The clinical implications of HIV persistence during therapy

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T cell activation declines during long-term HAART, but remains abnormal, even after many years of viral suppression.

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.
Untreated and to a lesser degree treated HIV infection is associated with increased inflammation, while the level of inflammation during treatment predicts risk of disease.
Most (> 80%) patients on effective HAART have persistent low level viremia.

Median 3.1 copies RNA/mL at week 60

Questions

• Does HIV persistence predict and possibly cause inflammation (or T cell activation) and non-AIDS morbidity?
• Does inflammation contribute to HIV persistence?
• Can therapeutic interventions aimed at reducing inflammation (broadly defined) accelerate the decline in the size of the reservoir and hence contribute to a cure?
Does residual HIV replication cause inflammation and perhaps non-AID morbidity?
Intensification of a suppressive HAART regimen increases CD4 counts and decreases CD8+ T-cell activation

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**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

Weeks:
- 2
- 0
- 4
- 8
- 12
- 16
- 20
- 24
Raltegravir Intensification Had No Effect on Cell-associated RNA or Proviral DNA (Blood)

**Cell-associated RNA**

- $p = 0.60$

**Proviral DNA**

- $p = 0.99$
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 and GALT) suggesting that active viral replication is not a cause of persistent inflammation.
The Effect of Raltegravir Intensification on Low-level Residual Viremia in HIV-Infected Patients on Antiretroviral Therapy: A Randomized Controlled Trial

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

Maria J Buzón, Marta Massanella, Josep M Llibre, Anna Esteve, Viktor Dahl, Maria C Puertas, Josep M Gatell, Pere Domingo, Roger Paredes, Mark Sharkey, Sarah Palmer, Mario Stevenson, Bonaventura Clotet, Julià Blanco & Javier Martínez-Picado
Does inflammation and/or T cell activation contribute to viral persistence?
The vicious circle of HIV-associated inflammation and HIV persistence

Microbial translocation and HIV causes activate PDCs leading to increased IDO, reduced tryptophan levels, a shift in Th17/Treg ratios and eventually more microbial translocation (“vicious circle”)

This process is not fully eliminated by HAART

End result: ongoing T cell activation, homeostatic proliferation and lower HIV-specific T cell responses

Favre STM 2010
Murray STM 2010
The size of HIV reservoir (as defined by RNA/DNA ratio) is associated with frequency of activated CD4+ T cells in rectal tissues.

Spearman's rho: 0.65
P=0.012

Hunt, Yukl and Wong
The Size of HIV Reservoir is Predicted by the Level of Activated CD8+ T cells (in Sigmoid Colon)

Sheth et al., Mucosal Immunology, 1: 382–388, 2008
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.
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
How HIV persists during antiviral therapy?

Viral replication

T cell survival

Proliferation

Nicholas Chomont, 2010
Inflammation may drive HIV persistence through several non-mutually exclusive mechanisms.

Microbial translocation, ↑ co-pathogens (CMV), thymic dysfunction, loss of regulatory cells

PD1/PD1L

Homeostasis

HIV replication
Residual Viral Replication
Persistent Viral Expression (in LN)
Loss of T_{reg}/Th17
Collagen Deposition
Microbial Translocation
High Pathogen Load (CMV, HCV)
Thymic Dysfunction

Suboptimal CD4 Gains
Residual Inflammation
Immunosenescence

Non-AIDS Events and Premature Mortality
| Impact of persistent immunodeficiency (as defined by peripheral CD4+ T cell count) on HIV persistence |
Biology associated with low CD4+ T cells on early HAART (most of whom will eventually reconstitute an effective immune system) is likely different from will likely prove to be different than

Kelley CF, CID ‘09
Among adults with durable viral suppression, a low CD4+ T cell count is associated with significant immunologic abnormalities, many of which are associated with CAD.
Greater lymphoid aggregate fibrosis maybe primary irreversible mechanism accounting for persistent immune dysfunction during HAART

*Hunt and Shacker CROI 2011*
Plasma RNA Levels May Be Higher in Low CD4 Group

Plasma HIV RNA (copies/mL)

Low CD4

High CD4

3.39 copies/mL vs. 0 copies/mL

*p = 0.09

*Excludes 2 outliers
Proviral DNA Levels May Be Higher in Low CD4 Group (per mil CD4)

Proviral DNA (copies/mil CD4)

Low CD4 | High CD4

574 copies vs. 240 copies

p = 0.12
Cell-associated RNA Levels Much Lower in Low CD4 Group (per mil CD4)

Cell-associated RNA (S/Co per mil CD4)

Low CD4

High CD4

$p < 0.0001$
Therapeutic approaches
Will combination therapy be needed to activate and then clear latently infected cells?

