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GLOBAL EDUCATION

Towards an HIV Cure

Steven G. Deeks, MD
Professor of Medicine in Residence
HIV/AIDS Division
University of California, San Francisco (UCSF)
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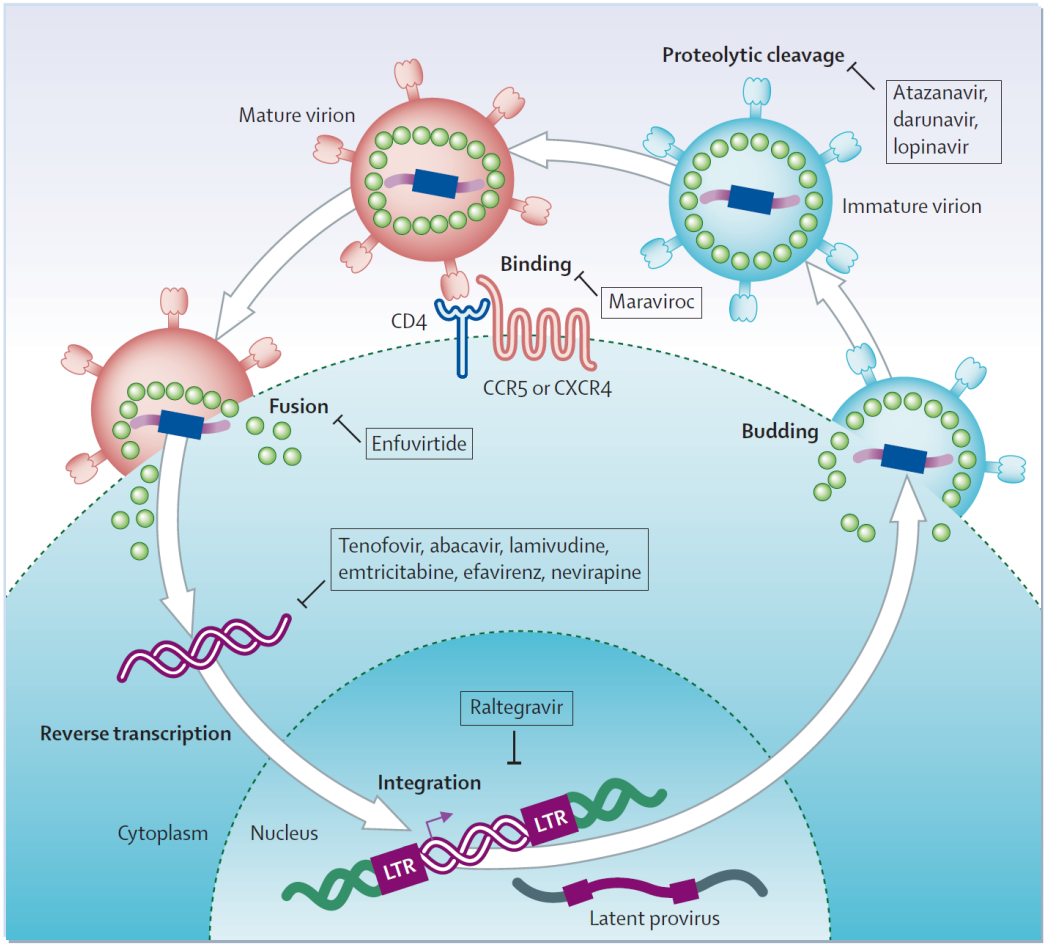
UCSF
University of California
San Francisco

