Immune-based Therapies

Peter W. Hunt, MD
Associate Professor of Medicine
Interim Chief, Division of Experimental Medicine
University of California San Francisco
Improving Life Expectancy*, but Gap Persists: HIV vs HIV-.

Gap only 6y if CD4 nadir >500 and no smoking, EtOH or hepatitis

Gap ~20y if CD4 nadir <350
(Samji, PLoS One, 2013)

*For 20yr old

Marcus JAIDS, 2016 (see also: Legarth/Obel, JAIDS, 2016; Samji for NA-ACCORD, PLoS One, 2013)
Many age-associated morbidities also increased in treated HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- Macular Degeneration [13]
- Frailty [11]

Potential Role of Inflammation in Driving Morbidity in Older HIV+ Individuals

- ART Toxicity
- Persistent Inflammation
- Lifestyle

Age-associated Morbidity

Deeks and Phillips, BMJ, 2009
Inflammation Predicts Disease in Treated HIV Infection

- **Mortality** (Kuller, PLoS Med, ‘08; Tien, JAIDS, ‘10; Tenorio, JID ‘14; Hunt, JID ‘14)
- **Cardiovascular Disease** (Duprez, Atherosclerosis, 2009)
- **Cancer** (Breen, Cancer Epi Bio Prev, 2010; Borges, AIDS, 2013)
- **Venous thromboembolism** (Musselwhite, AIDS, 2011)
- **Type II diabetes** (Brown, Diabetes Care, 2010)
- **COPD** (Attia, Chest, 2014)
- **Renal disease** (Gupta, HIV Med, 2015)
- **Bacterial pneumonia** (Bjerk, PLoS One, 2014)
- **Cognitive dysfunction** (Burdo, AIDS, 2013; Letendre CROI 2012)
- **Depression** (Martinez, JAIDS, 2014)
- **Frailty** (Erlandson, JID, 2013; Piggott, CROI 2017, #133)
Inflammation **Strongly and Durably Predicts Morbidity / Mortality in Treated HIV Infection** (IL-6 + D-dimer Score)


**SMART / ESPRIT / SILCAAT**
(Median Current CD4: 500; Nadir: 181)

**HR: 1.64 per 2-fold increase**

**Even in those starting ART early…**

**START**
(CD4 >500)

**HR: 1.61 per 2-fold increase**
Strategy for Interventional Trials

• Low-hanging fruit
  - Commonly used meds with antiinflammatory properties
  - Test in pilot studies with immunologic endpoints
  - Advance scalable “winners” to clinical endpoint trials
Statins Decrease Immune Activation and Aortic Plaque in Treated HIV Infection

sCD14 Declines with Rosuvastatin

Plaque Regression with Atorvastatin

Funderburg/McComsey, JAIDS, 2015

Lo/Grinspoon, Lancet HIV, 2015

(See also: Nakanjako, Trop Med Int Health, 2014)

Not all statin studies positive (A5275): target populations or dose?
• Potential to change clinical guidelines
• Does decreasing immune activation reduce morbidity / mortality?
  – Cardiovascular endpoints
  – Noncardiovascular: infections, cancer, etc.
• Which biomarker reductions correlate with reduced disease risk?
  – Essential for defining true surrogate markers
Aspirin Fails to Reduce Immune Activation or Improve Vascular Function (A5331)

Serum thromboxane (cyclooxygenase inhibition)

Placebo
100 mg ASA
300 mg ASA

O’Brien, OFID, 2017
Telmisartan (Angiotensin Receptor Blocker) Fails to Improve Lymphoid Fibrosis in Treated HIV (A5317)

Telmisartan + ART

ART Alone

*Analysis of other systemic markers ongoing

Utay, CROI 2017, Abstract 251
“Probe” Studies of Immune-based Therapeutics
Immune Activation As a Tree

Leaves
End-organ diseases

Branches
IL-6 (Inflammation)
D-dimer (Coagulation)
Lymphoid Fibrosis

Roots
HIV reservoirs
CMV
Microbial translocation
Targeting Roots and Branches: The Whack-a-Mole Problem

Hydroxychloroquine $\uparrow$ VL in untreated HIV

Paton, JAMA, 2012 (see also Jacobson ARHR, 2016)
Can we find the tree trunk?

**Branches**
- IL-6
- D-dimer
- Lymphoid Fibrosis

**Trunk**
- Jak/Stat: Ruxolitinib (A5336)
- mTOR: Sirolimus (A5337)

**Roots**
- HIV reservoirs
- CMV (A5351s)
- Microbial translocation
Targeting the Tree Trunk: IL-1β

Cholesterol Crystals → Pro-IL-1β → Active IL-1β → IL-1β → IL-6 → PAI-1, Fibrinogen, CRP, Liver

Neutrophil Extracellular Traps → Pro-IL-1β → Active IL-1β → IL-1β → IL-6 → PAI-1, Fibrinogen, CRP, Liver

Atheroprotective Flow → SREBP2 Activation → Pro-IL-1β → Active IL-1β → IL-1β → IL-6 → PAI-1, Fibrinogen, CRP, Liver

Hypoxia → O2 → Pro-IL-1β → Active IL-1β → IL-1β → IL-6 → PAI-1, Fibrinogen, CRP, Liver

