Patient issues

Pablo Tebas

- Antiretroviral therapy suppresses HIV replication and leads to immune reconstitution
- As a result of that patients live longer and have less clinical events
- Although initial ART regimens were toxic, currently approved treatments in use in the developing world are much better tolerated

Why rock the boat?

A case report that changed the field

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.

NEJM 2009; 360: 692

Future Directions for NIAID HIV Research

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

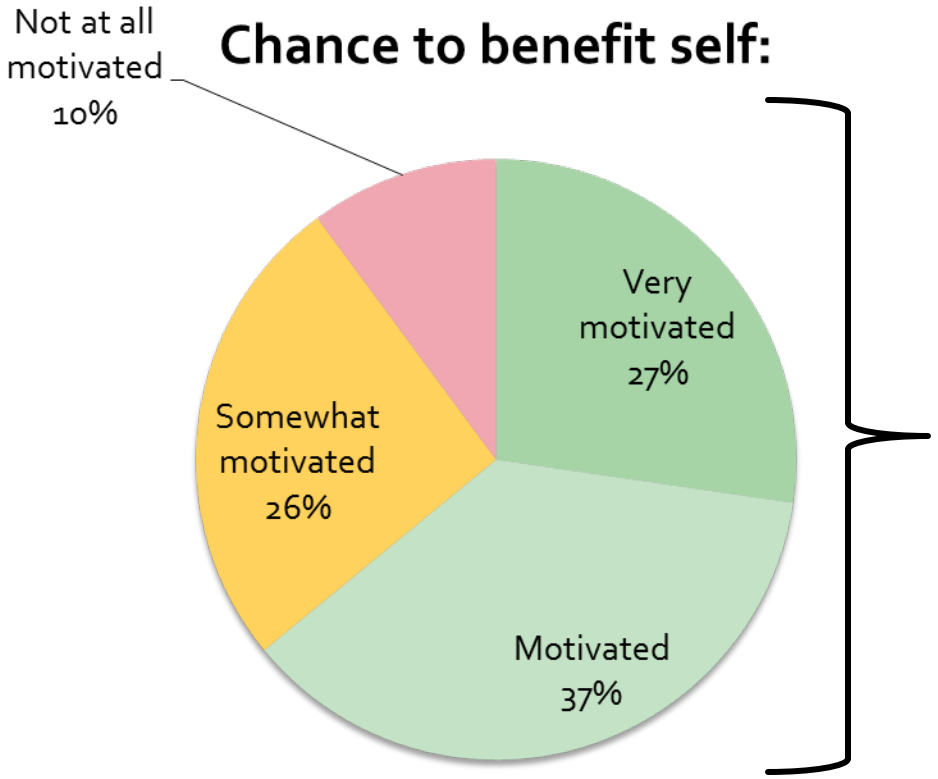
1. Finding a cure for HIV-infected individuals
2. Developing therapeutic strategies for preventing and treating tuberculosis (TB) and hepatitis C
3. Addressing the long-term consequences of treatment of HIV infection

Future Priorities for NIAID's HIV Prevention Research. June 2010
Carl W. Dieffenbach, Ph.D., Director of NIAID's Division of AIDS

Motivation to Participate in Cure Research.
A 1200 patient survey

Cure Research:
If we build it will they come?

- Assuming that entering a study might pose health problems and other risks, **how much would the chance to benefit yourself** by participating in the study motivate you to join the study?



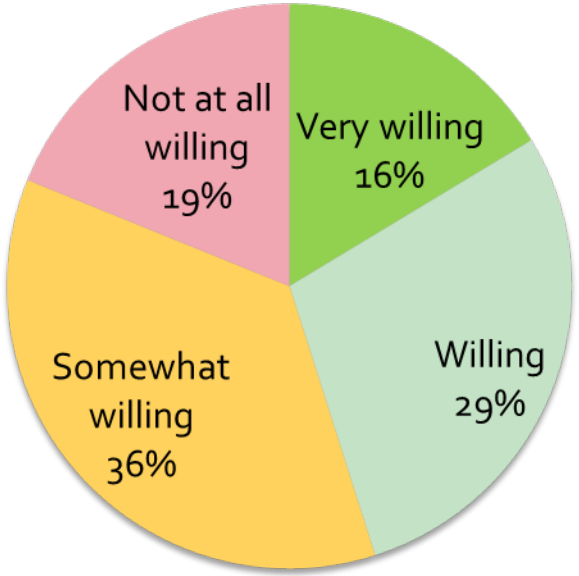
Almost 2/3 would do it

Cure Research:
If we build it will they come?