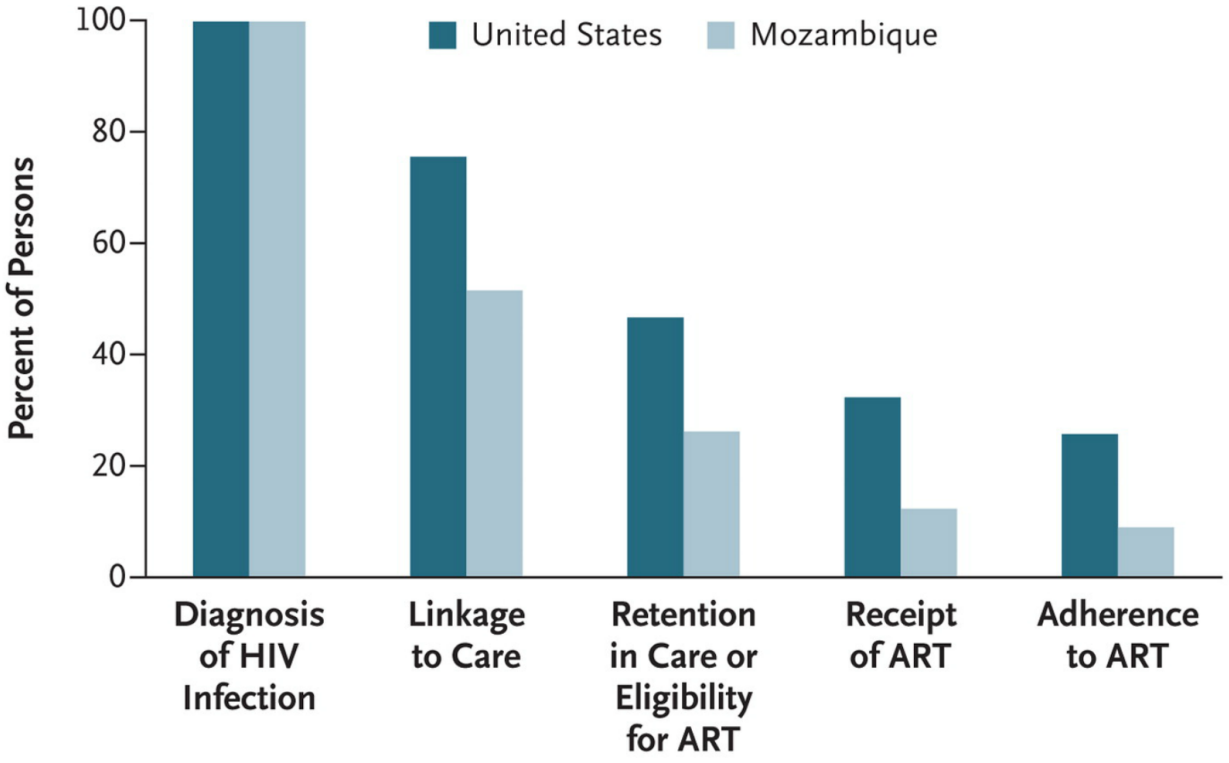
PositiveHealthProgram
HIV/AIDS Division at SFGH

With over 20 drugs and several viable regimens, the motivated patient with life-long access to therapy can control HIV indefinitely, eliminating the risk for AIDS



Volberding Lancet 2012

The major unmet need is getting treatment to all in need



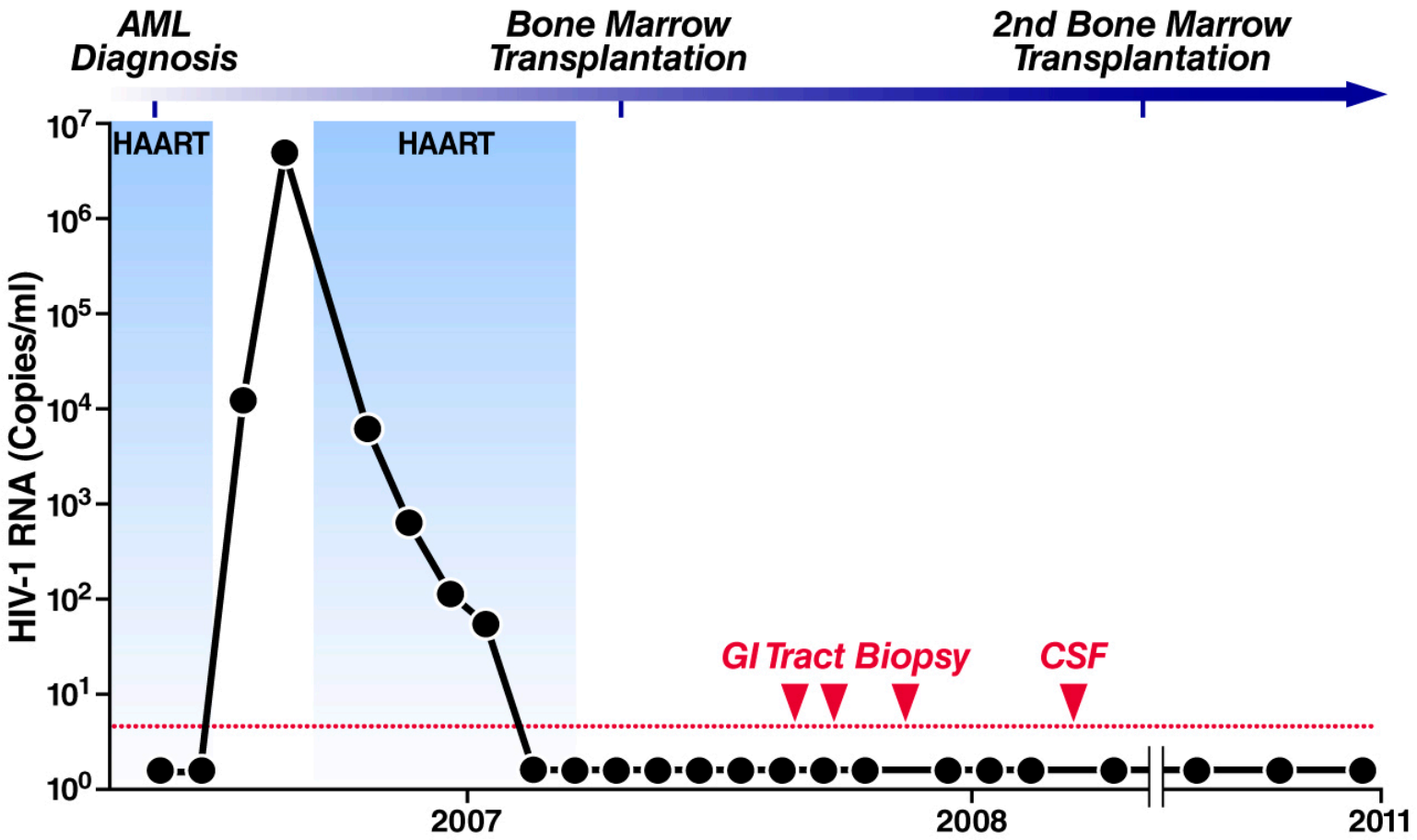
The majority of people globally (> 20 million) are not on therapy

