HIV and Biologics: Is There a Role?

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HIV Immune Activation
A Treatable State?

• BIOLOGICS for autoimmune / autoinflammatory complications of HIV disease

• BIOLOGICS as treatment adjuncts for HIV infection
HIV Disease
2012 Estimated Infections 35 Million

- 12 million AIDS
- 5.2 million new/97
- Deaths - 1.8 million/97
- Total deaths 9 million

HIV and Rheumatic Diseases
Pre HAART Era

- CTD
  - DILS
  - Myositis
  - Vasculitis
- Arthritis
  - Reactive arthritis / Psoriasis
  - HIV related
**Complication Rates by HAART Therapy**

- 44 in those not exposed HAART
- 4 in HAART exposed
- p<.001

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**New Forms of Rheumatic Disease in the post HAART era**

- Avascular necrosis of bone NIH 339 patients all asymptomatic, 15 (4.4%) had MRI evidence of AVN, 0% of 118 controls (Miller An Int Med 2002)
- Osteoporosis- increasing prevalence, clinical significance unknown (Reveille et al Best Prac Clin Rheum 20:1159,2006)
- Immune reconstitution syndrome- rare but clinically significant (Calabrese et al Sem Arth Rheum Vol 35:166,2005)
Immune Reconstitution Inflammatory Syndrome (IRIS)

- Inflammatory syndrome post cART
- Most often associated with occult infection
- Resurgence of CD4 counts
- Onset of symptoms: average 9 mo, range 3-27mo after HAART
- Pathogenesis believed to be augmented immune response to occult pathogens
- Self-limited inflammatory syndrome

IRIS non-infectious

- Reports of immune reconstitution in response to microbial pathogens: M. avium, TB, CMV, Hepatitis B/C
- Similar syndrome in auto-immune diseases:
  - Increase in SLE, RA, autoimmune thyroid dx
  - 20% represent flares of pre-existing disease

Lipman 2006
Calabrese et al Sem Arth Rheum Vol 35:166,2005
For Patients with Autoinflammatory Disease
Evidence for Reasonable Risk Benefit for Biologic Therapies in Controlled HIV Infection

- **TRANSPLANTATION**: HIV patients can tolerate anti-rejection regimens with CD4 > 200/ml and controlled viral loads
- **CANCER**: HIV patients with NHL can tolerate combination chemotherapy with CD4 > 50-100/ml
- **LIVE VACCINE**: Ongoing safety trials of ‘double dose’ Zostavax have revealed no safety issues at > 2 yrs with CD4 counts to 200/ml

Trials of TNF Blockade in HIV Disease

- Trials of weak TNF inhibitors (thalidomide and pentoxifyline) have been of clinical benefit in aphthous and wasting states (Wallis JID96, Jacobson NEJM 97)
- Small trial of 2 infusions of infliximab 10mg/kg in 6 patients with CD4<200 resulted in decreased TNF but no change in HIV-RNA or CD4 (Walker JID 96)
- Trial of single injection of etanercept 10mg in 11 patents 6 receiving concomitant IL2 resulting in blocking of IL6 and CRP responses but no change in HIV-RNA (Sha AIDS Res 2002)
- Etanercept pulmonary TB Wallis et al AIDS18:1-8,2004
HIV Rheumatic Treatment “Guidelines”

- No official recommendations
- In general drugs used for patients with HIV have the same cautionary notes as in the HIN non-infected population with several caveats
- TNF inhibitors demonstrated reasonably safe CD4 > 200; HIV-VL non detectable
- Avoid glucocorticoids in patients on ritonavir

(Vasilopoulos & Calabrese Arth Res Ther 2008)

Biologic Therapies as Candidates to Reduce Inflammation in HIV Disease
Immune-mediated Inflammatory Diseases

Initiation
Susceptibility
Triggers
Accelerants

Innate  Immune responses  Adaptive

Inflammation
(TNF, IL-1, IL-6, IL-17,
IL-23, IL-18, IL-15, Others)