Chance to benefit others:

More than 50% would do it

Motivated to Benefit field of research:



Almost half would do it

Current approaches to the "cure"

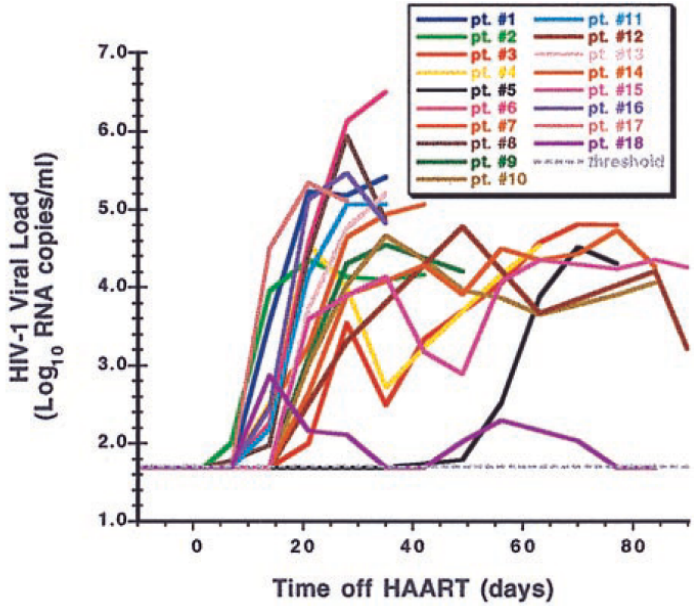
- Identifying each of the HIV reservoirs and finding ways to eliminate them
  - Activating the reservoir
  - Gene therapy approaches
- Maintaining and/or boosting the immune system, so that it can control HIV replication on its own when ART is discontinued
  - Therapeutic vaccines
  - Immunomodulators

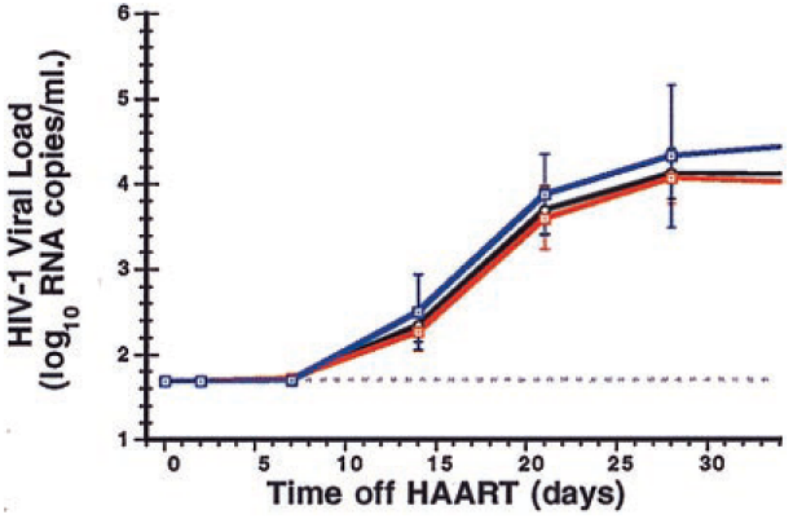
However…

- There is no laboratory assay that measures accurately the reservoir size
- There is no laboratory assay that reflects immune control. We do not know the immune correlates of protection
- This is why we will still need analytical treatment interruptions.