Piot and Quinn, NEJM 2013
Micek et al., JAIDS 2009
Gardner et al., CID 2011
Hall et al., JAMA IM 2013

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.



Mechanisms of HIV persistence (not mutually exclusive)

- Low-level ("cryptic") viral replication
  - If present, likely involves cell-to-cell transfer among tissue-based activated cells
- Long-lived reservoir of resting CD4+ T cells that harbor transcriptionally silent, integrated (latent) HIV genomes
  - Maintained in part by homeostatic proliferation, expression of negative regulators, myeloid-T cell interactions
- Long-lived reservoir of non-T-cell populations
- Lack of effective HIV-specific immunity in reservoirs where HIV persists

Functional Cure

- Long-term health in absence of therapy ("functional cure")
  - Cancer model (remission)
  - Occurs in ~1% of natural infections and may be occuring in recently identified "post-treatment controllers" (e.g., Visconti Cohort)
- Will there be residual disease?
- Approach: Enhance HIV-specific immunity

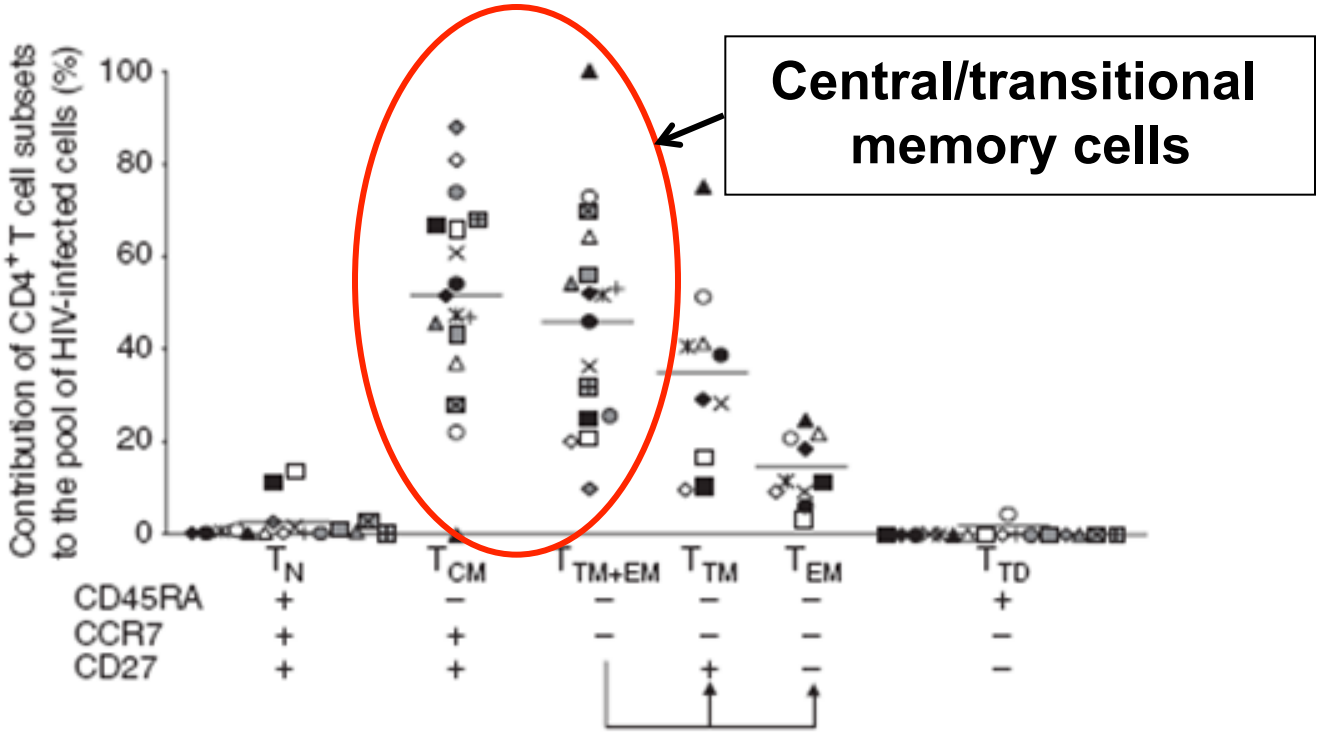
Sterilizing Cure

- Complete eradication of all replication competent virus (“sterilizing cure”)
  - Is this remotely possible?
  - Is this necessary?
  - How can this be proven?
- Approach: Induce transcription of latent HIV genomes in resting CD4+ T cells during completely effective antiretroviral therapy

A sterilizing cure may require potent host responses to clear virus-producing cells

Can we cure HIV with very early therapy?

