The clinical implications of HIV persistence during therapy

Steven G. Deeks
Professor of Medicine
University of California, San Francisco
Most (> 80%) patients on effective HAART have persistent low level viremia

Median 3.1 copies RNA/mL at week 60

Inflammatory Markers Are Higher In Treated HIV Disease than in HIV Seronegatives, Adjusted for Demographics and CV Risk Factors

Participants 45-76 years of age

Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty
- Immune system

Multiple factors likely explain this increased risk, including co-morbid conditions and antiretroviral drug toxicity
Questions

• Does HIV persistence predict and possibly cause inflammation (or T cell activation)?
• Does HIV persistence and/or inflammation predict and possibly contribute to the development of non-AIDS morbidity?
• Does inflammation contribute to HIV persistence?
• Can the inflammatory response contribute to the control of HIV persistence?
The frequency of infected cells (DNA, unspliced RNA) is higher in gut than in blood

Yukl et al, CROI 2010
See also Chun JID 2008
The Size of HIV Reservoir is Predicted by the Level of Activated CD8+ T cells (in Sigmoid Colon)

![Graph showing the correlation between Level of HIV Proviral DNA (copies/10^6 CD4+ cells) and Level of CD3+CD8+CD69+ T Cells (%). The graph includes a line of best fit with an r^2 value of 0.7 and a p-value of 0.02.]

Sheth et al., *Mucosal Immunology*, 1: 382–388, 2008
Does residual HIV replication cause T cell activation in mucosal tissues, or does T cell activation contribute to HIV persistence?
Raltegravir Intensification: Study Design

Randomized (n=30)
- VL < 40 copies/mL on HAART for ≥ 1 year
- CD4 < 350 for ≥ 1 year

+ Raltegravir (n=15)
  400mg BID
  24 weeks

+ Placebo (n=15)
  PBO BID
  24 weeks

GALT (n=21) Blood
Raltegravir Intensification Had No Effect on Cell-associated RNA or Proviral DNA (Blood)

Cell-associated RNA

Proviral DNA

$PBO \text{ RGV}$

Hiroyu Hatano, CROI 2010

$p = 0.60$

$p = 0.99$
Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy


Short-Course Raltegravir Intensification Does Not Reduce Persistent Low-Level Viremia in Patients with HIV-1 Suppression during Receipt of Combination Antiretroviral Therapy

Raltegravir Intensification Had No Effect on CD8+ T Cell Activation (Blood)

Hiroyu Hatano, CROI 2010
Raltegravir Intensification Had No Effect on CD8+ T Cell Activation (GALT)

Hiroyu Hatano, CROI 2010
Raltegravir Intensification Had No Effect on CD4+ T Cell Activation (GALT)

Week 6: $p = 0.08$

Week 22: $p = 0.14$

Hiroyu Hatano, CROI 2010
Raltegravir Intensification Had No Effect on HIV-specific T Cells (GALT)

$\rho = 0.81$

$\rho = 0.84$

Hiroyu Hatano, CROI 2010
Addition of raltegravir to a stable regimen resulted in transient increase in pre-integration DNA (2 LTR circles) and a decrease in T cell activation in a subset of subjects, most receiving protease inhibitor-based therapy
Does HIV persistence (replication or production) predict vascular dysfunction (and, by extension, non-AIDS morbidity)?
Although HAART improves vascular function (as defined by flow-mediated vasodilation of the brachial artery), it does not completely restore vascular health.

Hsue et al (CROI 2010)
Among a cohort of long-term treated patients with “undetectable viral loads” there was no association between viral persistence (RNA, DNA) and vascular function.
In contrast, numerous studies have shown a consistent and striking relationship between inflammation (T cell activation, CMV, CRP) and vascular function (during HAART)

Kaplan et al (CROI 2010)
HIV replication or production is unlikely to be a major determinant of persistent inflammation, vascular disease and perhaps morbidity during long-term HAART.

Volberding and Deeks, Lancet 2010
Does inflammation and/or T cell activation contribute to viral persistence?
During HAART, there is a higher frequency of HIV DNA in activated as compared to resting CD4+ T cells, which is not readily explained by activation of infected cells.
How HIV persists during antiviral therapy?

Viral replication

T cell survival

Proliferation

Nicholas Chomont, 2010
During HAART, a low CD4 predicts a higher frequency of infected cells and a shift in reservoir toward transitional and effector cells; this effect that may be due to IL-7 mediated T cell proliferation

Chomont et al, Nature Medicine, 2010
The Cycle of HIV Disease Progression

Acute infection
- TLR 7/9 activation
- IFNα response

Viral replication

Chronic Immune Activation

Loss of Mucosal Barrier Integrity
- Microbial translocation
- LPS/TLR4 signaling

CD4+ T cell depletion
- Gut mucosa

Induction of IDO
- Generation of HAA
- Loss of Th17 cells

David Favre and Mike McCune
Higher Levels of GALT HIV-specific CD8+ T Cells Are Associated with Lower Levels of Proviral DNA

Hiroyu Hatano, Tim Hayes, Peter Hunt and Barbara Shacklett
Conclusions

• There is no clear evidence that low level viremia causes inflammation and non-AIDS morbidity
  • No decrease in inflammation in response to treatment intensification

• There is extensive data that inflammation (IL6, CRP, cystatin C, T cell activation) during effective HAART predicts disease
  • Microbial translocation, co-infections, lymphoid fibrosis are likely causes of this inflammation

• There is a growing literature suggesting that chronic inflammation can drive HIV persistence through multiple mechanisms, including increased numbers of target cells, increased homeostatic proliferation, and/or alteration in HIV-specific T cell function
Acknowledgements

UCSF SCOPE Cohort
Hiroyu Hatano
Becky Hoh
Priscilla Hsue
Jeff Martin
Peter Hunt

Ft Miley VA/UCSF
Steve Yukl
Joe Wong
Harry Lampiris
Paul Volberding

UCSF CFAR Core Labs
Elizabeth Sinclair
Lorrie Epling

DEM
Mike McCune
David Favre

BSRI
Eric Delwart
Mike Busch

Elsewhere
Sarah Palmer
Robert Kaplan
Tri Do
Nicolas Chomont
Tae-Wook Chun
Jason Brenchley
Danny Douek
Tim Hayes
Barbara Shacklett

NIAID RO1
AI087145,
K24AI069994