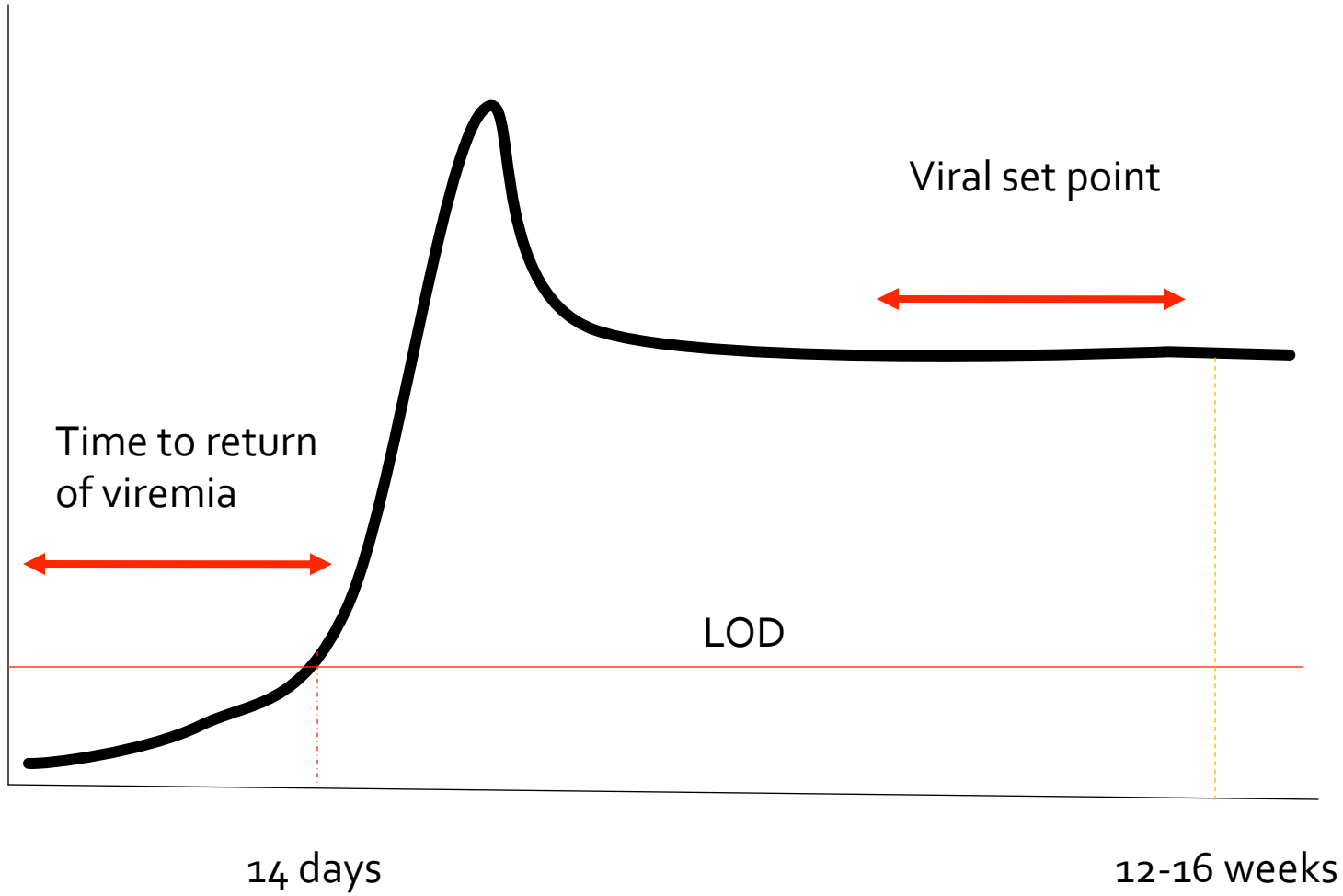
HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression

Richard T. Davey, Jr.*†, Niranjan Bhat*, Christian Yoder‡, Tae-Wook Chun*, Julia A. Metcalf*, Robin Dewar§, Ven Natarajan§, Richard A. Lempicki§, Joseph W. Adelsberger§, Kirk D. Miller‡, Joseph A. Kovacs‡, Michael A. Polis*, Robert E. Walker*, Judith Falloon*, Henry Masur‡, Dennis Gee¶, Michael Baseler§, Dimiter S. Dimitrov¶, Anthony S. Fauci*, and H. Clifford Lane*