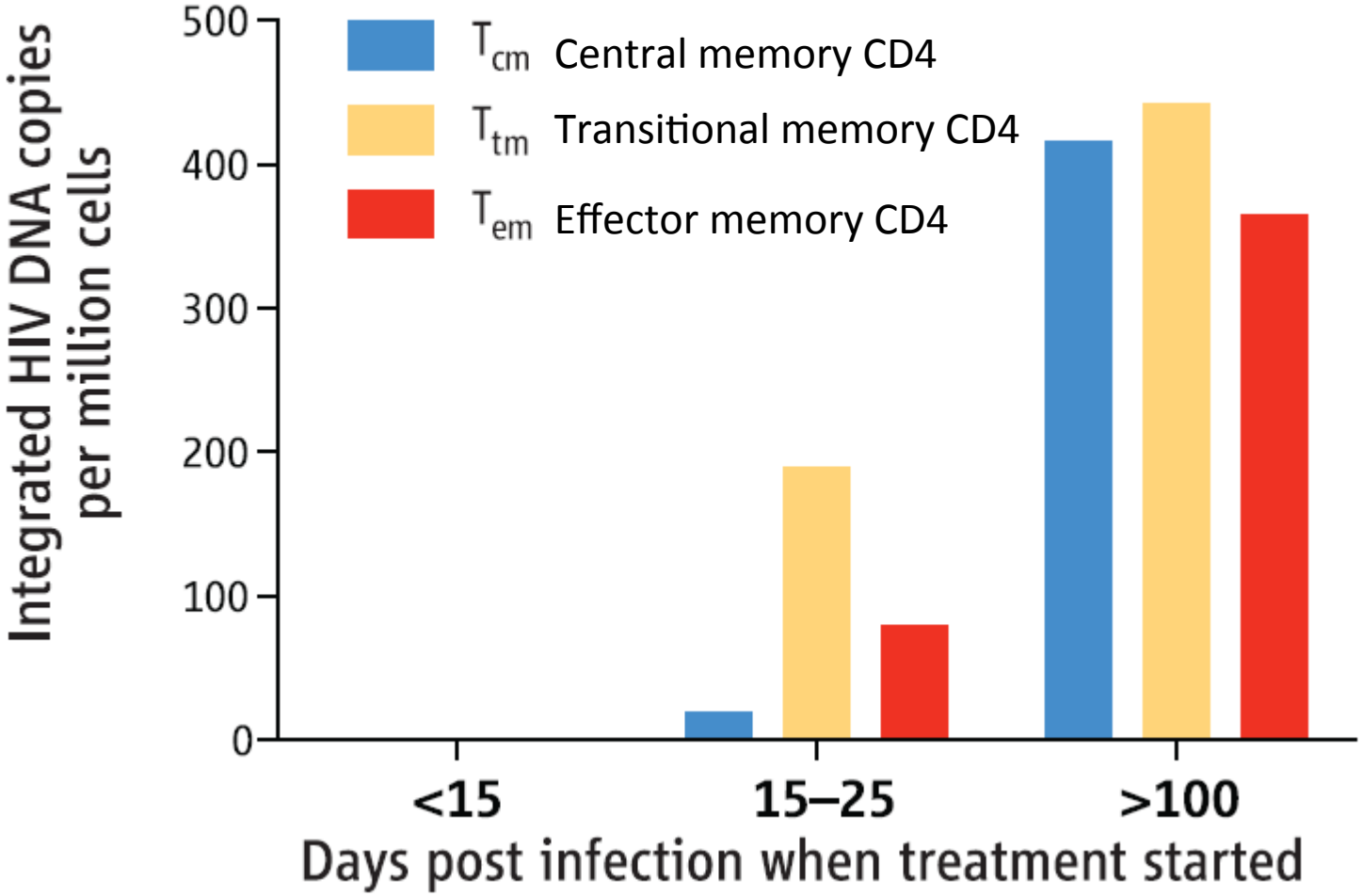
After decades of "complete" viral suppression, all virus may reside in (or originate from) long-lived memory CD4+ T cell subsets



