Immune Activation and HIV Persistence: New Therapeutic Approaches

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Which is Cause vs. Effect?

HIV Persistence and Viral Replication

T Cell Activation and Inflammation
Viral Persistence

HIV Persistence and Viral Replication

T Cell Activation and Inflammation

If viral persistence causes inflammation, strategies to decrease viral production/replication should reduce inflammation
Although intensification does not affect plasma viremia, it does alter episomal DNA levels (2-LTR circles), suggesting replication is occurring at low levels.

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

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Effect of raltegravir-containing intensification on HIV burden and T-cell activation in multiple gut sites of HIV-positive adults on suppressive antiretroviral therapy

Steven A. Yukl, Amandeep K. Shergill, Kenneth McQuaid, Sara Gianella, Harry Lampiris, C. Bradley Hare, Mark Pandori, Elizabeth Sinclair, Huldrych F. Günthard, Marek Fischer, Joseph K. Wong & Diane V. Havlir

Increase in 2–Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial

Hiroyu Hatanaka, Matthew C. Strain, Rebecca Scherzer, Peter Buucchetti, Deborah Wentworth, Rebecca Hoh, Jeffrey N. Martin, Joseph M. McCane, James D. Neaton, Russell P. Tracy, Priscilla Y. Hsu, Douglas D. Richman, and Steven G. Deeks
PI Effect?

- Increase in 2-LTR circles more likely to occur in subjects taking PI-based ART (Buzon, Nat Med ‘10; Hatano, JID ‘13)
- In ART-suppressed subjects with CD4<350, no effect of RGV intensification on SCA
  - Significant decrease in ultrasensitive plasma RNA in subset of subjects taking PI-based ART (Hatano, JID ‘11)
- Residual viral replication may be occurring in anatomic compartments that are less accessible to PI’s (Fletcher, CROI ‘12)
- For PI’s with a shorter half-life and steep dose response curve, new infection events may be occurring when drug concentrations are low (Shen, Nat Med ‘08; Jilek, Nat Med ‘12)
Controllers had Significant Decrease in RNA with ART

**Plasma RNA**

- Week 4: \( p < 0.001 \)
- Week 12: \( p < 0.001 \)
- Week 24: \( p < 0.001 \)

**Rectal RNA**

- Week 6: \( p = 0.001 \)
- Week 22: \( p = 0.01 \)

* *P*-values refer to change from baseline at each timepoint

**Decrease in Rectal RNA at Week 22:**
Rectal RNA: \(-0.61 \log_{10} \text{ copies/mil CD4}+ (p = 0.01)\)

Hatano et al, PLoS Path 2013
Controllers had Significant Decrease in Immune Activation with ART

Decrease in T cell activation at Week 24/22:

CD8 activation (blood): - 9.0 % (p < 0.001)
CD8 activation (GALT): - 12.2% (p = 0.01)

* P-values refer to change from baseline at each timepoint

Hatano et al, PLoS Path 2013
Controllers had Trend Towards Decrease in C-Reactive Protein with ART

* P-values refer to change from baseline at each timepoint

Hatano et al, PLoS Path 2013
“Elite” Controllers had Trend Towards Decrease in Immune Activation with ART

**Decrease in T cell activation at Week 24/22:**
- CD8 activation (blood): - 6.0 % ($p = 0.091$)
- CD8 activation (GALT): - 24.0 % ($p = 0.11$)

* P-values refer to change from baseline at each timepoint

Hatano et al, PLoS Path 2013
Maximal Suppression of HIV Replication

- Effective, highly bioavailable ARVs that have robust lymphoid tissue penetration (Fletcher, CROI ‘12)
- Initiation of ARVs as early as possible during acute infection (Jain, JID ‘13; Saez-Cirion, PLoS Path ’13; Ananworanich, CROI ’13; Persaud, NEJM ‘13)
Inflammation

HIV Persistence and Viral Replication

- More virus production
- More target cells
- Homeostatic proliferation
- Upregulation of negative regulators (PD-1)
- Poor clearance mechanisms

T Cell Activation and Inflammation
If inflammation causes persistence, anti-inflammatory approaches may accelerate cure.
Multiple Factors Cause Persistent Inflammation During ART