Two key parameters

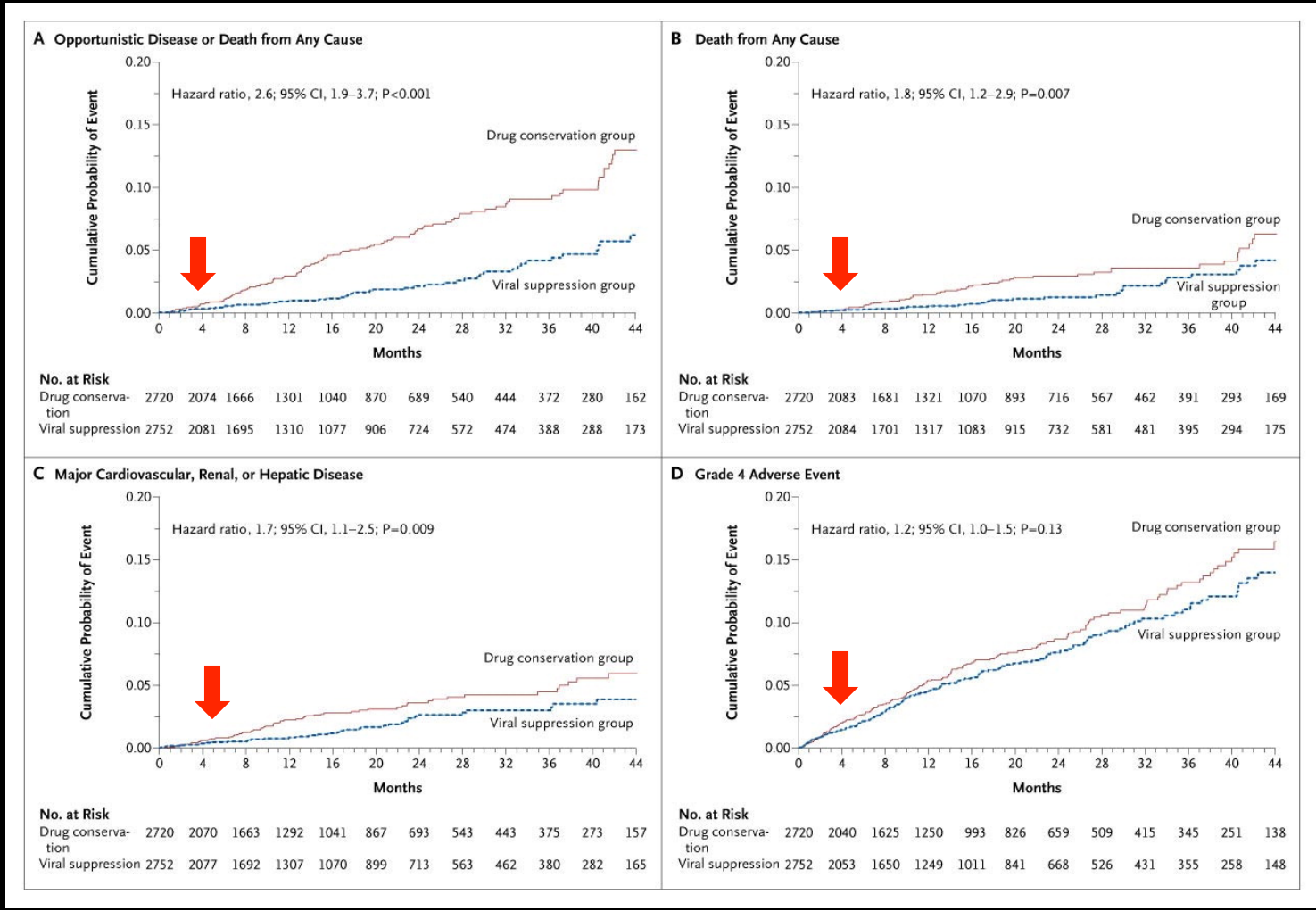


- The kinetics of the return of viremia is very well known.
- Usually takes the virus 2-3 weeks to reappear
- The HIV virus levels tend to go back where they were before the interruption

What are the risks of ATIs?

- Increased rate of clinical events associated with treatment interruption in patients with $CD4$ T cell counts between 250 and 350 cells/mm3 seen in the SMART study
- However the absolute rate of events was very low and there were no differences in the first 3-4 months after study entry.
- Viral resistance. Mostly theoretical, but requires PK considerations when stopping drugs with different half lives

Cumulative Probability of the Primary End Point (Panel A); Death from Any Cause (Panel B); Major Cardiovascular, Renal, or Hepatic Disease (Panel C); and Grade 4 Adverse Events (Panel D).