HIV DNA levels increasing enriched in self-renewing memory stem cells over time

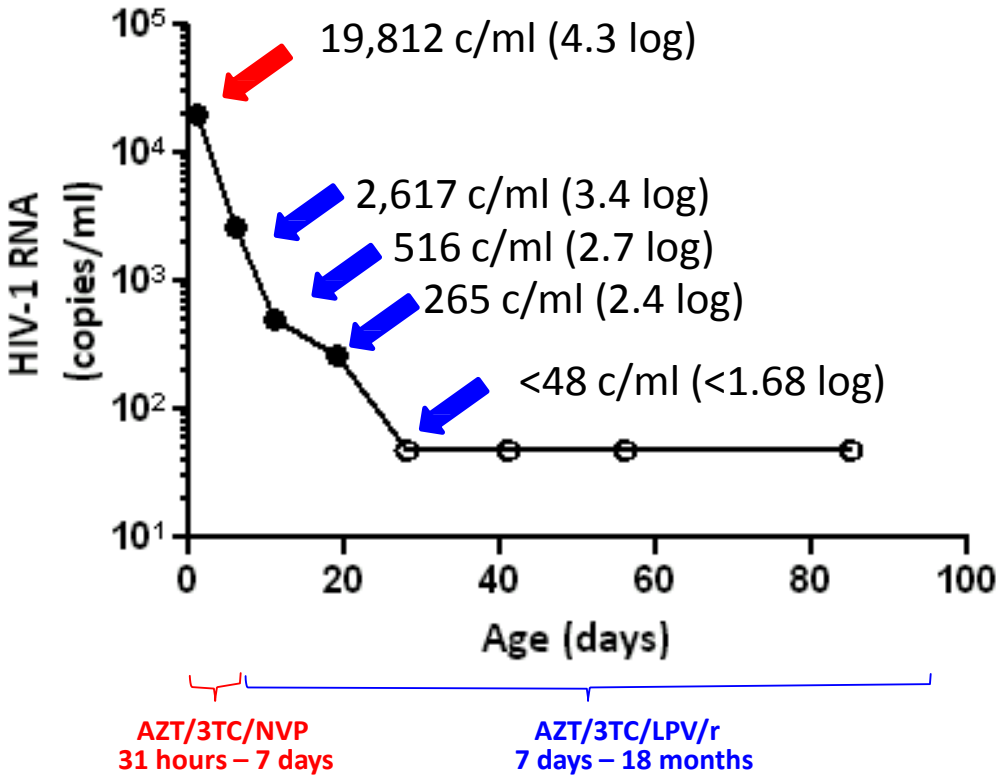
Chomont, Nature Medicine 2009
Buzon et al, CROI 2013

Restricted integration of HIV DNA in memory CD4+ T cells during acute HIV in SEARCH 010/RV254 study



Ananworanich et al, CROI 2013

Very early ART in an infant resulted in an apparent cure



- **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**

Persaud et al, CROI 2013

Can we create a "functional" cure (defined as host control of persistent virus) with early therapy?

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PLOS | PATHOGENS

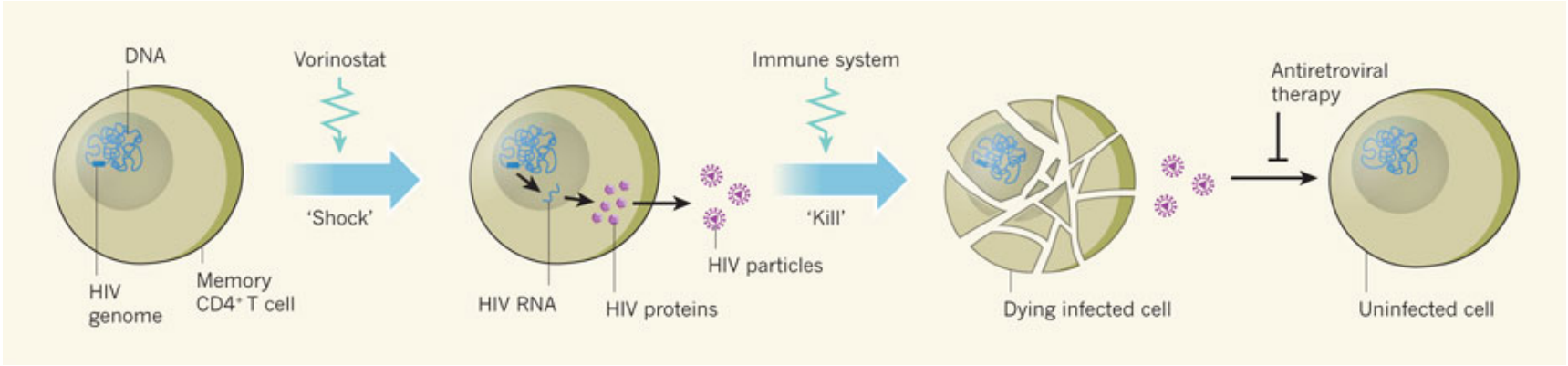
Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

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[¶]