HIV production and replication

ART toxicity, lipodystrophy, and traditional risk factors

Cytomegalovirus and other copathogens

Loss of regulatory cells

Microbial translocation

Inflammation
- ↑ Monocyte activation
- ↑ T-cell activation
- ↑ Endothelium adhesion
- Dyslipidaemia
- Hypercoagulation

Comorbidities
- Cardiovascular disease
- Cancer
- Kidney disease
- Liver disease
- Osteopenia/osteoporosis
- Neurocognitive disease

Deeks, Lewin, Havlir; Lancet 2013
Potential Interventions to Decrease Microbial Translocation

• Rifaximin (ACTG 5286)
  – Minimally absorbed oral antibiotic that is concentrated in GI tract and has broad spectrum bactericidal activity

• Sevelamer (ACTG 5296)
  – Oral phosphate binder that binds bacterial endotoxin in GI tract
Prebiotics and Probiotics

• Overrepresentation of pathogenic bacteria and underrepresentation of beneficial bacteria in HIV infection (Gori, JCM ’08; Cunningham-Rundles, Nutrients ‘11)

• Gut “dysbiosis” associated with mucosal immune disruption, T cell activation, and chronic inflammation in treated HIV-infected individuals (Vujkovic-Cvijin, Sci Transl Med ‘13)

• RCT in untreated HIV-infected individuals, prebiotic x12 weeks improved gut microbiota composition and decreased sCD14 (Gori, Mucosal Immunol ‘11)
Prebiotic and Probiotic Supplementation in Treated SIV

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques

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- ARVs = RTIs: PMPA, FTC & INIs: L’812, L’564
- Probiotics = VSL#3 (Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus Streptococcus thermophilus) & Culturelle (Lactobacillus GG & prebiotics)

Klatt et al, JCI 2013
Prebiotic and Probiotic Supplementation in Treated SIV

- Increased colonic CD4 reconstitution
- Increased frequency/functionality of APCs in colon
- Decreased lymphoid fibrosis in the colon

Klatt et al, JCI 2013
Multiple Factors Cause Persistent Inflammation During ART

- HIV production and replication
- ART toxicity, lipodystrophy, and traditional risk factors
- Cytomegalovirus and other copathogens

Loss of regulatory cells

- $T_{reg}$
- $T_{eff}$

Inflammation
- Monocyte activation
- T-cell activation
- Endothelium adhesion
- Dyslipidaemia
- Hypercoagulation

Comorbidities
- Cardiovascular disease
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Deeks, Lewin, Havlir; Lancet 2013
**Blockade of Type I Interferon Signaling may be Beneficial in Chronic HIV Infection**

- IFN-alpha has antiviral effects in untreated HIV
- LCMV infection
  - Acute infection: IFN-alpha has **antiviral** effects
  - Chronic infection: chronic and persistent signaling by IFN-alpha leads to potent **immunomodulatory** effects that prevent adaptive immune responses (eg, through expression of PD-1) and promote viral persistence
  - Blockade of IFN-alpha led to decreased immune activation, decreased PD-1 expression, restored lymphoid architecture, and enhanced viral clearance
Therapeutic Options in Development

- **Anti-inflammatory drugs**
  - Chloroquine, hydroxychloroquine
  - NSAIDs (aspirin, mesalamine, COX-2 inhibitors)
  - Statins
  - Minocycline
  - Methotrexate
  - Lenalidomide
  - Biologics (IL-6 inhibitors, anti-INFa)

- **Anti-coagulants**: low dose warfarin, aspirin, clopidogrel

- **Anti-infective therapy**: CMV, HCV/HBV, HSV, EBV

- **Microbial translocation**: rifaximin, sevelamer, prebiotics/probiotics, colostrum

- **Anti-fibrotic drugs**: ACE inhibitors, ARBs

- **Enhance T cell renewal**: IL-7

- **Anti-aging**: sirolimus caloric restriction, omega-3 fatty acids, diet, exercise

- **Chemokine receptor inhibitors**: maraviroc

*Multiple mechanisms account for HIV persistence, many of which are being addressed therapeutically.*
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