Where are we now in the quest for an HIV cure?

Mario Stevenson, PhD

University of Miami Miller School of Medicine.

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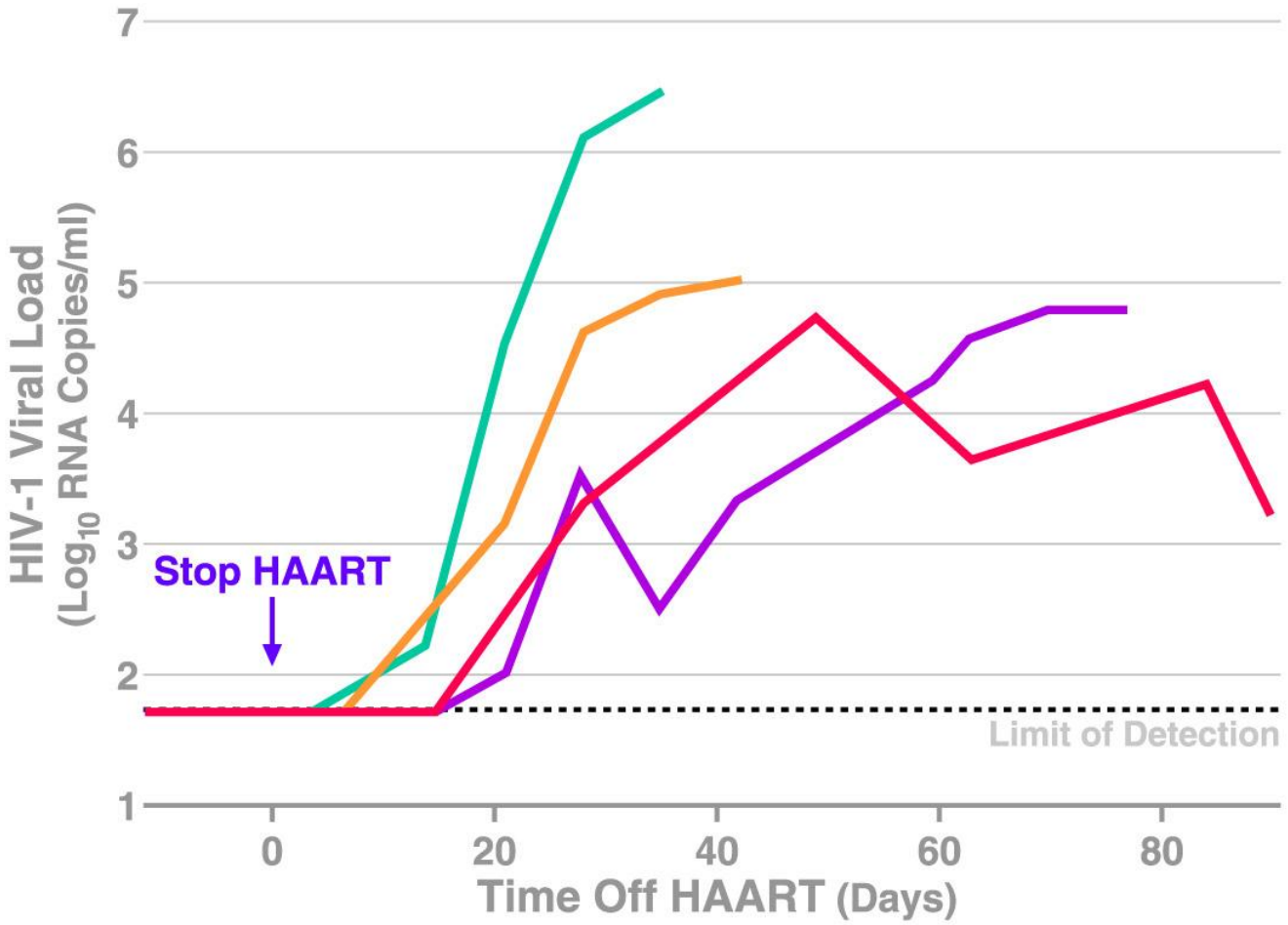
Main topics:

- Review of the obstacles to viral eradication
- Berlin Patient; Visconti Patients; Mississippi Baby; Boston Patients
- Gene therapy approaches
- Shock and kill
- Immune-based strategies

HIV cure research is a religion!


I Survived
Catholic
School

Viral Rebound After HAART Interruption



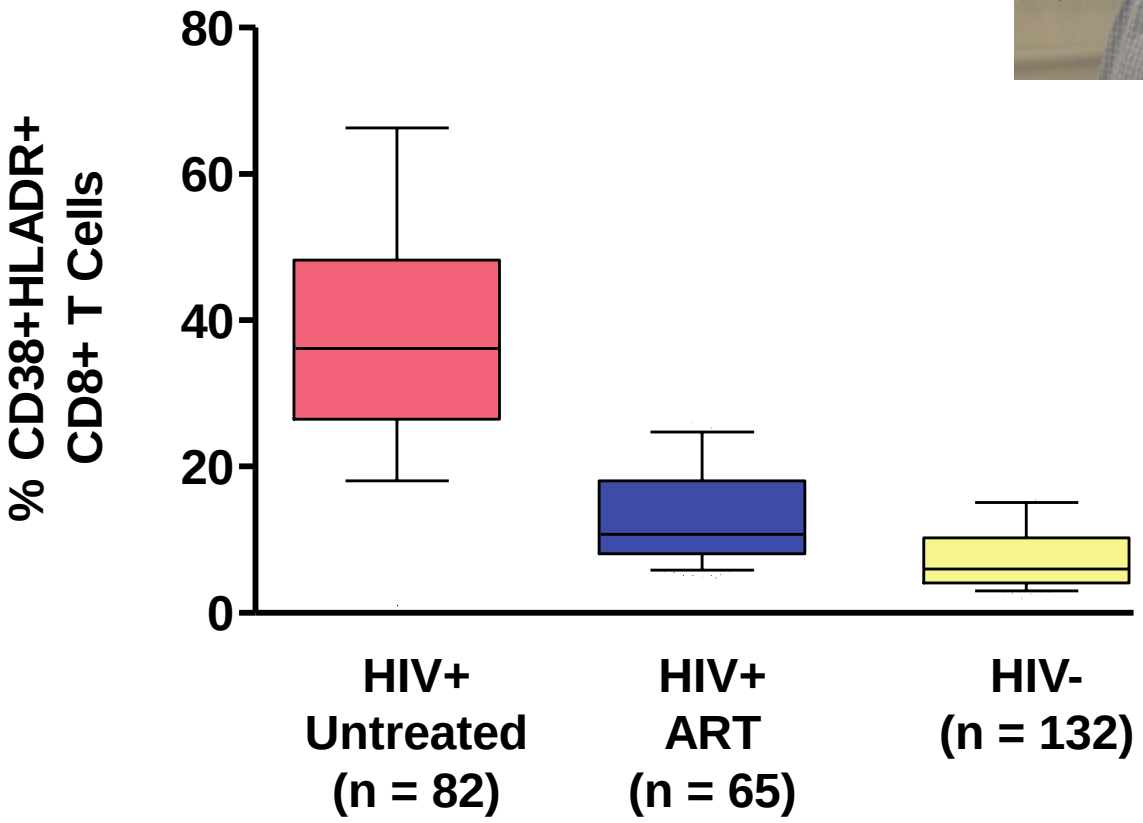
02.0084B

Current therapies are extremely effective - reduced pill burden, fewer side effects. Virus in blood can be reduced to undetectable levels for years.

Why not maintain the status quo and go with life-long ART?

Immune inflammation causes co-morbidities!

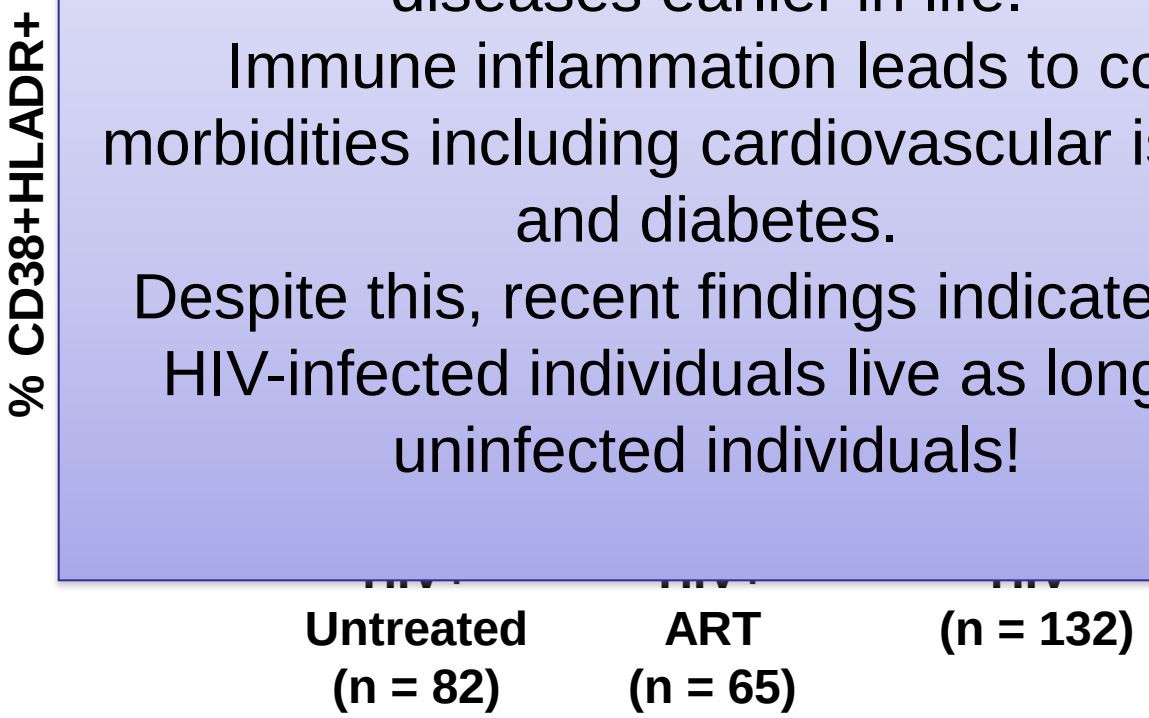
Immune inflammation, as measured by T-cell activation, is lower in treated than untreated adults, but consistently higher than “normal”



Hunt et al JID 2003, PLoS ONE 2011 and unpublished

Immune inflammation, as measured by T-cell activation, is lower in treated than untreated adults, but consistently higher than "normal"

Individuals on ART develop "aging" diseases earlier in life.
Immune inflammation leads to co-morbidities including cardiovascular issues and diabetes.
Despite this, recent findings indicate that HIV-infected individuals live as long as uninfected individuals!



Hunt et al JID 2003, PLoS ONE 2011 and unpublished

The changing face of ART

15 years ago!