Damage / Destruction / Symptoms
(RA, SLE, PsA, IBD, AS, MS)

DM, CHF, Alzheimer's, Transplant, Sepsis, Allergy, Vasculitis, ASO, HIV

Idealized Natural History of HIV Infection: Viral,
Immune Activation and Clinical Features

Idealized Natural History of HIV Infection: Viral,
Immune Activation and Clinical Features

Immune responses

CD4+ cell count

Plasma virus RNA

Culturable virus in blood

Clinical Disease

1° Infection

1° Infection

Months

Years

Immune Activation Markers

<table>
<thead>
<tr>
<th></th>
<th>1° Infection</th>
<th>Late Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>IL-6</td>
<td>++/+</td>
<td>++</td>
</tr>
<tr>
<td>IL-2R</td>
<td>+/0/+</td>
<td>++</td>
</tr>
<tr>
<td>CD8-DR</td>
<td>+/0/+</td>
<td>++</td>
</tr>
<tr>
<td>CD8-CD38</td>
<td>+/0/+</td>
<td>++</td>
</tr>
</tbody>
</table>

Disease

1° Infection

Late Disease
**Background**

- Incidence of non-HIV associated events (myocardial infarction, non-HIV associated malignancies) is elevated in ART-treated HIV+ individuals
  - Related to inflammation, immune activation, and incomplete CD4 recovery
  - In L-SOCA and SCOPE, soluble markers of immune activation shortly before a fatal event were dramatically higher than in controls matched for time of virologic suppression
- Inflammation remains elevated despite virologic suppression in most treated patients 2 - 6 years after initiating ART.
  - SMART showed an association between elevated baseline levels of IL-6, d-dimer and sCD14, and mortality, independently of viremia and CD4+ T-cells.
  - ART-treated HIV+ patients with high levels of IL-6, d-dimer and soluble CD14 have higher all-cause mortality.

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**Immune Failure After Suppressive Antiretroviral Therapy:** high level CD4 and CD8 T Cell activation but only Memory CD4 cells are Cycling

The Cleveland Immune Failure (CLIF) Project
Background and Rationale

- Failure to "normalize" circulating CD4 T cells despite virologic control is seen in as many as 25% of ARV-treated patients.
- Failure to normalize circulating CD4 T cell counts is associated with increased morbidity.
- Determinants of immune failure are incompletely understood.

Increased Proportions of Activated CD4 and CD8 T Cells in Immune Failure

- Chart showing increased proportions of activated CD4 and CD8 T cells in immune failure with statistical significance indicated.

- Graphs displaying the comparison of % CD38+ HLADR+ CD4+ and CD8+ T cells between CLIF, HIV+, and Control groups with corresponding p-values.
Hypothesis

Heightened immune activation and inflammation is associated with increased non-accidental mortality and incident non-AIDS morbidities in virologically suppressed ART-treated HIV+ patients.

METHODS Nested case control study within the ALLRT cohort.
Cases: Virologically suppressed (VL < 400 copies/ml @ 1y)
Non-accidental death
Incident non-AIDS-related morbidity
Myocardial infarction
Stroke
Malignancy
Baseline Soluble Markers Relate to Outcome

