REVIEW

Immunologic strategies for HIV-1 remission and eradication

Dan H. Barouch[1,2] and Steven G. Deeks[3]

Immunotherapy: Reduce T cell activation/proliferation (sirolimus, JAK/STAT inhibitors, anti-INFα)

Immunotherapy: Improve T cell function (anti-PD-1, anti-INFα)

Immunotherapy: Kill virus producing cells (vaccines, BNabs)

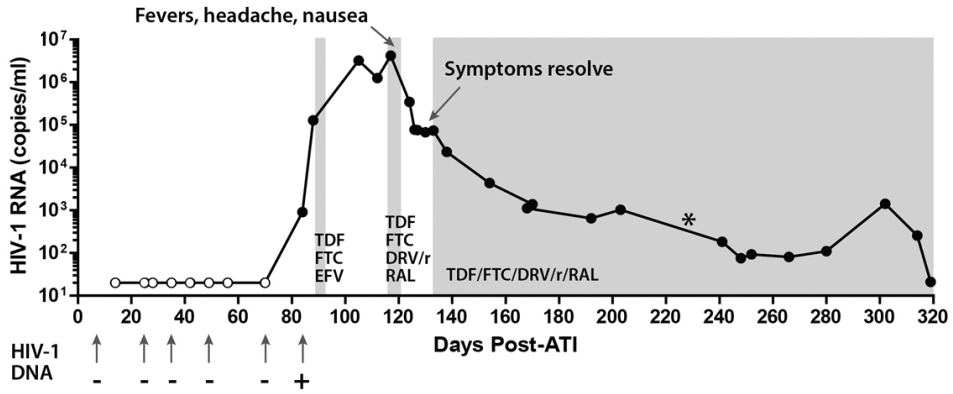
Will we need to eradicate all HIV?

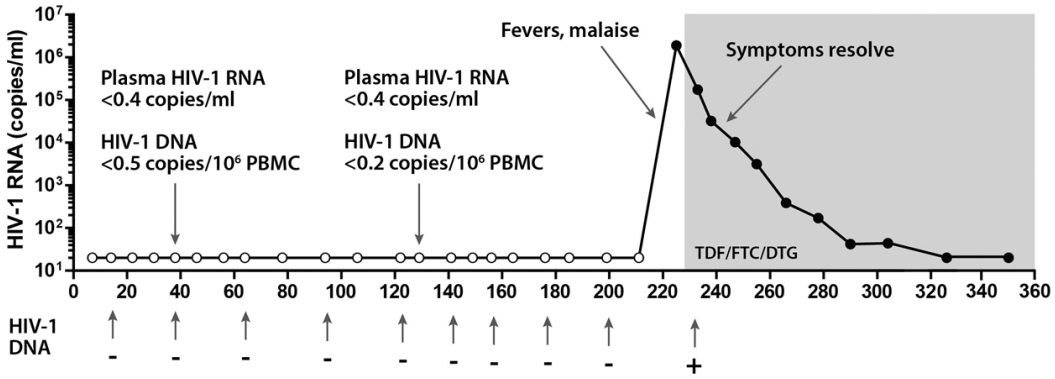
Annals of Internal Medicine | ORIGINAL RESEARCH

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 Heisey, BS; Alison L. Hill, PhD; Michael P. Busch, MD, PhD; Philippe Armand, MD, PhD; Robert J. Soiffer, MD; Marcus Altfeld, MD, PhD; and Daniel R. Kuritzkes, MD





Despite dramatic (1000 to 10,000 fold) reductions in "reservoir", virus rebounded after several months

Late rebounds will be hard to diagnose and could have profound effects on patient and his/her partners

Modeling: latent reservoir will have to be depleted > 10^5 log10 fold or a durable cure to be likely (Hill, PNAS 14)

Summary

- There will be no scalable and safe cure in the foreseeable future
- Treatment of hyperacute HIV may still be curative; early ART reduces reservoir and protects immune function (VISCONTI)
- Shock (HDAC inhibitors) work, but are not sufficiently potent
- A number of adjunctive anti-proliferation/anti-inflammation drugs are moving through pipeline
- In absence of host control, profound depletions in reservoir needed, and life long surveillance for late failures needed
- A biomarker for reservoir may be highest priority

Acknowledgements

SCOPE Cohort / UCSF

Hiroyu Hatano
Peter Hunt
Satish Pillai
Charlene Wang
Ma Somsouk
Jeff Martin
Rebecca Hoh
Rick Hecht
Michael Busch
Peter Stock
Elizabeth Sinclair
Steve Yukl
Joe Wong
Mike McCune

Elsewhere

Nicolas Chomont
Rafick Sekaly
Remi Fromentin
Mario Stevenson
Sarah Palmer
Daria Hazuda
Sharon Lewin
Bob Siliciano
Janet Siliciano
Danny Douek
Michael Lederman
Barbara Shacklett
Tim Schacker

NIAID

U19 AI096109, RO1 AI087145, K24AI069994, CNICS (5R24AI067039), CLIC

ARCHE
amfAR Research Consortium on HIV Eradication

CFAR
CENTER FOR AIDS RESEARCH
University of California San Francisco
Gladstone Institute of Virology and Immunology

Delaney AIDS Research Enterprise
DARE
to find a cure