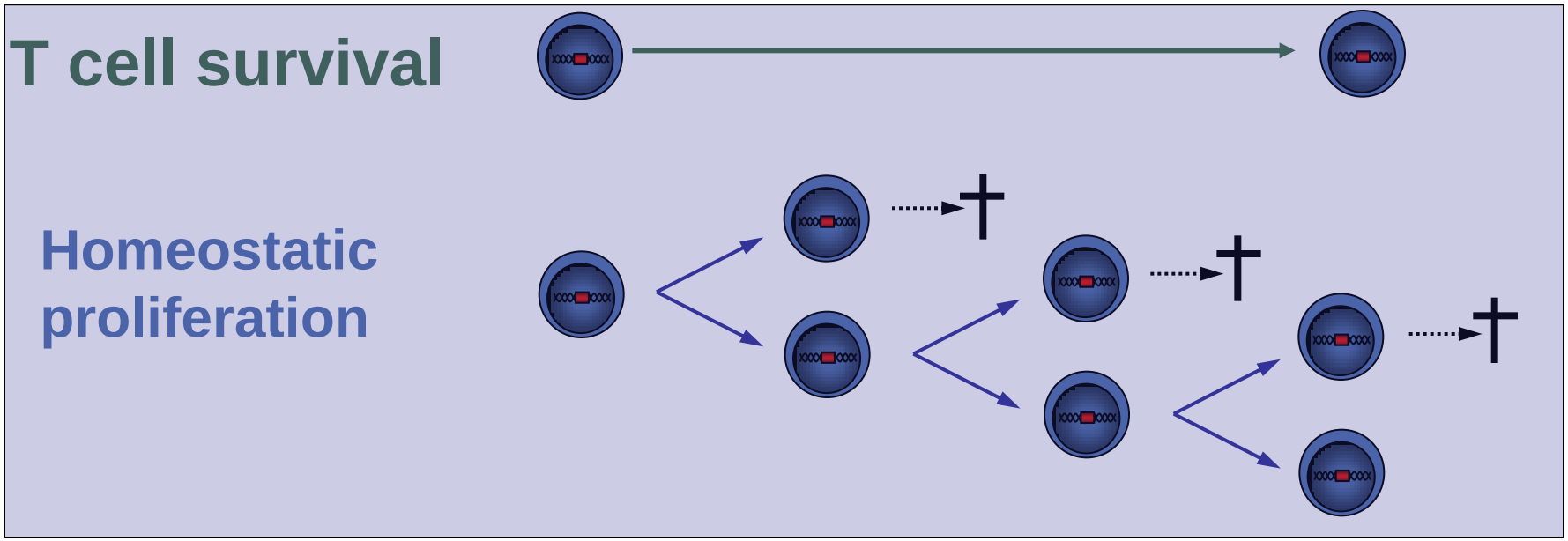
Today!

Tomorrow?

What are the obstacles to eliminating HIV infection?

Mechanisms of HIV persistence

Latent reservoir



Finzi et al. Science 1997 ; Wong et al. Science 1997 ; Chun et al. PNAS 1997 ; Palmer et al. PNAS 2008 ; Chomont et al. Nat Med 2009

Courtesy N. Chomont

Mechanisms of HIV persistence

Latent reservoir

Memory CD4 T cells confer immunologic memory so that pathogens encountered in childhood are rapidly resolved if encountered again in adulthood

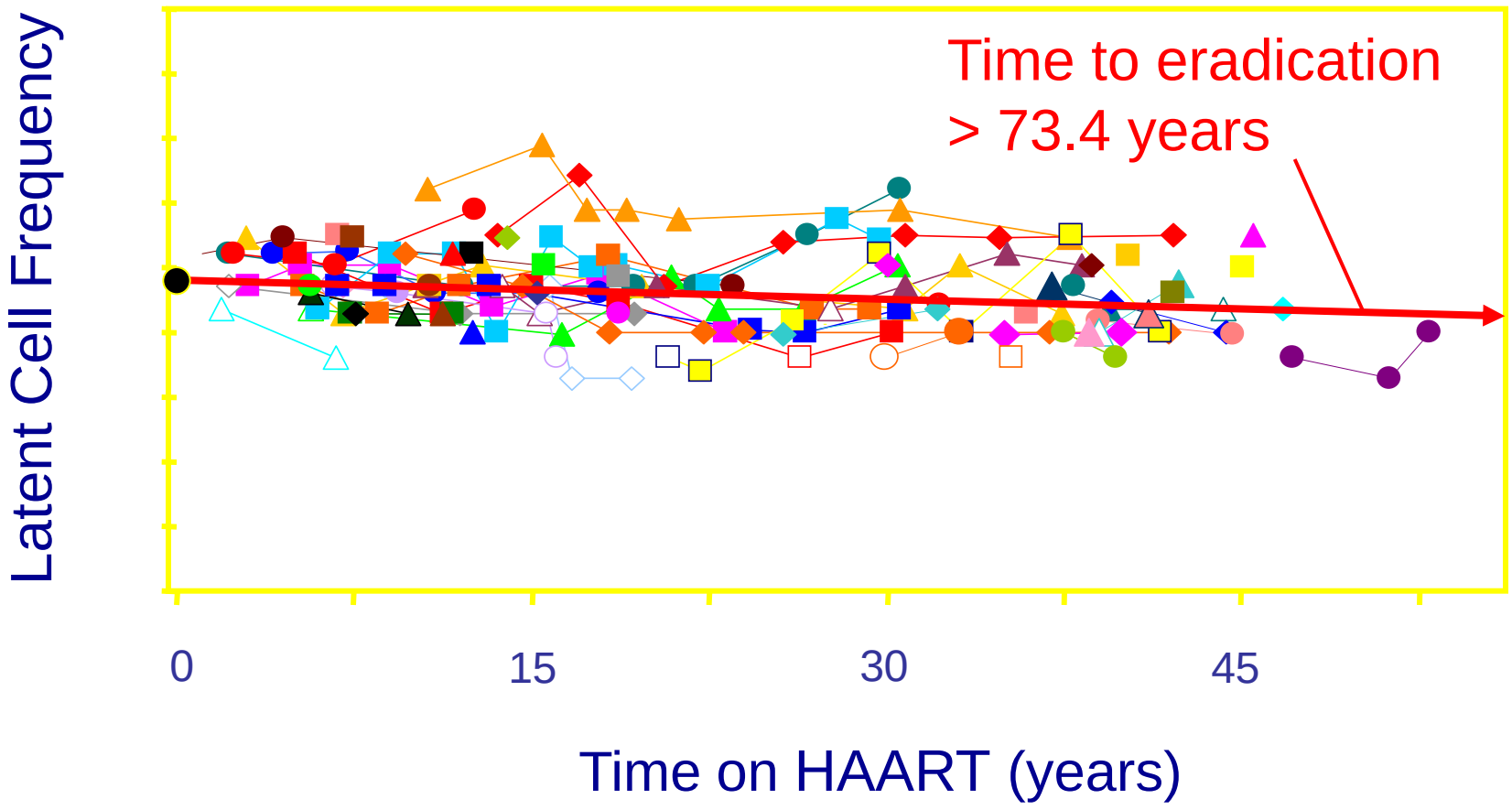
The ability of HIV-1 to take up residence in these cells confers life-long persistence.

This reservoir is considered the single biggest obstacle to curing HIV-1 infection

Finzi et al. Science 1997 ; Wong et al. Science 1997 ; Chun et al. PNAS 1997 ; Palmer et al. PNAS 2008 ; Chomont et al. Nat Med 2009

Courtesy N. Chomont

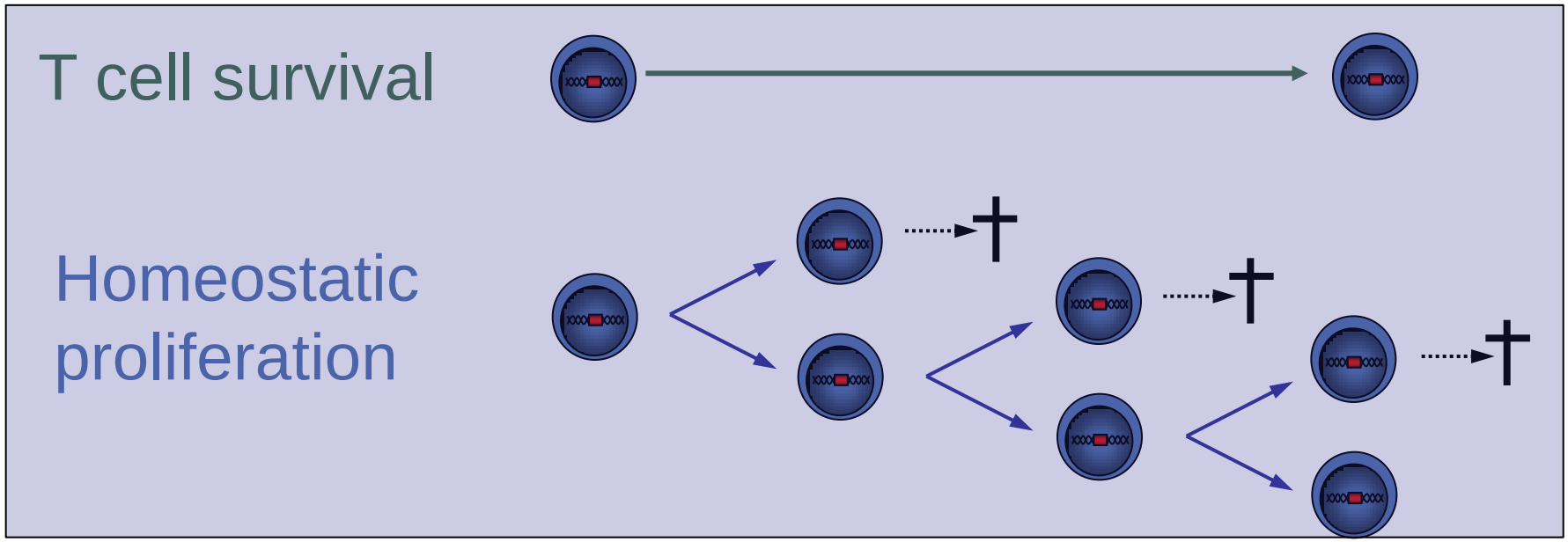
Slow decay of latently infected CD4$^+$ T cells