Reversal of host mechanisms (anti-PD1, chemokine antagonists, anti-inflammation, MCSF inhibition)
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↑ DNA transcription via chromatin modification (HDACi, HMTi, NF-kB activators)
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Clearance of activated cells (therapeutic vaccine, immunotoxin)
Therapeutic Options: HIV replication/persistence

- HAART intensification
- Reversal of latency
  - HDAC inhibitors
  - Prostratin
  - Interleukin-7, interleukin-15
  - Immunomodulatory (anti-PD-1 antibodies)
  - MCSF inhibitors
- Anti-inflammatory drugs
- Stem cell therapy (CCR5 zinc finger, siRNA)
Therapeutic Options: Inflammation (HIV)

- Chemokine receptor inhibitors
  - Maraviroc, TB-652
- Anti-infective therapy
  - HCV, CMV
- Microbial translocation
  - Sevelamer, colostrum, rifaximin
  - KGF, glucagon agonists (gut epithelium)
- Enhance T cell renewal
  - Growth hormone
  - IL-2, IL-7
  - Stem cell transplant
Therapeutic Options: Inflammation

- Anti-inflammatory drugs
  - Prednisone, hydroxyurea, cyclosporin, mycophenolic acid
  - Chloroquine, hydroxychloroquine
  - Minocycline
  - NSAIDs (COX-2 inhibitors), aspirin
  - Statins
  - Methotrexate (low-dose; CIRT)
  - Talidomide, lenalidomide, pentoxyfylin (weak TNFα inhibitors)
  - ACE inhibitors, angiotensin receptor II antagonists (mediated via reduced aldosterone)

- Biologics
  - TNF inhibitors, IL-6 inhibitors, anti-CD20 ab, abatacept (CTLA4Ig), IL-1 receptor inhibitor
Therapeutic Options: Fibrosis

- Perfenidone
- Lupron
- Renin-angiotensin-aldosterone blockers
  - ACE inhibitors, angiotensin receptor blockers
- Angiotensin receptor blockers
- Anti-TGFβ antibody
- Resveratrol
- Connective tissue growth factor (CTGF) antibodies
In the absence of ongoing viral replication, strong HIV specific T cell responses in the gut mucosa are associated with lower levels of viral persistence.

Hatano et al.; JID 11
Can HIV-associated inflammation can not yet be treated, can it be prevented?
CD8+ T cell activation after long-term HAART is lower but not normal in those who started therapy during recent infection than those who started during late infection

Jain et al, CROI 11
Cell-associated DNA and RNA also lower after long-term HAART among those starting early versus late

On-ART Proviral DNA Levels

On-ART Cell-assoc. RNA Levels

Jain et al. (CROI 2011)
Conclusions

• Although there is no consistent association between plasma HIV RNA levels and any host-response or therapy-response (intensification) in blood, there emerging data suggesting associations in GALT.

• Data collectively support possible role of residual viral replication in tissues as cause of inflammation and a barrier to eradication.

• Despite a growing consensus that this question has been resolved, there remains several critical unanswered questions.
Conclusions

• Multiple mechanisms might account for how an inflammatory environment—which likely persists in all individuals—might contribute to persistence
  • Increased target susceptibility
  • Increased homeostatic expansion
  • Upregulation of negative activator of T cell activation (e.g., PD-1, CTLA-4)
  • Reduced clearance of virus by host mechanisms
• Immune-based therapeutics that address these host responses may have benefits on inflammation-associated disease and size of the latent reservoir
• Curative strategies may need to be individualized based on CD4+ T cell count and other measures
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