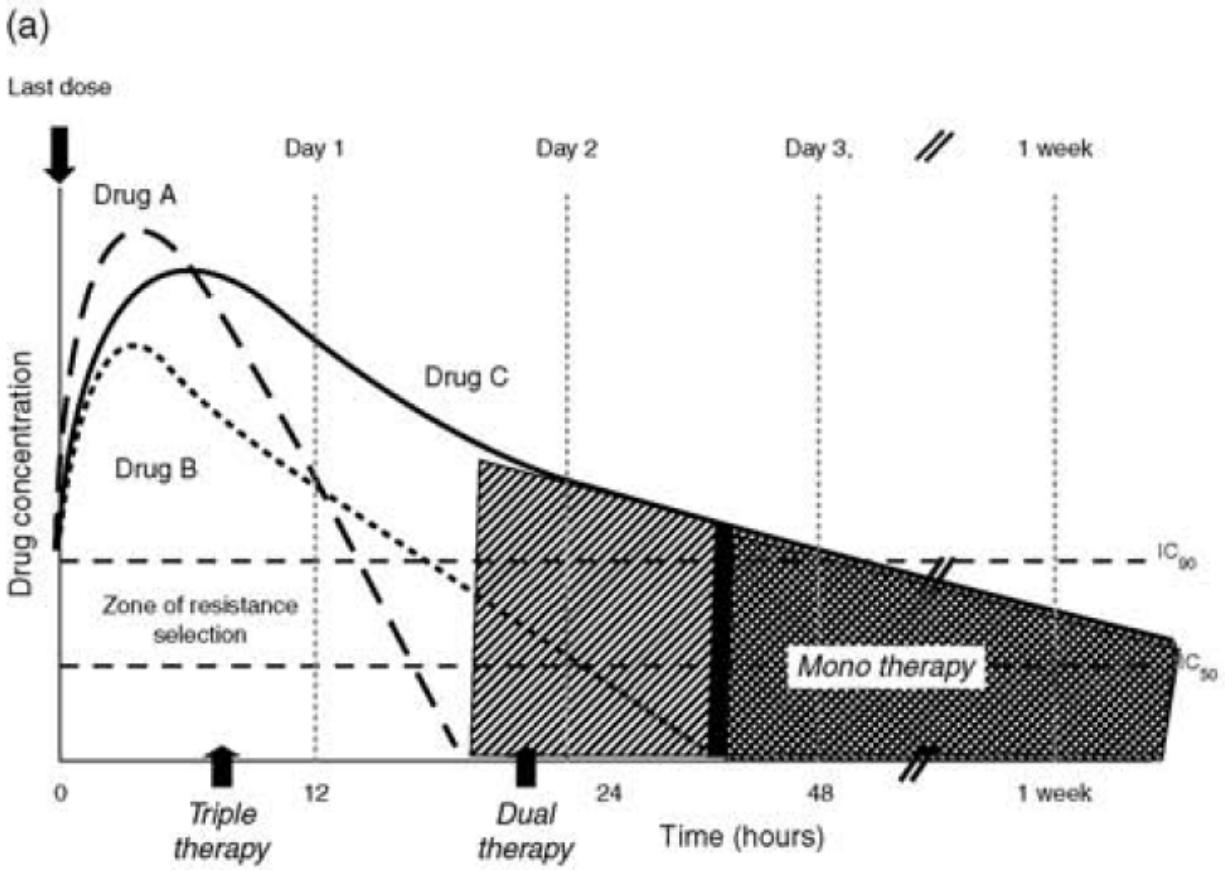
The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. N Engl J Med 2006;355:2283-2296.

The NEW ENGLAND JOURNAL of MEDICINE

Stopping antiretroviral therapy

Stephen Taylor[a,b], Marta Boffito[c], Saye Khoo[d], Erasmus Smit[b,e] and David Back[d]