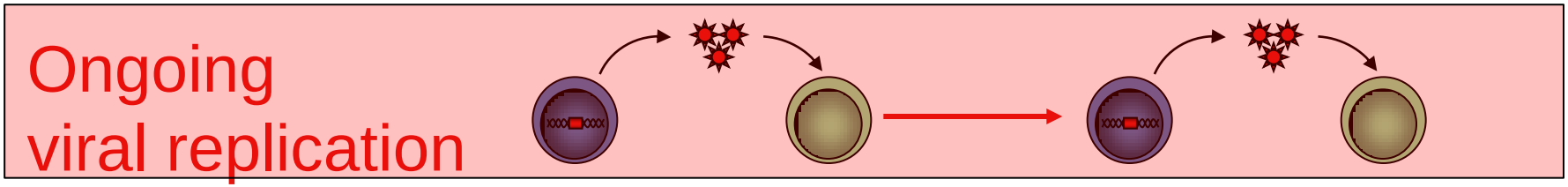
Courtesy Bob Siliciano

Mechanisms of HIV persistence

Latent reservoir



Active reservoir



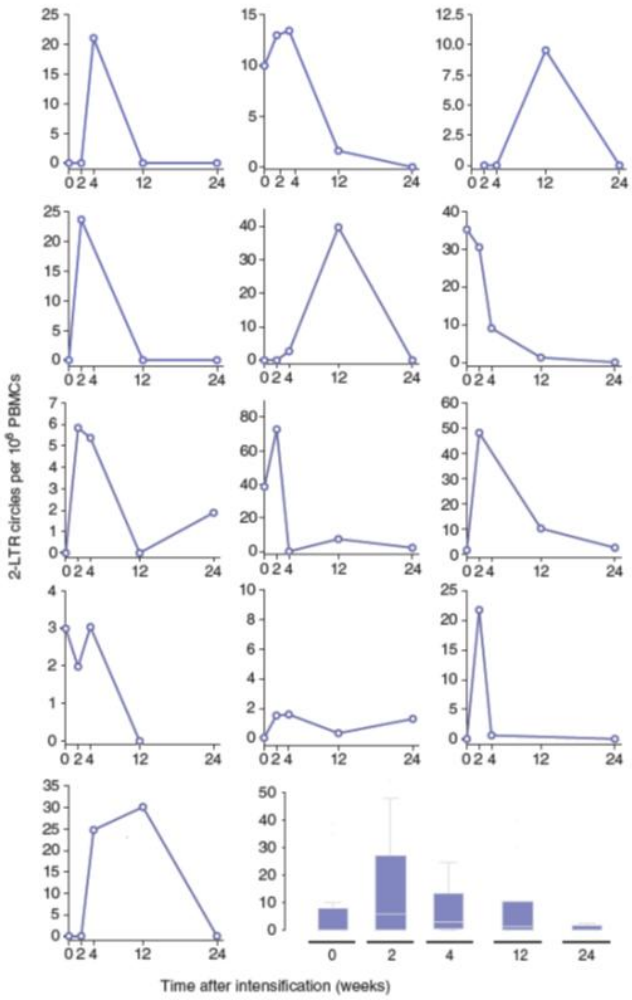
Courtesy N. Chomont

Finzi et al. Science 1997 ; Wong et al. Science 1997 ; Chun et al. PNAS 1997 ; Palmer et al. PNAS 2008 ; Chomont et al. Nat Med 2009

nature medicine

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

Maria J Buzón[1,9], Marta Massanella[1,9], Josep M Llibre[2], Anna Esteve[3], Viktor Dahl[4], Maria C Puertas[1], Josep M Gatell[5], Pere Domingo[6], Roger Paredes[1,2], Mark Sharkey[7], Sarah Palmer[4], Mario Stevenson[7], Bonaventura Clotet[1,2], Julià Blanco[1] & Javier Martinez-Picado[1,8]

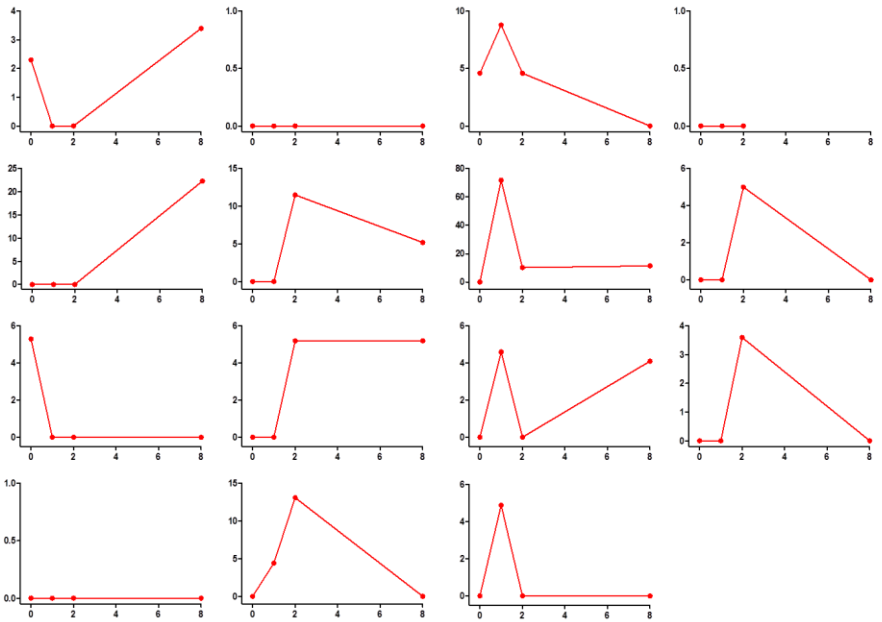


Raltegravir: 13/45 had detectable 2-LTR circles at any timepoint during the study

42 **Increase in 2-LTR Circles after Raltegravir Intensification in HAART-suppressed Patients with High CD4$^+$ T Cell Counts: A Randomized, Controlled Trial**

Hiroyu Hatano*[1], M Strain[2], R Scherzer[1], E Sinclair[1], S Palmer[3], M Busch[1,4], P Bacchetti[1], P Hsue[1], D Richman[2], and S Deeks[1]

The Journal of Infectious Diseases

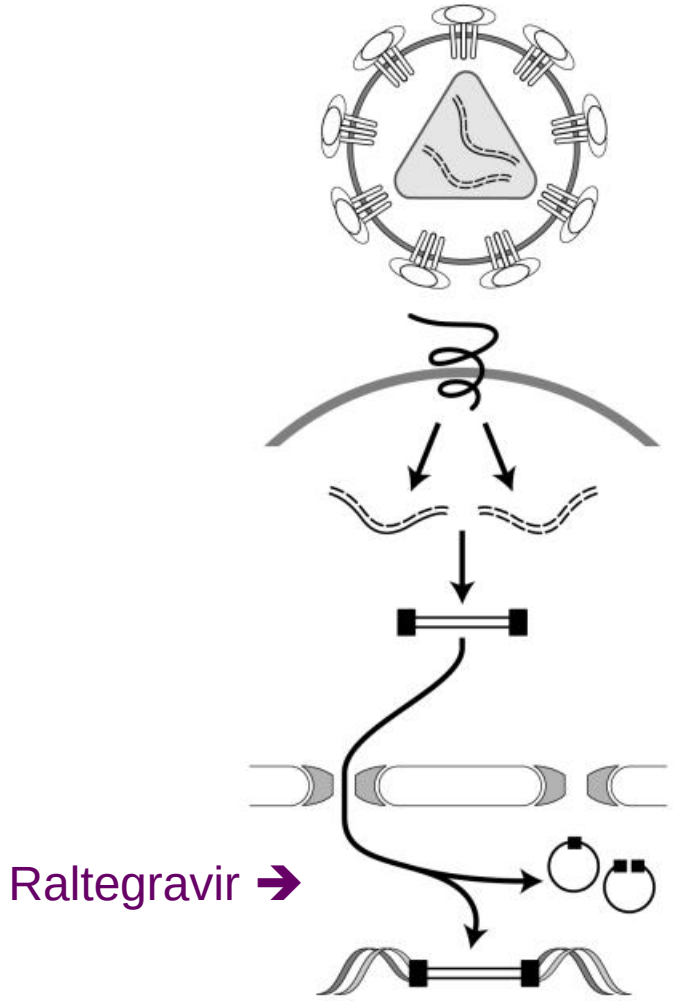


Raltegravir: 9/15 had increase in 2-LTR circles at Wk1 or Wk2

Increase in episomes following Raltegravir intensification can only be explained by *de novo* infection.

Cytoplasm

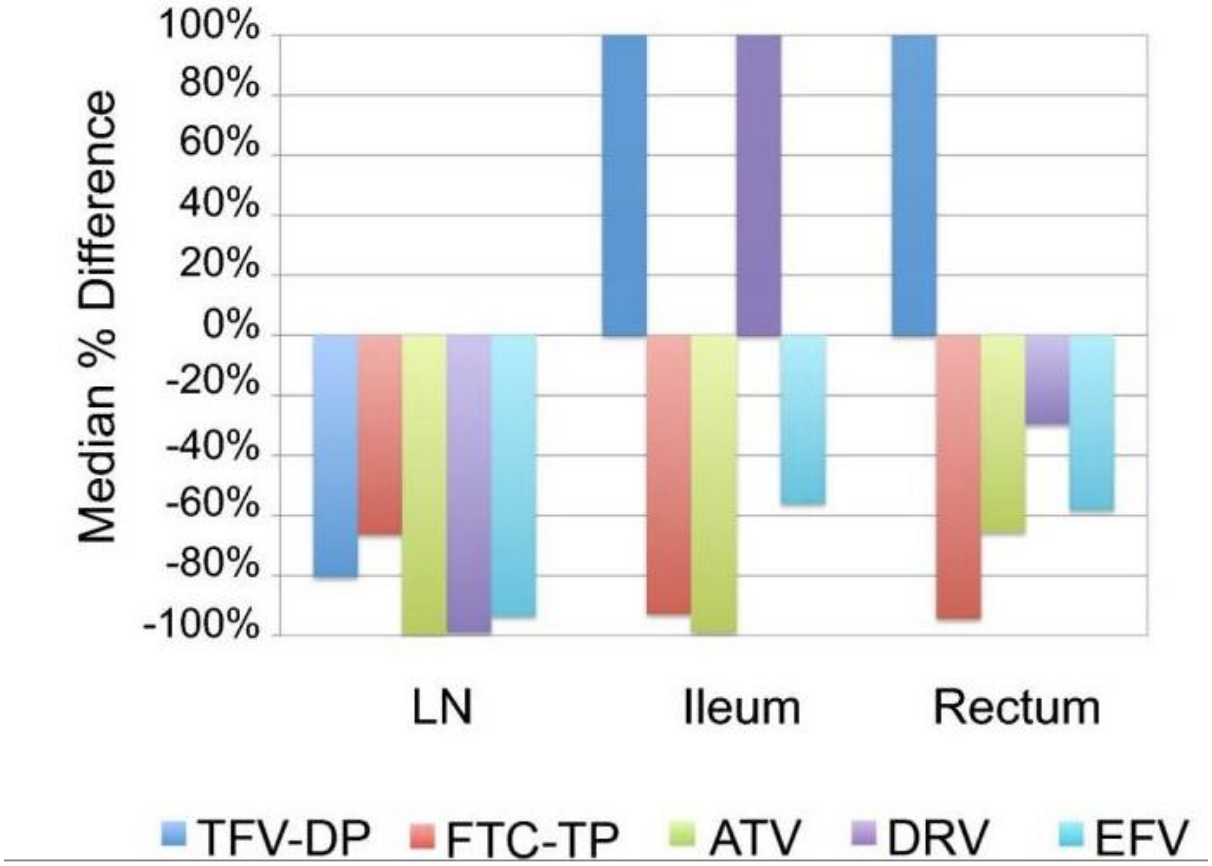
Nucleus



Infectious virions
(*in face of protease inhibitors*)

Reverse transcription of linear cDNA substrates
(in face of RT inhibitors)

Median % difference of lymphoid tissue from PBMC concentration



Mechanisms of HIV persistence

Latent reservoir

T

H

p

Is there an active reservoir and are there surrogates that could inform on the dynamics of the reservoir and its contribution to viral persistence?