<table>
<thead>
<tr>
<th>Baseline Marker</th>
<th>Odds Ratio per 1 IQR increase</th>
<th>P Value</th>
<th>OR at baseline for:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death CA MI/Stroke</td>
</tr>
<tr>
<td>IL6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.65 (1.25-2.16)</td>
<td>&lt;.001**</td>
<td>2.7**</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.70 (1.29-2.25)</td>
<td>&lt;.001**</td>
<td>3**</td>
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<tr>
<td>IP-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.11 (0.85-1.45)</td>
<td>0.433</td>
<td>1.1</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.16 (0.88-1.54)</td>
<td>0.296</td>
<td>1.1</td>
</tr>
<tr>
<td>sTNFα</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.45 (1.09-1.93)</td>
<td>0.011</td>
<td>2.5*</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.60 (1.17-2.19)</td>
<td>0.003**</td>
<td>3*</td>
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<tr>
<td>sTNFα-III</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.45 (1.10-1.92)</td>
<td>0.009**</td>
<td>2*</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.69 (1.23-2.33)</td>
<td>0.001**</td>
<td>2.7*</td>
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<tr>
<td>Soluble CD14</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.55 (1.17-2.07)</td>
<td>0.003**</td>
<td>2.1</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.81 (1.30-2.51)</td>
<td>&lt;.001**</td>
<td>3.2*</td>
</tr>
<tr>
<td>D-Dimer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.34 (1.06-1.68)</td>
<td>0.014**</td>
<td>1.8*</td>
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<tr>
<td>Adjusted*</td>
<td>1.38 (1.09-1.76)</td>
<td>0.008**</td>
<td>2.2*</td>
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<tr>
<td>CD8+ %DR+38+</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.03 (0.77-1.38)</td>
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<td>1.4</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.06 (0.78-1.47)</td>
<td>0.623</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Adjusted by HIV-1 RNA viral load

Conclusions

• In treated patients with mostly suppressed viral replication, soluble markers of inflammation, and coagulation are strong correlates of non-AIDS defining complications
• These associations are stronger for fatal events
• IL-6 was the strongest and most consistent correlate of outcome, independent of virologic and immunologic indices of disease progression
### Similarities Between Atherosclerosis, Rheumatoid Arthritis and HIV

<table>
<thead>
<tr>
<th>Candidate Molecules / Pathways</th>
<th>Atherosclerosis</th>
<th>Rheumatoid Arthritis</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage activation</td>
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<td></td>
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</tr>
<tr>
<td>TNF-α</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Metalloproteinase expression</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Interleukin-6</td>
<td>↑ (UA)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>T-cell activation</td>
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<td></td>
<td></td>
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<tr>
<td>Soluble IL2 receptor</td>
<td>↑ (UA)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CD3⁺DR⁺</td>
<td>↑ (UA)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CD4⁺CD28⁻</td>
<td>↑ (UA)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>B-cell activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies (oxLDL, HSP)</td>
<td>0 or ↑</td>
<td>0 or ↑</td>
<td>0 or ↑</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>0</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>↑ (UA)</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Endothelin</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Monocytes</td>
<td></td>
<td></td>
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<tr>
<td>Classic CD14⁺CD16⁻</td>
<td>↑↑</td>
<td>↑^</td>
<td>↑</td>
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<tr>
<td>Intermediate CD14⁺CD16⁻</td>
<td>↑↑ (ACS)</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Non-classical CD14⁺CD16⁻</td>
<td>↑↑ (ACS)</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

### Candidate Molecules / Pathways

- **TNF**
- **IL-6**
- **B cell targeting**
- **T cell targeting**
- **Small molecules**
- **Other**

**Major immunologic MOA/biologic effects with relevance to HIV**

**Major AE profile of relevance to HIV**
IL-6 is Produced by Multiple Cell Types and Is Associated with Numerous Biologic Activities\textsuperscript{1,2}

Monocytes/macrophages

T-cell activation
T cell differentiation
TH17

Endothelial cells

Mesenchymal cells, fibroblasts/synoviocytes

Hepatocytes

Acute-phase response
Hepidin, CRP
↓ CYP450

Maturation of megakaryocytes

B-cells

Osteoclast activation
Bone resorption

Thrombocytosis

Auto-antibodies (RF)

Hyper-\gamma-globulinemia


Effects of IL-6 blockade in Treated HIV Infection
CD4 <350, VL - ND
Fall 2013

I. To examine the effects of systemic IL-6 inhibition on the pathogenesis of immune failure and inflammation in treated HIV infection.

II. To examine the effect of systemic IL-6 inhibition on indices of cardiovascular risk in treated HIV-1 infection.

III. To examine the effects of systemic IL-6 inhibition on the inflammatory transcriptome and plasma metabolomes in treated HIV-1 infection.
Cleveland Clinic

Every life deserves world class care.