AIDS 2007, **21**:1673–1682



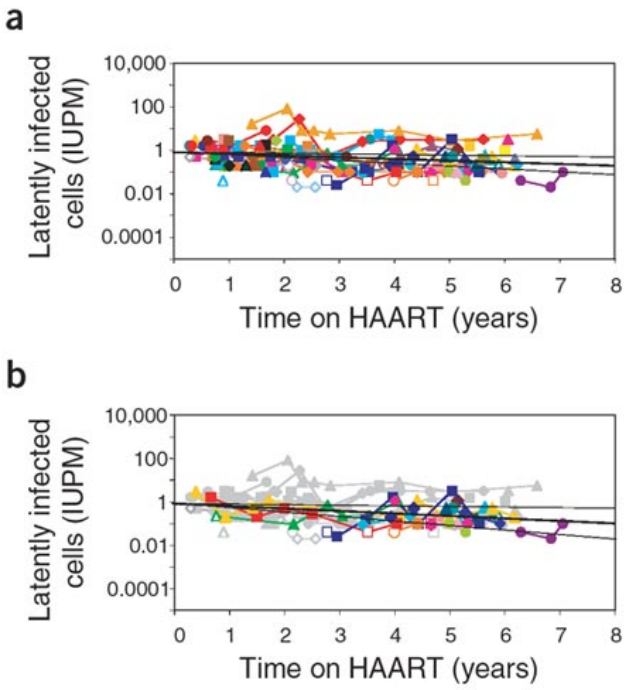
Will the reservoirs increase during ATIs?

BRIEF COMMUNICATION

Nature Medicine **9**, 727 - 728 (2003)
Published online: 18 May 2003; | doi:10.1038/nm880

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

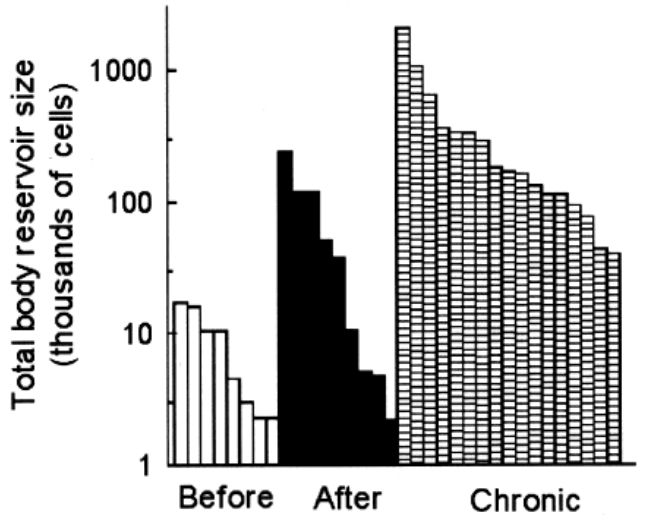
Janet D Siliciano[1], Joleen Kajdas[1], Diana Finzi[2], Thomas C Quinn[1, 2], Karen Chadwick[3], Joseph B Margolick[3], Colin Kovacs[4], Stephen J Gange[5] & Robert F Siliciano[1]



Nature Medicine **9,** 727 - 728 (2003)

Effect of Treatment, during Primary Infection, on Establishment and Clearance of Cellular Reservoirs of HIV−1

Matthew C. Strain,[1,2] Susan J. Little,[3] Eric S. Daar,[5] Diane V. Havlir,[6] Huldrych F. Günthard,[8] Ruby Y. Lam,[2] Otto A. Daly,[4] Juin Nguyen,[4] Caroline C. Ignacio,[4] Celsa A. Spina,[4] Douglas D. Richman,[2,4] and Joseph K. Wong[2,4,7]



JID 2005:191 (1 May)

How to protect the patients?

- Close monitoring
- Enrollment of subjects in ATI studies with current CD_4 over 500 cells/mm^3
- Enrolment of subjects with nadir CD_4>200 cells/mm^3 and no history of opportunistic infections
- Frequent monitoring (at least monthly) of CD_4 cell counts during ATI
- Making sure that PK of drugs are considered before interruption