Cell-associated RNA

Ac

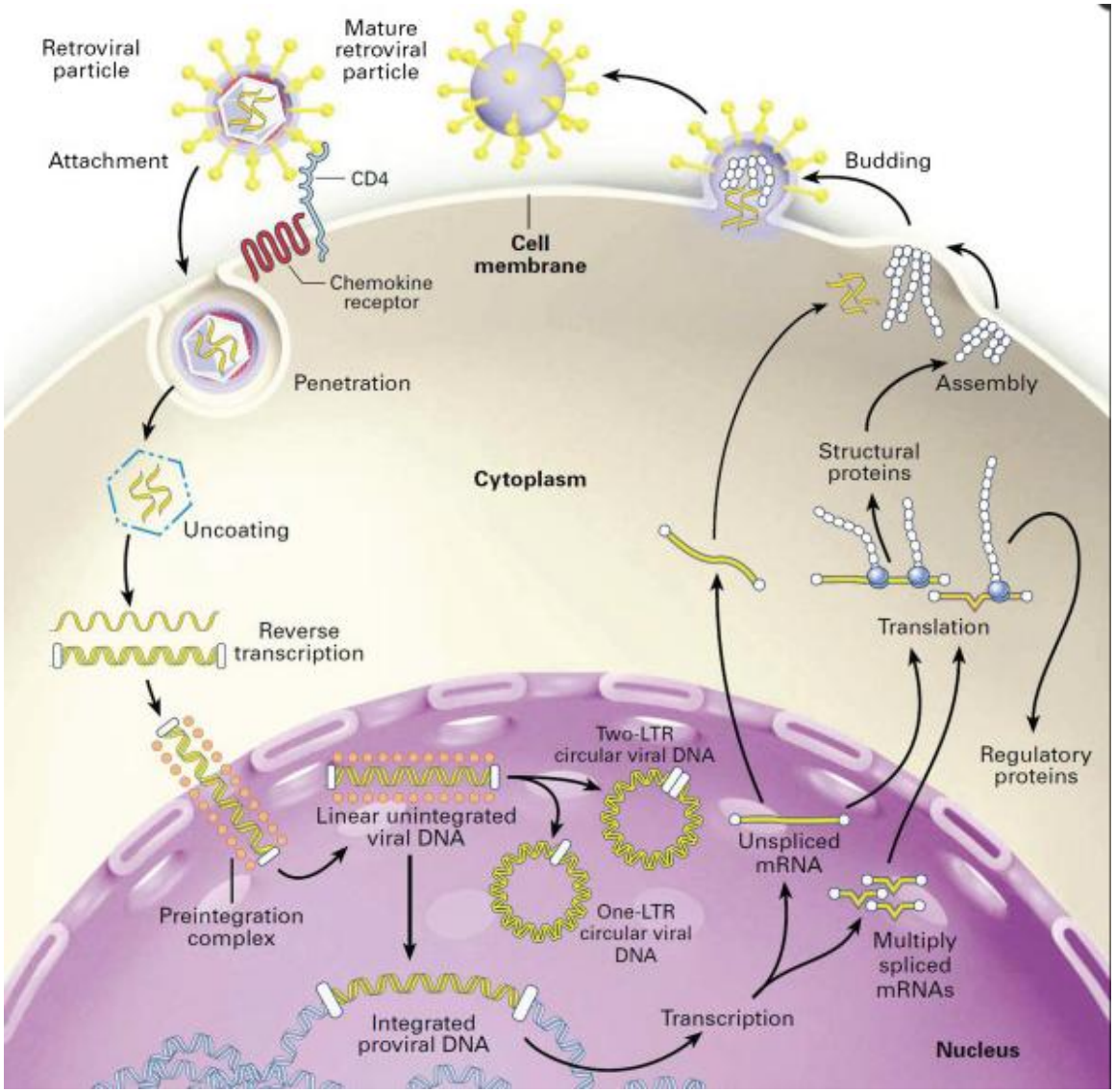
O

viral replication

Courtesy N. Chomont

Finzi et al. Science 1997 ; Wong et al. Science 1997 ; Chun et al. PNAS 1997 ; Palmer et al. PNAS 2008 ; Chomont et al. Nat Med 2009

Multiple viral RNA species produced in infected cells

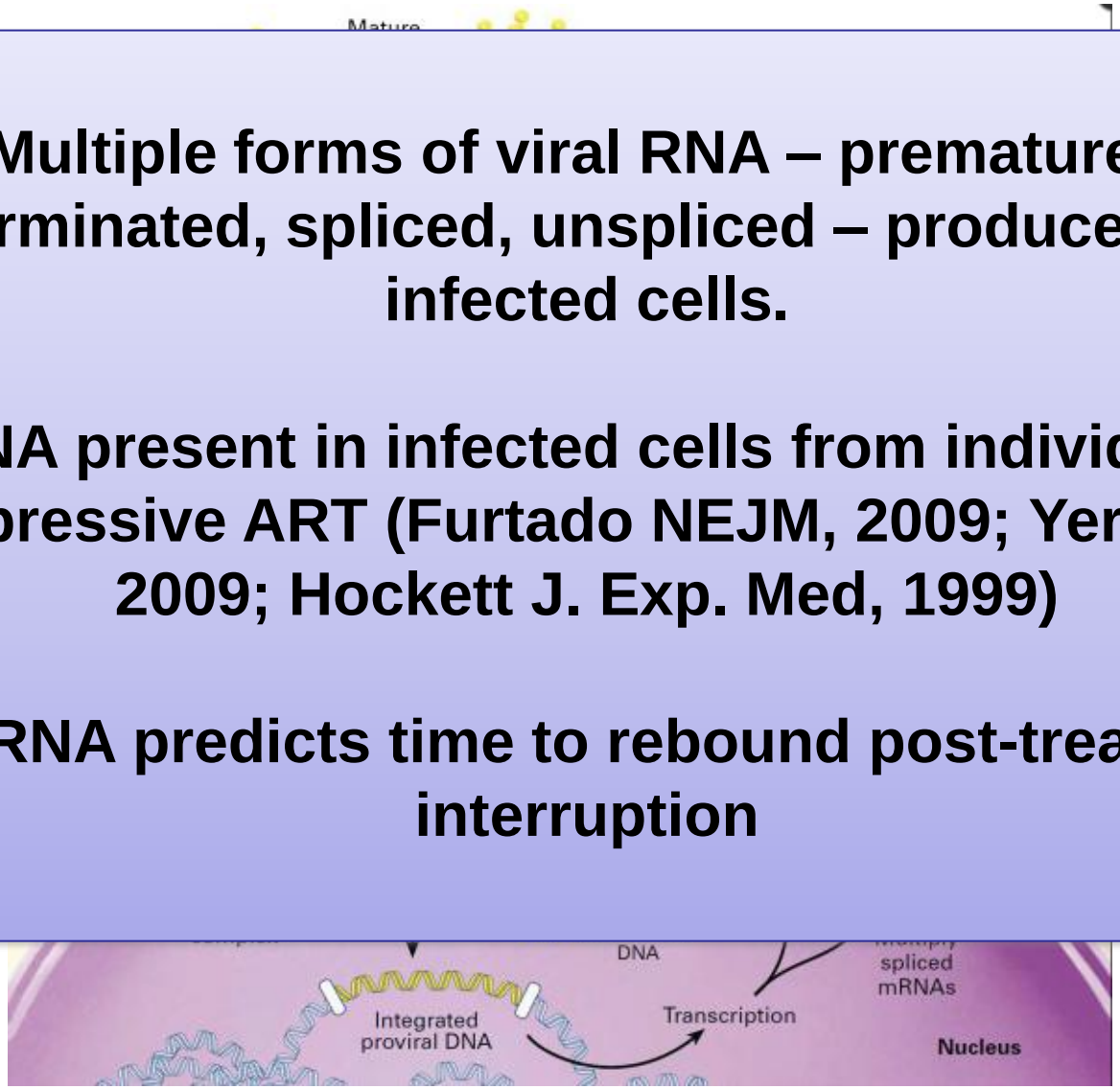


Multiple viral RNA species produced in infected cells

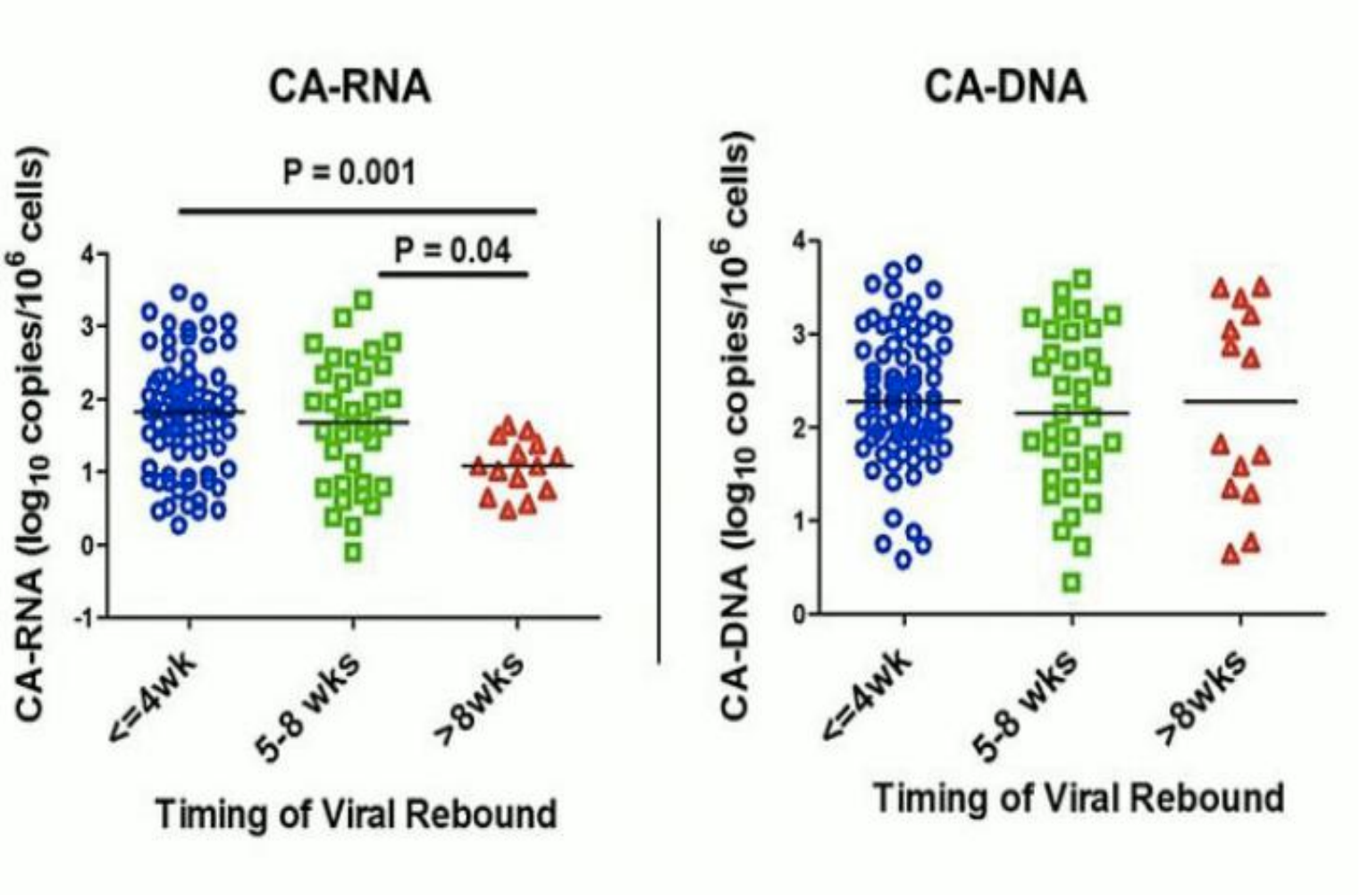
Multiple forms of viral RNA – prematurely terminated, spliced, unspliced – produced in infected cells.