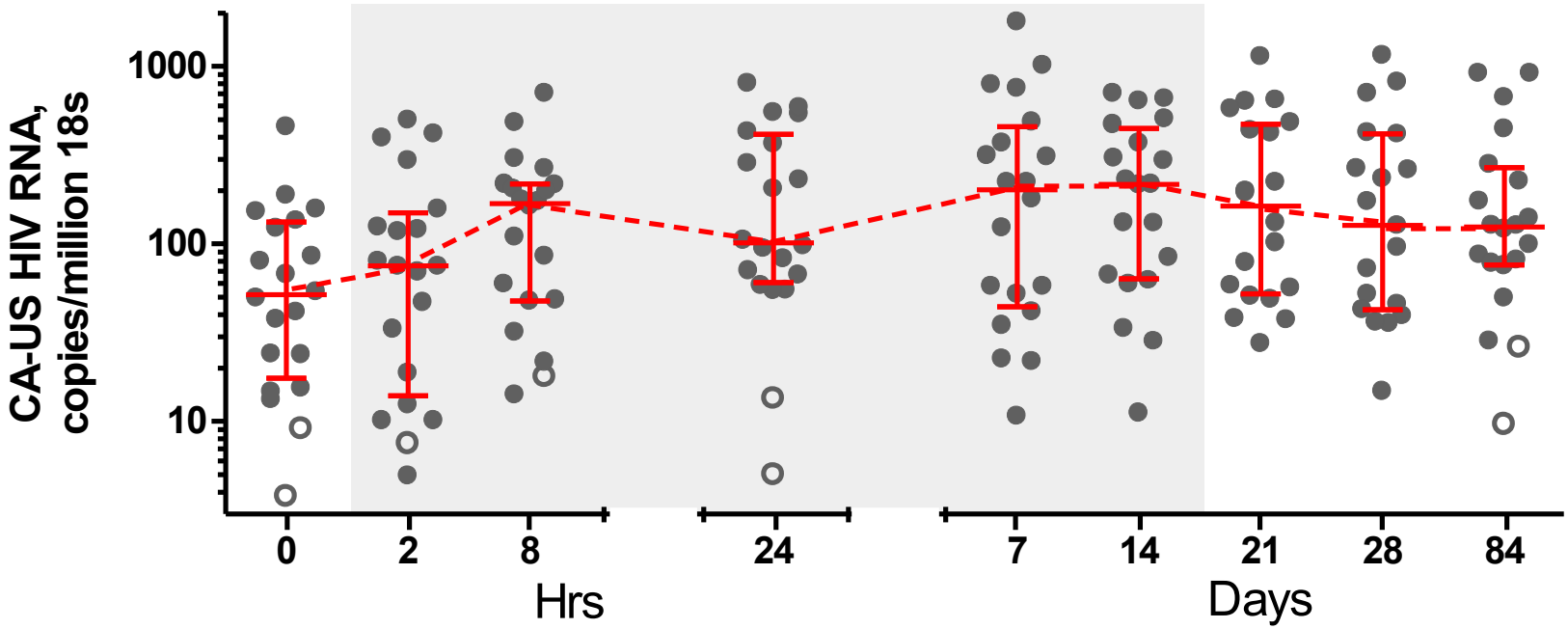
- **14 subjects who started therapy early (but not Fiebig I/II), remained on therapy for years, and had no rebound after stopping therapy**
- **Lack CTL and protective HLA alleles**
- **Very low reservoir (comparable to controllers)**
- **Relative sparing of naïve and central memory CD4+ T cells**
- **HIV DNA declines in absence of ART (n=4)**
- **Very low T cell activation**

Can we cure HIV with latency “reactivation” drugs?

Shock and Kill



Vorinostat (HDAC inhibitor) results in sustained increase in cell-associated RNA, with no inflammation



Elliott et al, CROI 2013
See also Archin/Margolis, Nature 2012

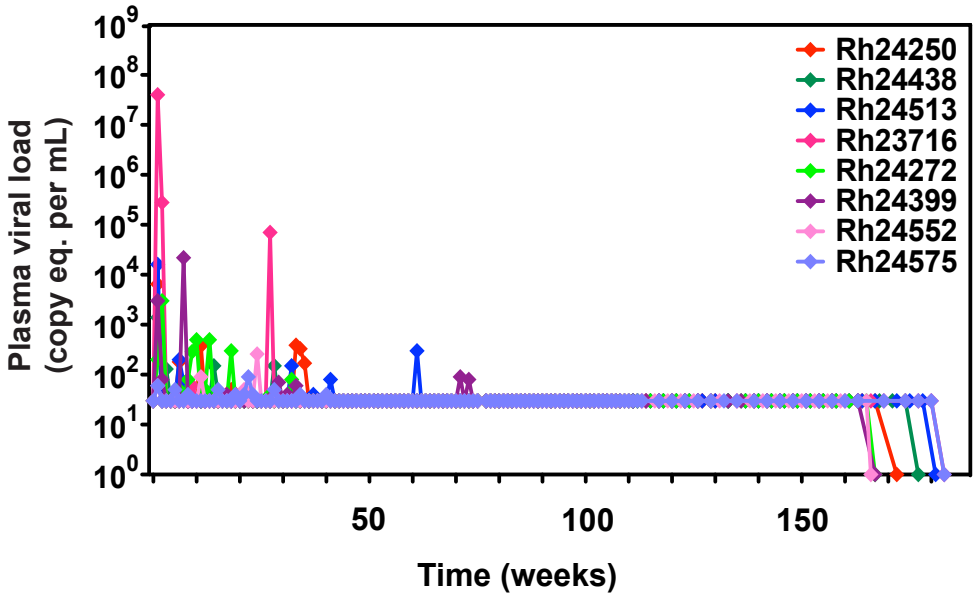
Immunity
Article

Stimulation of HIV-1-Specific Cytolytic T Lymphocytes Facilitates Elimination of Latent Viral Reservoir after Virus Reactivation