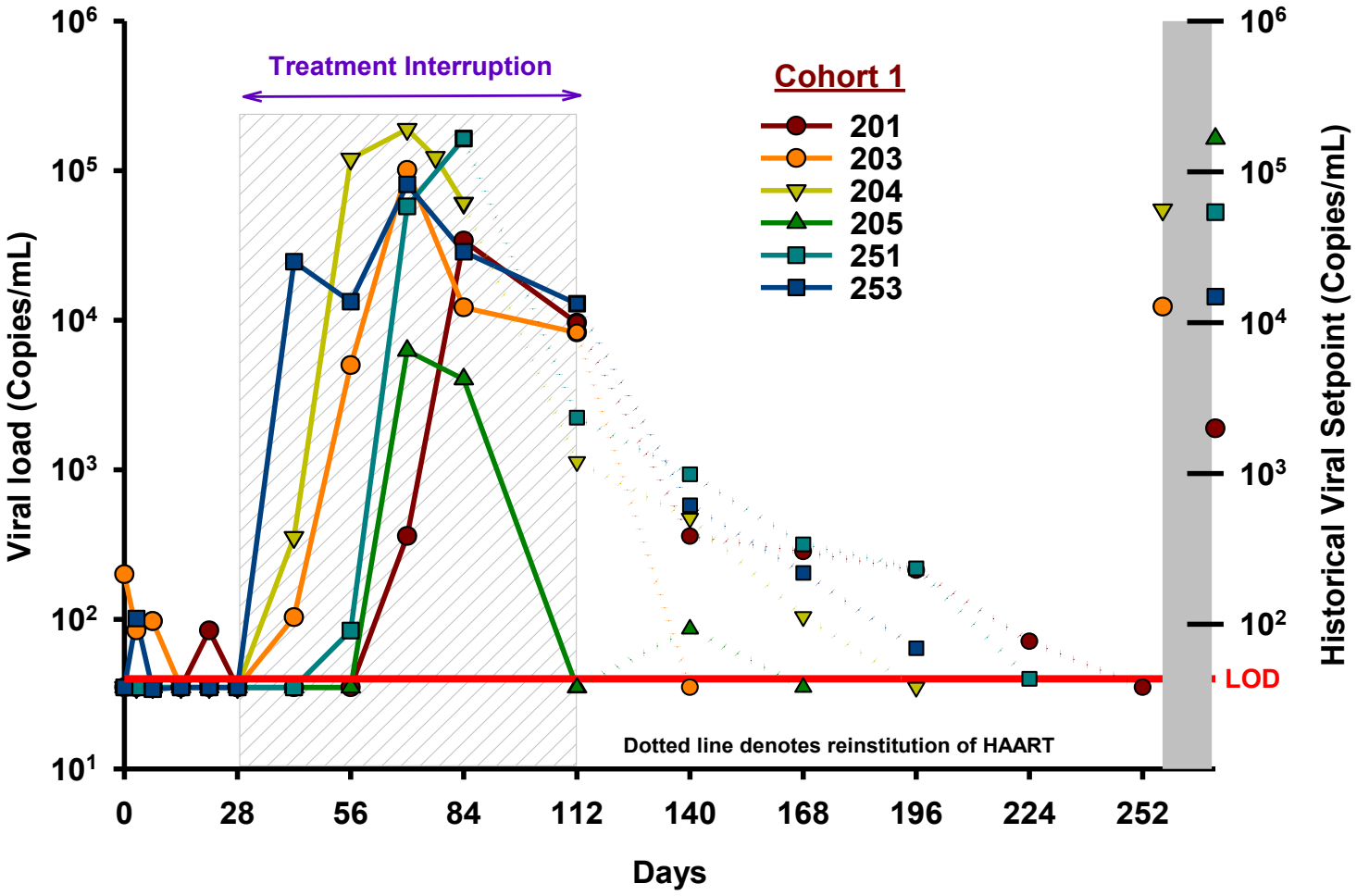
ATIs will need to be flexible and study driven. One model will not fit all

- **Study 1: strategy for erradication using a intervention that "purges the reservoir"**
  - Endpoint: % of subjects with return of viremia
  - ATI needed: ATI of 4 weeks may be sufficient.
- **Study 2: Therapeutic vaccine that "boost immune control"**
  - Endpoint: viral set point
  - ATI needed: at least 12 to 16 weeks.

ATIs will need to be flexible and study driven. One model will not fit all

- **Study 3: gene therapy study that edits out CCR5 with a Zinc finger nuclease in the setting of chemotherapy for lymphoma**
  - Endpoint 1: % of subjects with return of viremia
    - ATI needed: ATI of 4 weeks may be sufficient.
  - Endpoint 2: survival advantage of modified T cells
    - ATI needed: at least 12 to 16 weeks.

An example


Treatment Interruption
Cohort 1
201
203
204
205
251
253
Viral load (Copies/mL)
Historical Viral Setpoint (Copies/mL)
LOD
Dotted line denotes reinstitution of HAART
Days
10^6
10^5
10^4
10^3
10^2
10^1
0
28
56
84
112
140
168
196
224
252