CA-RNA present in infected cells from individuals on suppressive ART (Furtado NEJM, 2009; Yerly JID, 2009; Hockett J. Exp. Med, 1999)

CA-RNA predicts time to rebound post-treatment interruption



Baseline reservoir size and timing of viral rebound

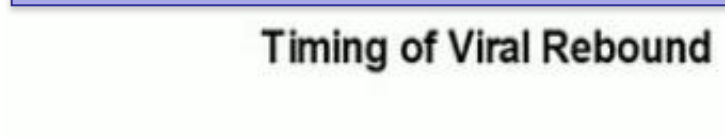


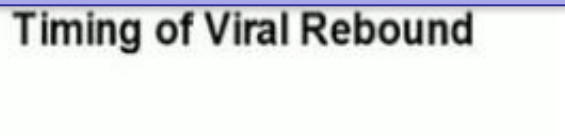
Baseline reservoir size and timing of viral rebound

Size of active reservoir (CA-RNA and residual viremia) are associated with timing of viral rebound

Significantly lower levels of CA-RNA in individuals treated during acute infection

Suggests infected cells may be recognizeable to immune system. Therefore, boosting antiviral immunity may help clear the viral reservoirs





Is HIV curable?

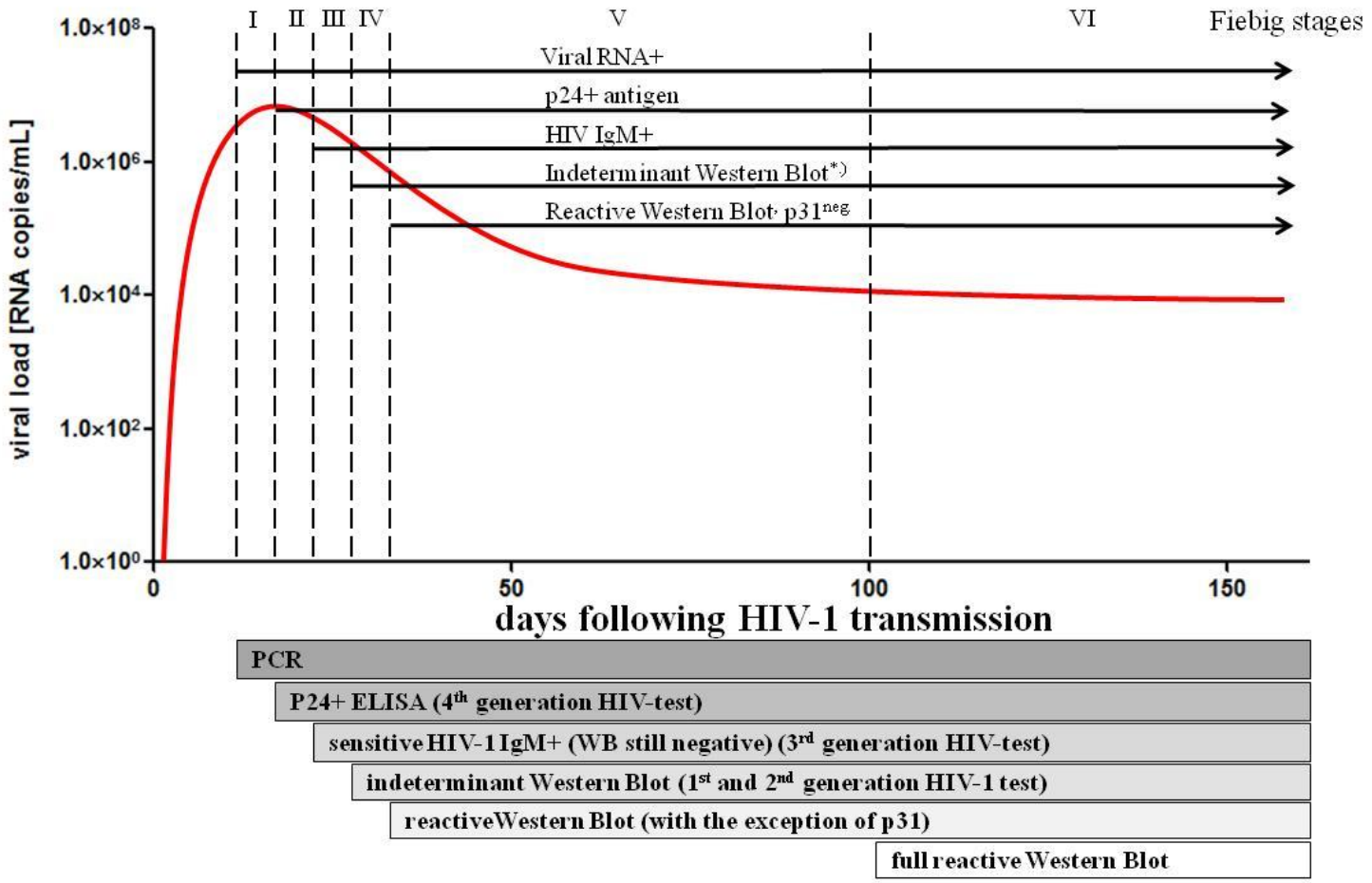
Lessons from early ART initiation!

Sterilizing cure- all virus has been eliminated from the body

Functional cure- virus remains but doesn't rebound after antiviral cocktails are removed

Early phases of HIV-1 infection

Figure 1



*.) the presence of HIV-1-specific Western blot bands that fail to meet interpretative criteria for reactive Western blot defined by the USA FDA as reactivity to two of the following three bands: p24, gp 41, gp 120/160

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[¶]

- **20 adults (and one child) who started therapy early (but not in "hyperacute" stage), remained on therapy for years, and had no rebound after stopping therapy**
- **Virus still remains detectable in blood but under control-even in absence of ART-functional cure?**

The NEW ENGLAND JOURNAL of MEDICINE

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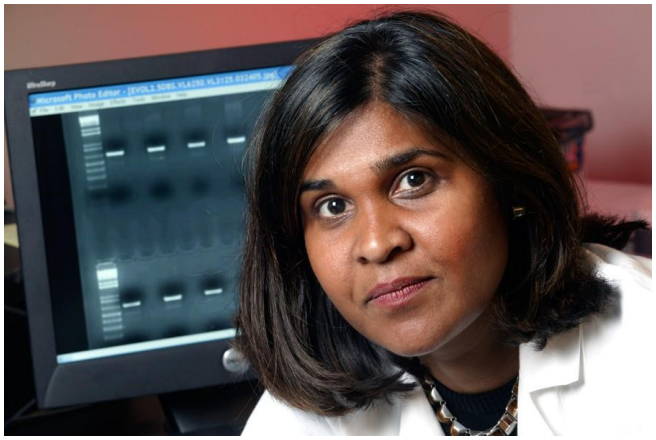
ORIGINAL ARTICLE

BRIEF REPORT

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

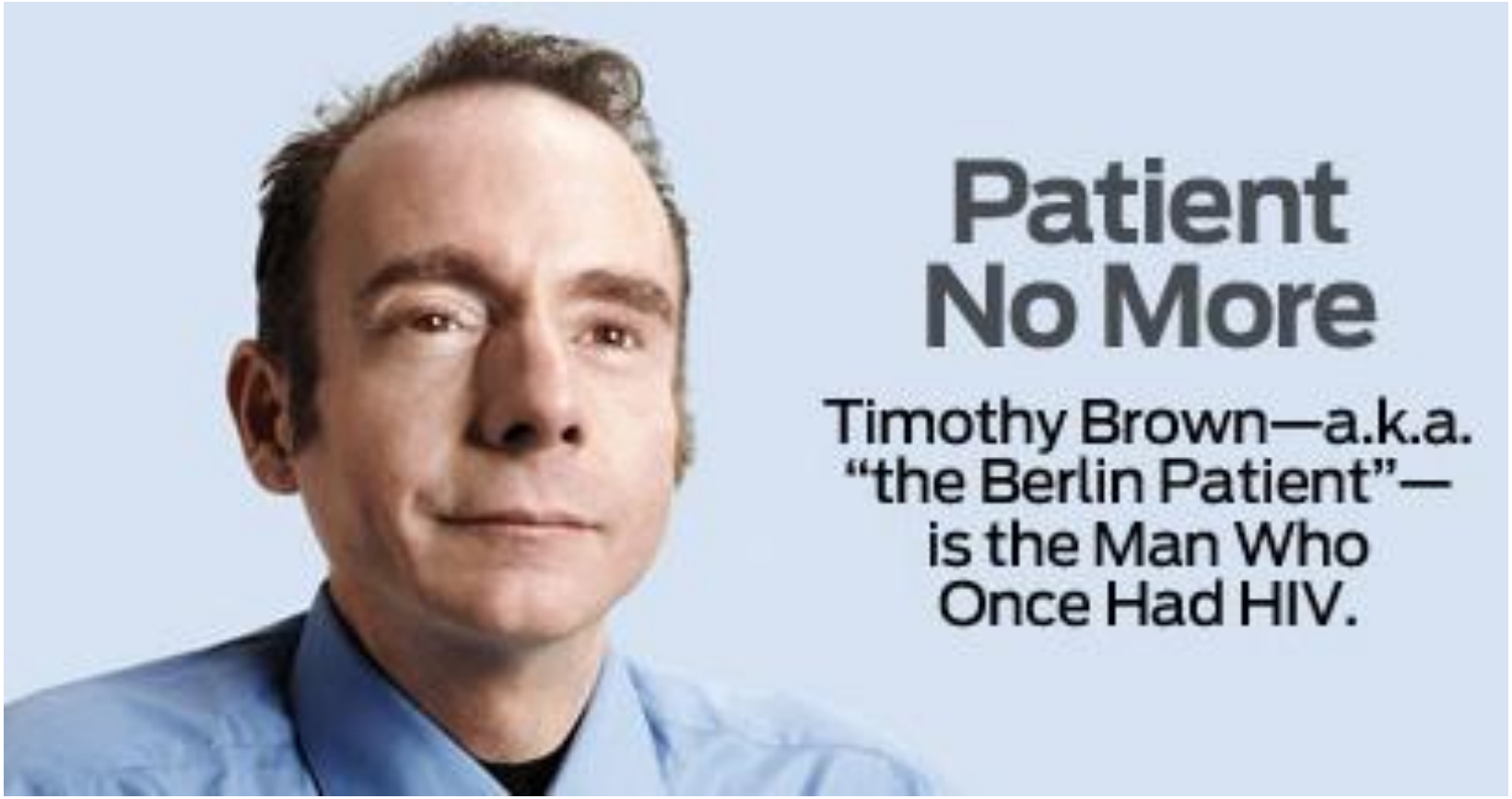
Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

N Engl J Med 2013; 369:1828-1835 | November 7, 2013 | DOI: 10.1056/NEJMoa1302976



- **"Mississippi baby" born to an HIV-positive mother who had not received antiretroviral treatment during pregnancy. Infant was treated from 30 hours after birth but parents stopped therapy after 18 months. Infant remained off drugs for next 27 months yet virus remained undetectable in blood until virus rebounded two months shy of infant's 4th birthday.**

44 million HIV infections; 1 validated cure, Timothy Brown (Berlin Patient)



44 million HIV infections; 1 validated cure, Timothy Brown (Berlin Patient)