Liang Shan,[1,2] Kai Deng,[1] Neeta S. Shroff,[1] Christine M. Durand,[1] S. Alireza. Rabi,[1] Hung-Chih Yang,[3] Hao Zhang,[4] Joseph B. Margolick,[4] Joel N. Blankson,[1] and Robert F. Siliciano[1,5,*]

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

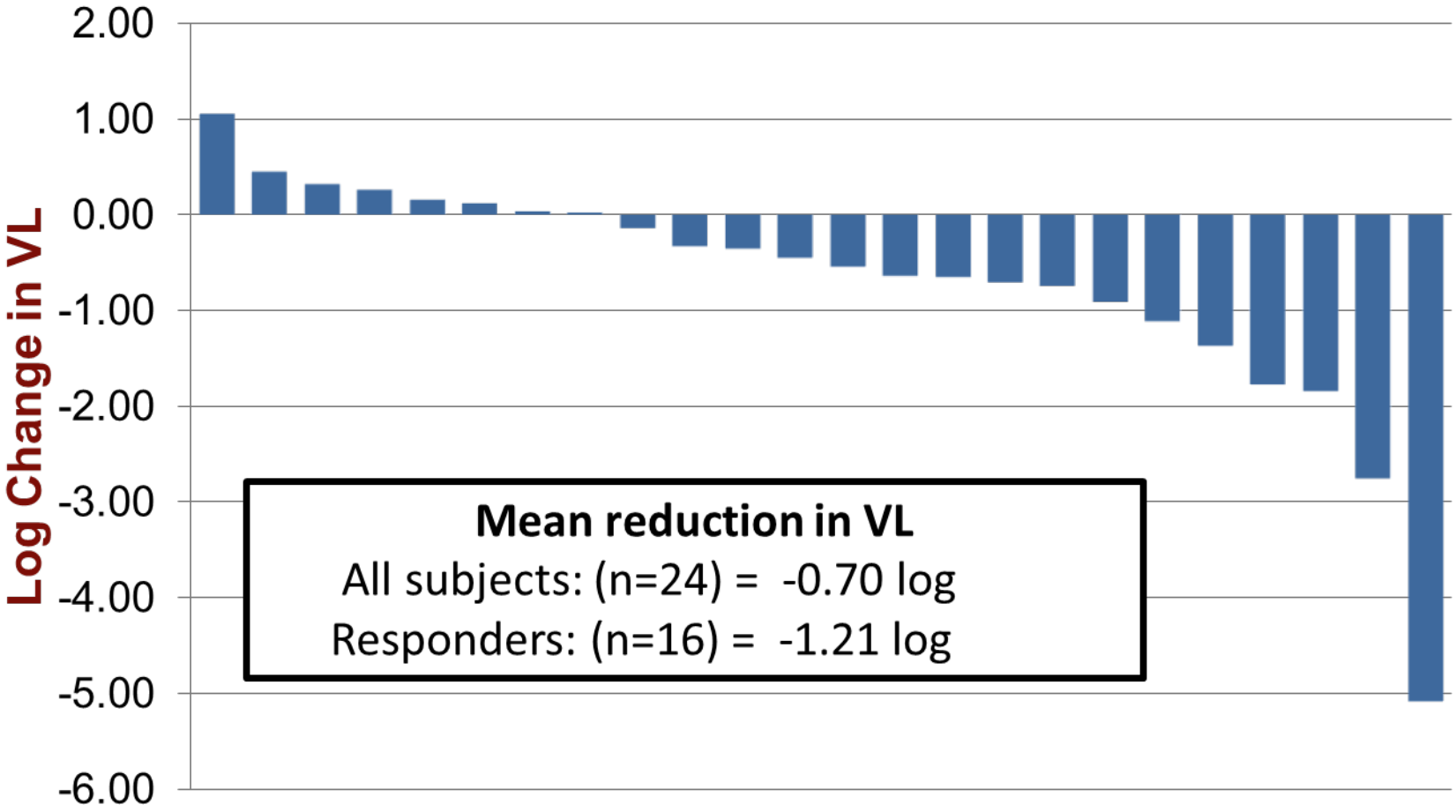
Scott G. Hansen[1], Julia C. Ford[1], Matthew S. Lewis[1], Abigail B. Ventura[1], Colette M. Hughes[1], Lia Coyne-Johnson[1], Nathan Whizin[1], Kelli Oswald[2], Rebecca Shoemaker[2], Tonya Swanson[1], Alfred W. Legasse[1], Maria J. Chiuchiolo[3], Christopher L. Parks[3], Michael K. Axthelm[1], Jay A. Nelson[1], Michael A. Jarvis[1], Michael Piatak Jr[2], Jeffrey D. Lifson[2] & Louis J. Picker[1]



- **CMV as SIV vaccine vector causes high levels of effector CD8+ T cells that reside in lymphoid/mucosa tissues**
- **SIV-specific CD8+ T cells prevent/clear latency during early infection, resulting in cure (as shown by challenge studies)**

nature International weekly journal of science

Denditic cell vaccine using patient-derived virus and CD40L reduces viral load set-point, with at least one becoming a controller (Argos)



Jean-Pierre Routy and colleagues

Can we cure HIV infection with allogenic stem cell transplants?