CMV, HIV, LPS

INOS, Endothelin-1, Chemokines, Cytokines, Adhesion Molecules, Macrophage Activation, Smooth Muscle Proliferation

Vascular Inflammation, Endothelial Dysfunction, Atherosclerosis

Liver

CRP: hsCRP Risk
- High: >3
- Intermediate: 1-3
- Low: <1

Canakinumab, Anakinra
Colchicine, Tocilizumab
Low-Dose Methotrexate
IL-1b Inhibition with Canakinumab* Appears to Reduce Inflammation in Treated HIV
(N = 10, Uncontrolled Pilot Study)

*Single subcutaneous dose of 150mg

A 30% ↓ in IL-6 associated with a 25% ↓ odds of Non-AIDS event (Tenorio, JID 2014)

Hsue, CROI 2017, Abstract 126
IL-1β Inhibition Also Appears to Decrease Aortic Inflammation (by FDG/PET)
(N = 10, Uncontrolled Pilot Study)

Aortic Inflammation

Bone Marrow Activity

Hsue, CROI 2017, Abstract 126
IL-1b Inhibition Transiently ↓ Neutrophil Cts
Long-term Safety Needs to Be Established

Safety Labs
- Transient declines in neutrophils
- ↓ monocyte IL-1b and IL-6 response to LPS stimulation
- No significant change in CD4 count (median 758 to 714 at wk8)
- No sig change in CD4/CD8 ratio
- No loss of HIV VL suppression

Clinical Safety
- One case of zoster, typical course
Indoelamine 2,3-dioxygenase-1 (IDO1) As a Therapeutic Target in Treated HIV Infection

Tryptophan → IDO1 → Kynurenine → Catabolites that:
- ↓T-cell proliferation
- ↑Tregs
- ↓Th17 cells

- Impaired Pathogen Control
- Dysbiosis
- Impaired HIV-specific response
- CMV/EBV Reactivation
- Mucosal Barrier Dysfunction
- HIV Translocation

- Immune Dysfunction
- PD-1
- Th17
- Treg
- CD4 Depletion

- Immuno-regulation

- Non AIDS Diseases
- HIV Persistence

Adapted From D. Douek

Dunham, CROI 2017, Abstract 252
Higher IDO1 Activity (K/T ratio) Predicts ↑ Mortality during ART in HIV+ Ugandans

Each tertile increase in baseline K/T ratio associated with a 2.1-fold greater hazard of death after adjustment for pre-ART BMI and CD4 count (P = 0.01).

Byakwaga, JID, 2014
Higher KT Ratio Continues to Predict Mortality during Suppressive ART (VL <400 at Month 6 of ART)

Each tertile increase in month 6 K/T ratio associated with a 2.9-fold increased hazard of death after adjusting for BMI, CD4 count, and %CD38+HLA-DR+ CD8+ T cells (P=0.042).

Byakwaga, JID, 2014 (see also: Hunt, JID, 2014; Tenorio, JID 2014)

Independent of: IL-6, D-dimer, sCD14, sCD163, T-cell activation (Lee et al, JID, 2017)

Also associated with increased atherosclerosis in WIHS (Qi et al, CROI 2017, #636LB)
IDO Blockade ↑CD4/CD8 Ratio and ↓T-Cell Activation in Treated SIV+ Macaques (INCB024360)

**CD4/CD8 Ratio**

- Placebo
- IDOi

**%CD38+HLA-DR+ CD8+ T-cells**

- Placebo
- IDOi

ANOVA Interaction- p=0.024

Interaction p-value = 0.01
Treatment p-value = 0.0062

*Dunham, CROI 2017, Abstract 252*
Lifestyle Interventions Are Important!
Traditional Risk Factors More Important for MI Risk Than HIV-related Factors

NA-ACCORD

- Ever smoking (vs. never): 38%
- Hypertension (vs. none): 41%
- Hypercholesterolemia (vs. none): 43%
- Diabetes (vs. none): 2%
- Stage 4 CKD (vs. none): 3%
- CD4 <200 (vs. ≥200 cells/mm3): 10%
- HIV RNA >400 (vs. ≤400 copies/mL): 6%
- Clinical AIDS diagnosis (vs. none): 2%
- HCV infection (vs. none): 8%

Althoff, CROI 2017, #130
Quitting Smoking Decreases Cancer Risk in Treated HIV Infection

D:A:D Study

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<th>Smoking status</th>
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<td>Ex: &lt; 1 year</td>
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<td>Current smoker</td>
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<td>Ex at baseline</td>
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</table>

Shepherd, CROI 2017, #131
Moderate Exercise Appears to Decrease Inflammation in Treated HIV Infection

- 3x per week brisk walking for 60 minutes
- +/- 30 min strength training

Bonato, BMC ID, 2017
Summary

- Despite optimal ART, HIV shortens life expectancy and ↑ age-associated morbidities.
- Immune activation / inflammation persist despite ART and may predict these morbidities, even in those starting ART early.
- Statins show early promise and are now advanced to a clinical outcomes trial.
- Probe studies may get us closer to the “tree trunk” and more potent / targeted interventions.
  - Inhibition of IL-1β or IDO1?
- Lifestyle interventions (diet, exercise, smoking cessation) are important!