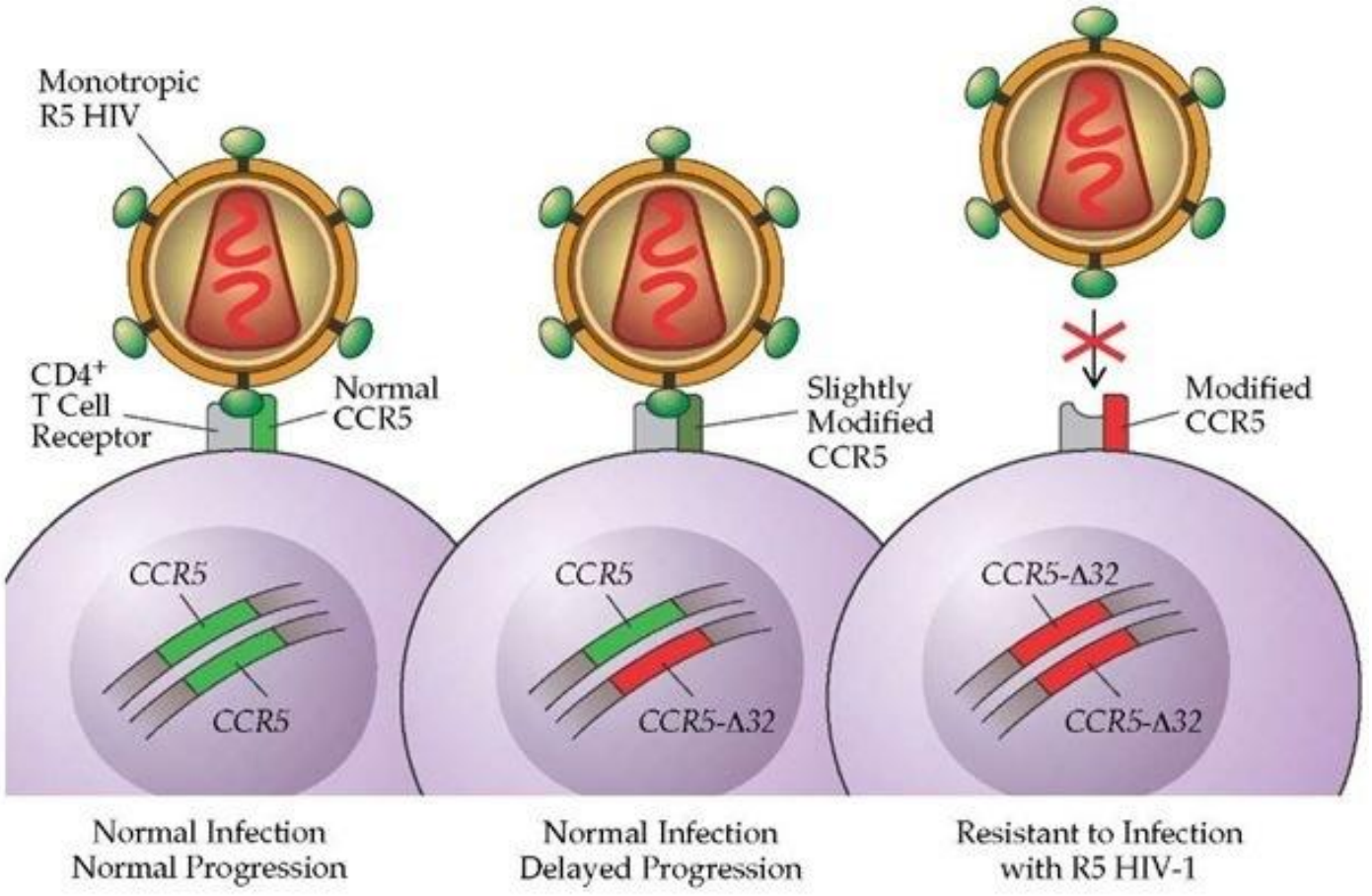
Infected 1995. On ARVs until 2006 where he develops acute myeloid leukemia.

Fails chemotherapy then receives two bone marrow transplants from a donor who had a mutation in CCR5- a co-receptor for the virus.

8 years later, virus is undetectable in all tissues even though Timothy Brown is not on therapy.

What was different about this case?

CCR5 alleles



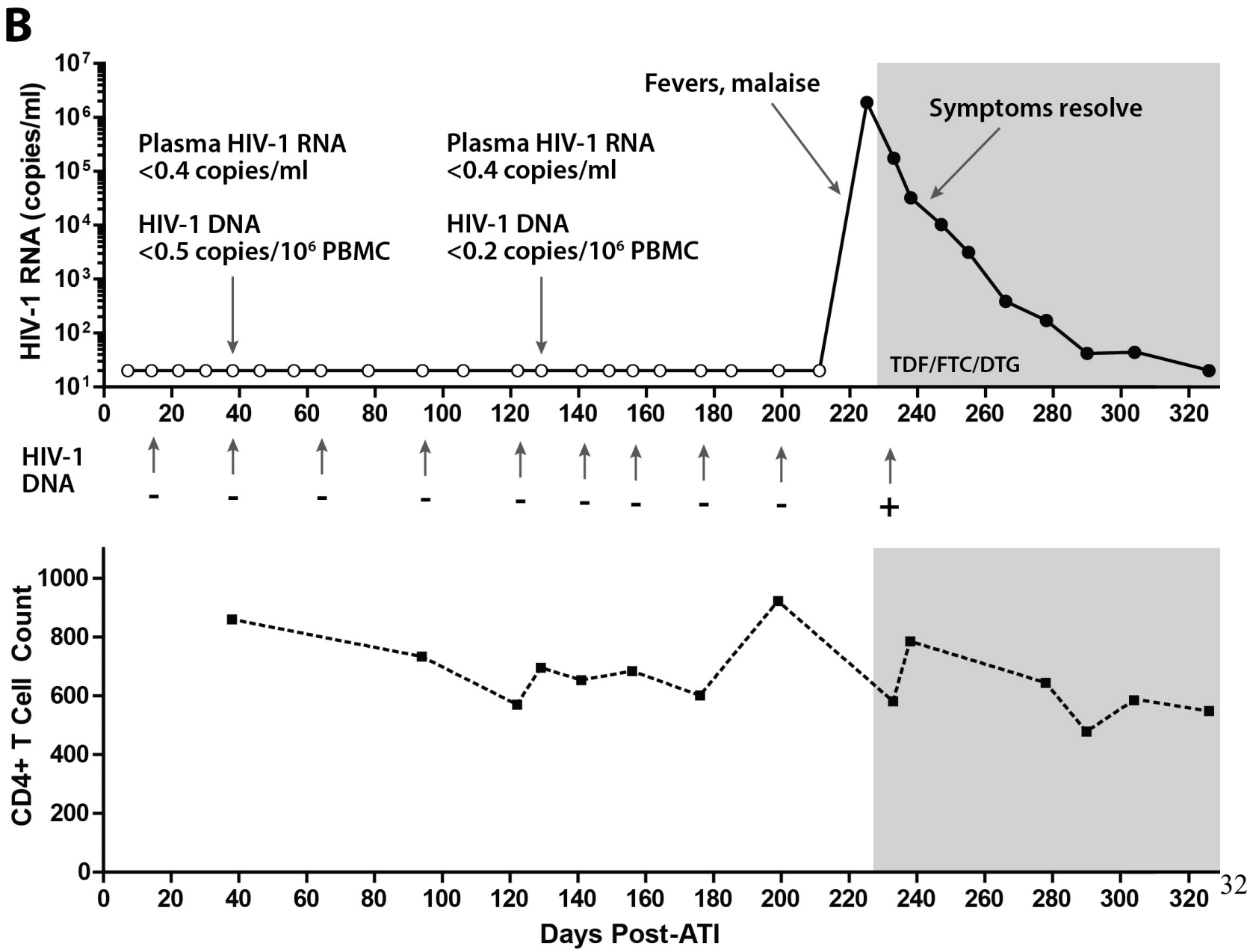
US Presidents have taken an interest in this discovery!

The Journal of Infectious Diseases

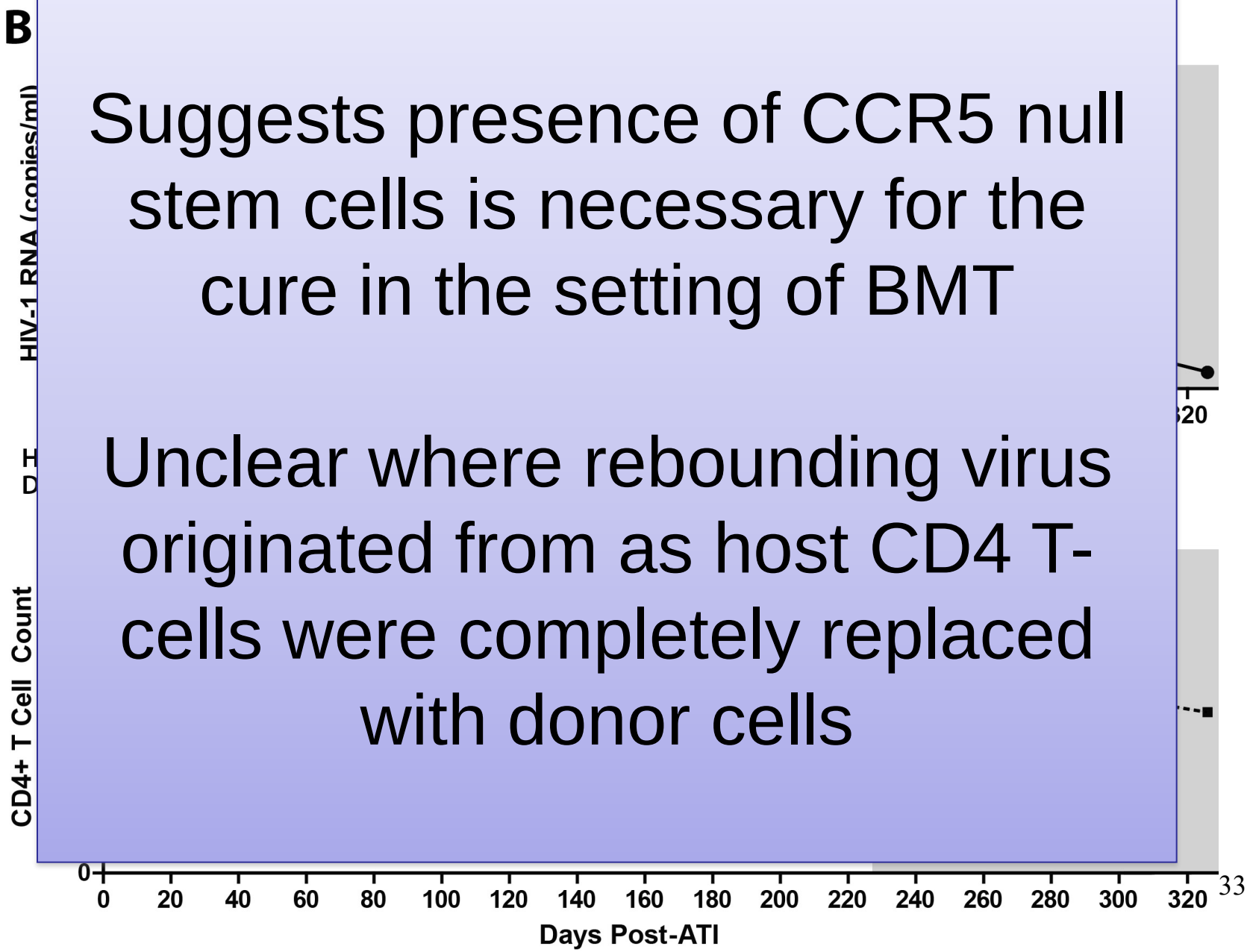
Long-Term Reduction in Peripheral Blood HIV Type 1 Reservoirs Following Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation