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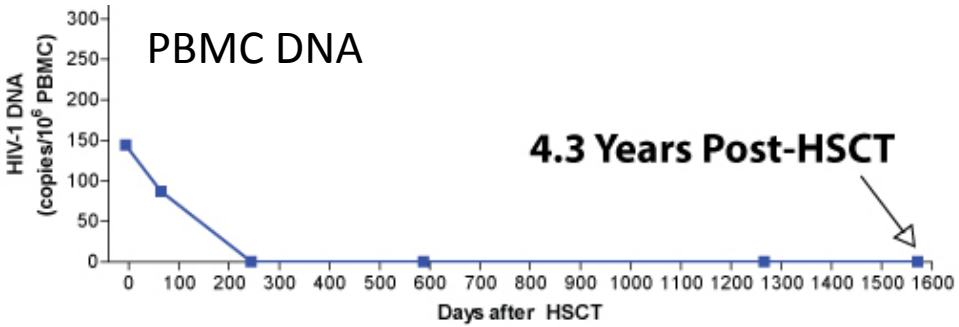
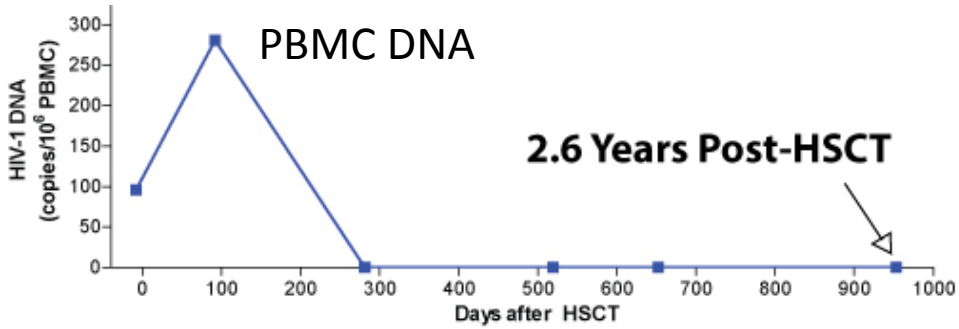
Challenges in Detecting HIV Persistence during Potentially Curative Interventions: A Study of the Berlin Patient

Steven A. Yukl[1*], Eli Boritz[2*], Michael Busch[3], Christopher Bentsen[4], Tae-Wook Chun[5], Daniel Douek[2], Evelyn Eisele[6], Ashley Haase[7], Ya-Chi Ho[6], Gero Hütter[8], J. Shawn Justement[5], Sheila Keating[3], Tzong-Hae Lee[3], Peilin Li[1], Danielle Murray[5], Sarah Palmer[9], Christopher Pilcher[10], Satish Pillai[1], Richard W. Price[11], Meghan Rothenberger[7], Timothy Schacker[7], Janet Siliciano[6], Robert Siliciano[6,12], Elizabeth Sinclair[10], Matt Strain[13], Joseph Wong[1], Douglas Richman[13], Steven G. Deeks[10]

- Doing well off therapy > 5 years
- No replication-competent HIV
- No PBMC DNA, intermittent very-low plasma HIV RNA and rectal DNA
- Waning HIV antibodies
- No HIV-specific T cells
- Normal levels T cell activation
- Normal rectal collagen content

Reduced conditioning, allogenic HSC transplant (CCR5+), may be curative (the "Boston Patients")





No HIV RNA rebound 7 and 15 weeks post-interruption

HIV antibodies waning

GVHD and immune-suppression (both received siroliums) likely important

Henrich and colleagues, IAS 2013

Conclusion: Although the barriers are real, there are reasons to be optimistic

- Hematopoietic stem cell transplant from CCR5-delta 32 donor (the "Berlin Patient") (Huetter, NEJM, 2009)
- Early therapy in an infant (Persaud, CROI 2013)
- Early and prolonged therapy results in "functional cure" (VISCONTI, PLoS Pathogens 2013)
- Allogeneic stem cell transplant under ART may be curative (Henrich, IAS 2013)
- Dendritic cell vaccines may be curative (Argos, IAS 2013)
- Latency can be reversed therapeutically (Arch Nature 2012; Lewin CROI 2013, Tolstrup IAS 2013)

Conclusions

- A safe, scalable cure may prove impossible, and will take years to decades to develop even if possible, but there are reasons to be optimistic
- Barriers to advancing cure agenda
  - Current ART is not fully suppressive in many (perhaps most) people
  - No sensitive, high-throughput assay of relevant reservoir exists
  - Many drugs may not work as monotherapy
  - Industry support is growing, but likely not yet sufficient