Timothy J. Henrich[1,2], Zixin Hu[1,2], Jonathan Z. Li[1,2], Gaia Sciaranghella[3,a], Michael P. Busch[6,7], Sheila M. Keating[6,7], Sebastien Gallien[1,8], Nina H. Lin[2,4], Francoise F. Giguel[4], Laura Lavoie[4], Vincent T. Ho[2,5], Philippe Armand[2,5], Robert J. Soiffer[2,5], Manish Sagar[1,2,a], Ann S. LaCasce[2,5] and Daniel R. Kuritzkes[1,2]

ATI: Patient B



ATI: Patient B



Suggests presence of CCR5 null stem cells is necessary for the cure in the setting of BMT

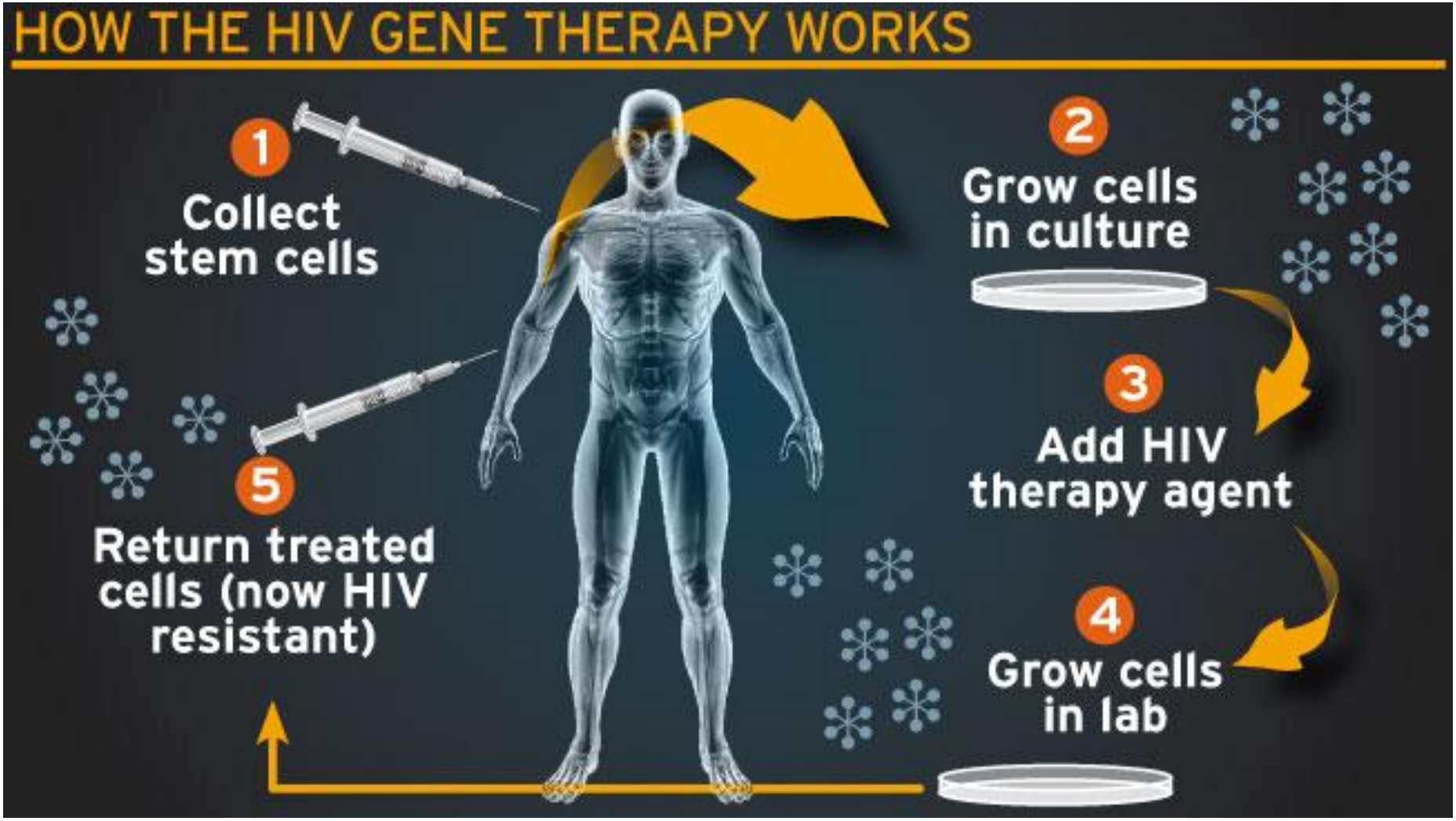
Unclear where rebounding virus originated from as host CD4 T-cells were completely replaced with donor cells

Genetic approaches to eliminating HIV infection!

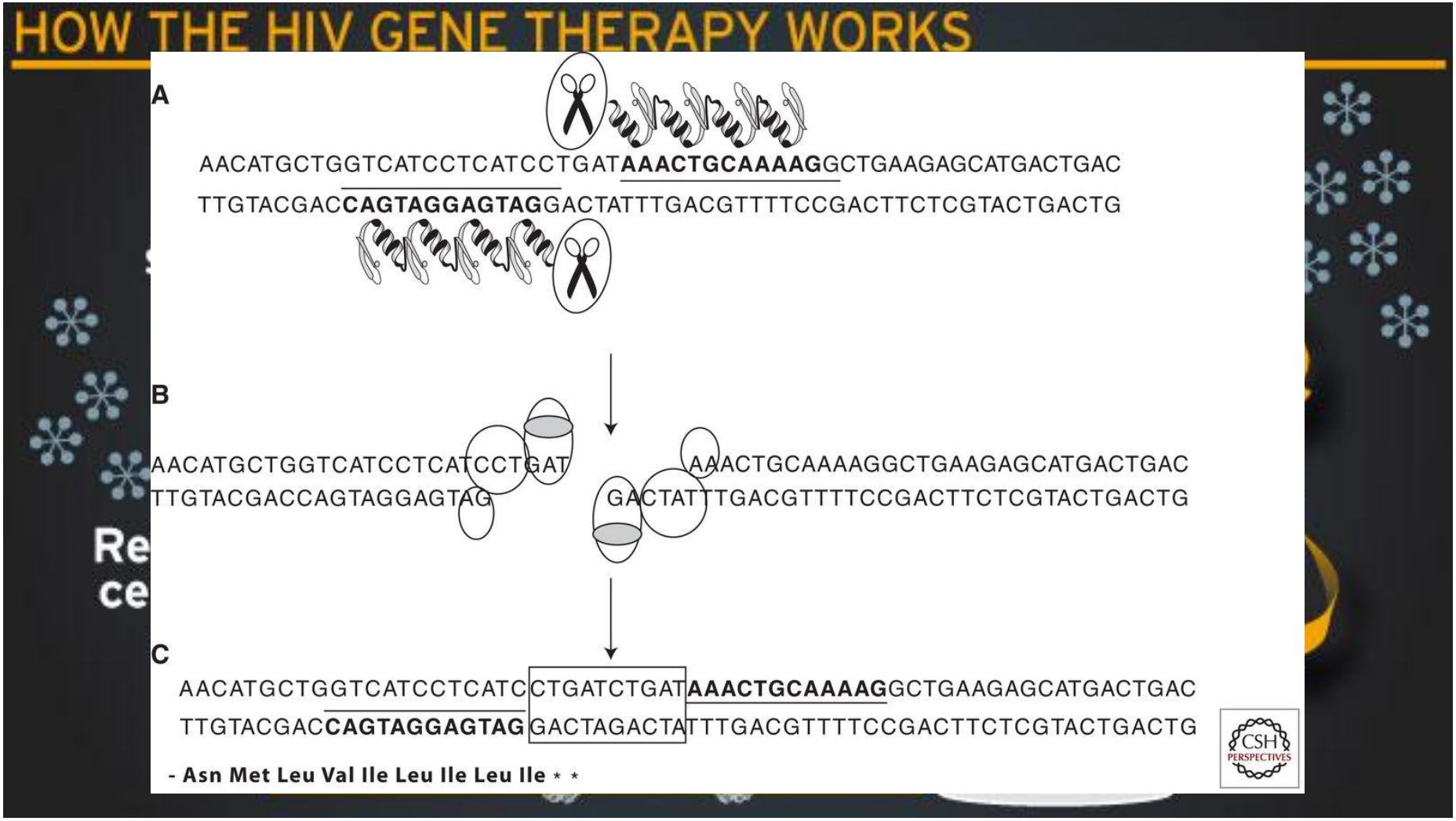
Why can't we use bone marrow transplant to cure HIV infection?

- Identification of immunologically matched donors with CCR5 mutation is challenging
- BMT carries a 25% mortality rate.
- BMT to cure HIV is unethical when ARVs sustain survival. Physician can not increase risk for patient.
- Costs are significant ~300K
- Scientists are developing approaches to create the CCR5 mutation in an infected individuals stem cells

Gene therapy for cure of HIV-1



Gene therapy for cure of HIV-1



Challenges behind genetic therapies to cure HIV-1 infection!

- Cost- $100K!
- Most of the 40 million infections worldwide are in resource-limited regions where average per capita healthcare expenditure is several hundred dollars
- Long-term concerns with modifying an individuals DNA.
- Challenges in delivering the agent to the rare cells that harbor functional viral DNA

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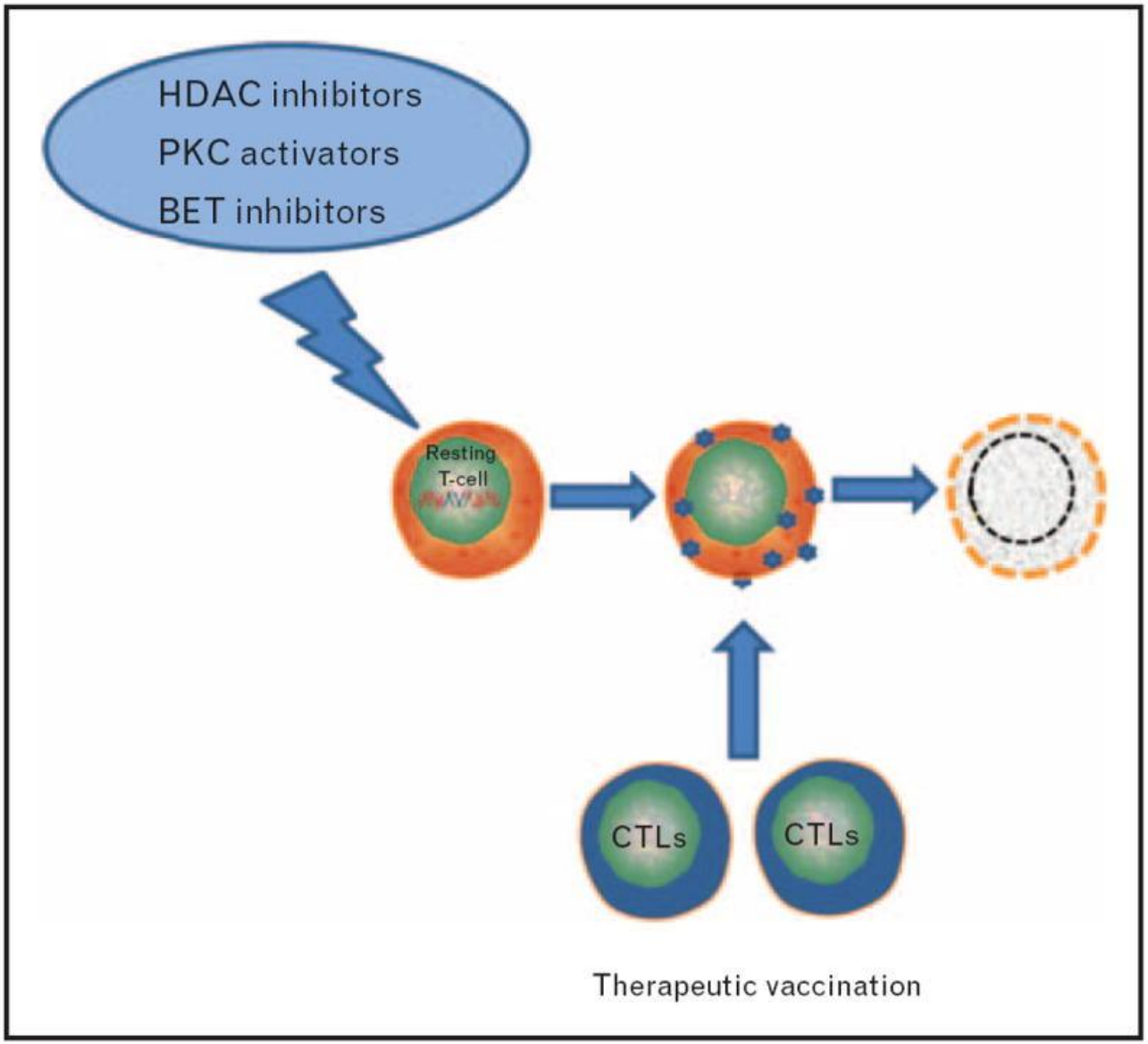
Eliminating the latent reservoir using kick and kill approaches!

Shock and kill approach for cure of HIV!



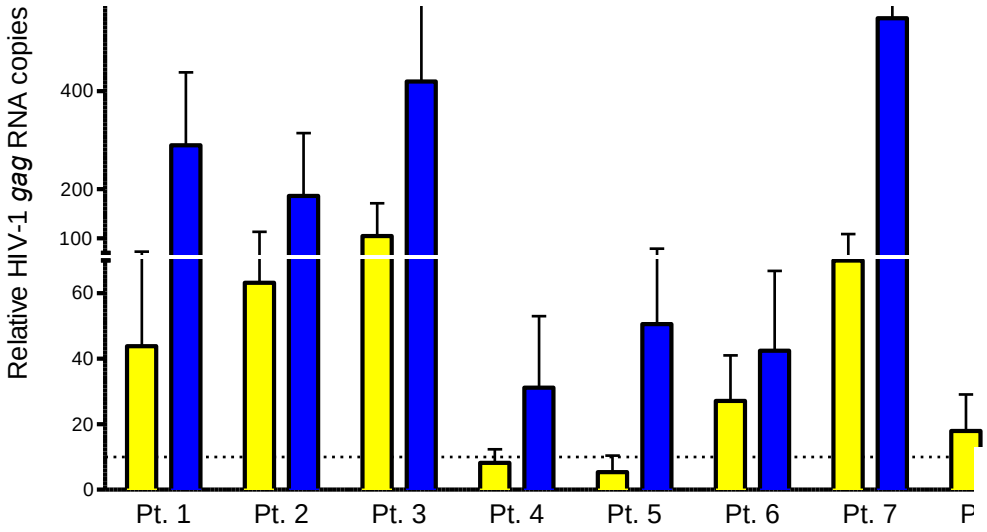
“Kick and Kill” Pilot study of vorinostat (SAHA) in long-term treated adults

LETTER

nature
International weekly journal of science

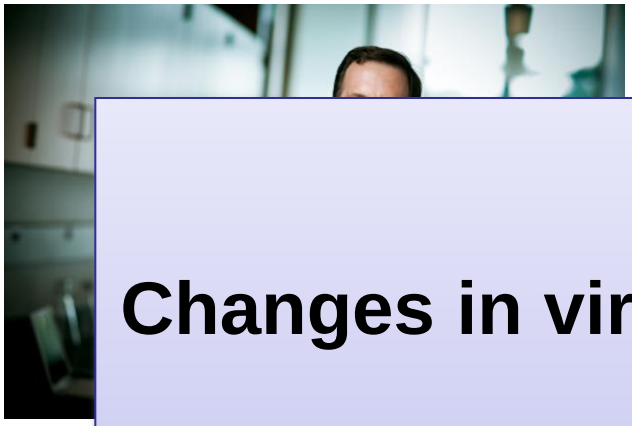
Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

N. M. Archin[1], A. L. Liberty[1], A. D. Kashuba[1], S. K. Choudhary[1], J. D. Kuruc[1], A. M. Crooks[1], D. C. Parker[1], E. M. Anderson[2], M. F. Kearney[2], M. C. Strain[3], D. D. Richman[3], M. G. Hudgens[1], R. J. Bosch[4], J. M. Coffin[2], J. J. Eron[1], D. J. Hazuda[5] & D. M. Margolis[1]



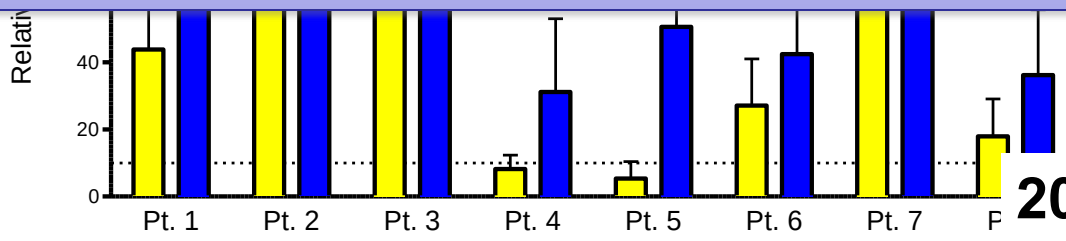
2012!

“Kick and Kill” Pilot study of vorinostat (SAHA) in long-term treated adults



Changes in viral RNA levels were very modest

Unclear whether viral protein- the essential target of “shock and kill” strategy, was produced



2012!

Immune-based approaches to eliminate the viral reservoirs!

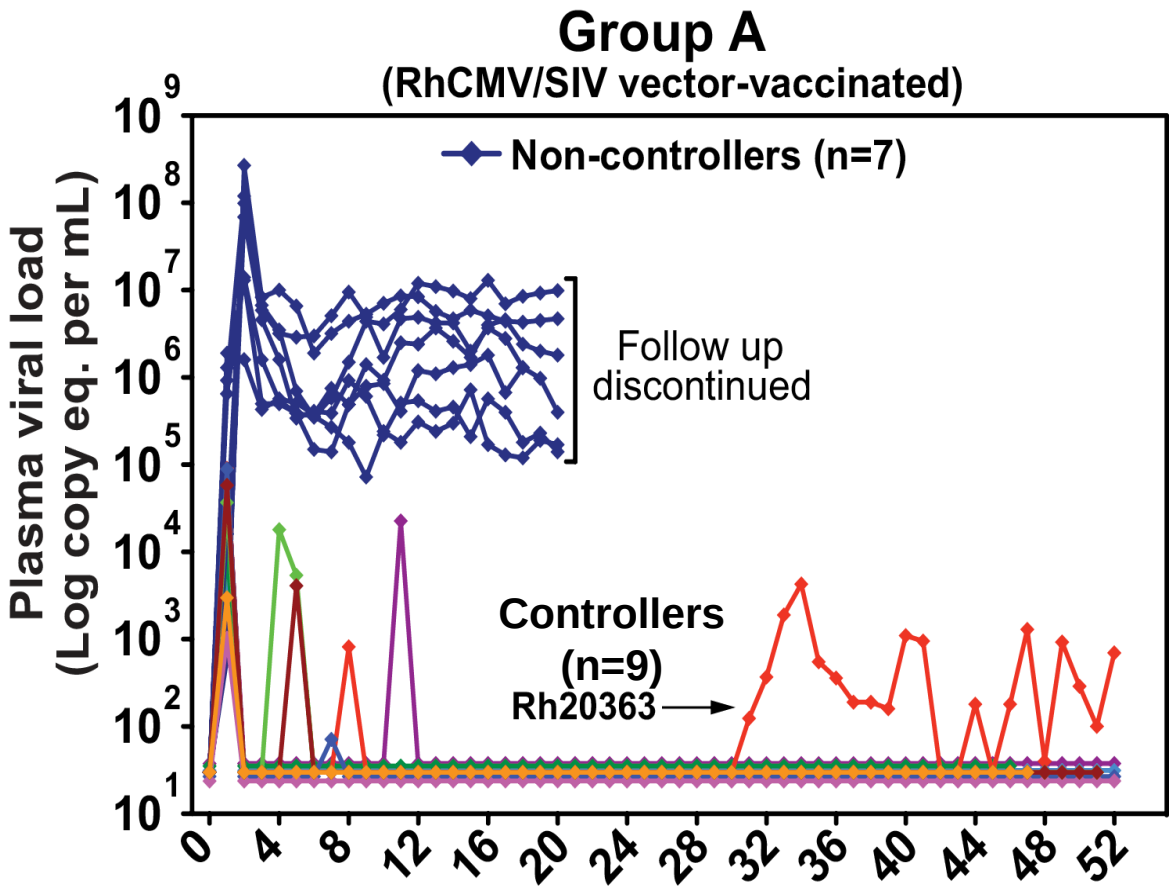
nature International weekly journal of science

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 engineered as a live HIV/SIV vaccine causes high levels of tissue-based "killer" CD8+ T cells that target novel parts of the virus**
- **Vector stimulates "unconventional" MHC II/HLA E restricted CD8+ T cell responses that are potent, effector memory differentiated, widely distributed and indefinitely persistent**
- **These cells clear latency during early infection, resulting in first clear documentation of a "cure" in this model**

Novel vaccine given before exposure may aid in viral control: SIV/macaque model



No protection

but

Virus **eradicated** in 50%

Hansen SG and Picker LJ, Nature 2013

Getting CD8 T-cells to the right place!

Obstacles to Cure

Reservoir of long-lived, latently infected cells.

Residual viral replication and potential replenishment of viral reservoirs. Reservoir may be dynamic

The presence of an active reservoir, if validated, supports the rationale for therapeutic intervention strategies- even if “Shock and Kill” approaches fail.

Colleagues/Collaborators/Contributors:

IRSI Caixa, Barcelona
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University of Minnesota
Tim Schacker
Ashley Haase

UCSF
Steve Deeks
Mike McCune
DARE Collaboratory

University of Nebraska
Courtney Fletcher

Delaney AIDS Research Enterprise
DARE
to find a cure

NATIONAL INSTITUTES OF HEALTH

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MIAMI CENTER FOR AIDS RESEARCH