HIV Disease Pathogenesis

What Do We Mean by Pathogenesis Today?

Increased life expectancy in the era of HAART


Life span of ART-treated patients is 10 years less than that of uninfected people, esp. if therapy is started late.

Non-AIDS events are greater in treated HIV disease than in uninfected people even after adjusting for age, ART, and traditional risk factors.

- Cardiovascular disease\(^1-3\)
- Cancer (non-AIDS)\(^4\)
- Bone fractures/osteopenia\(^5,6\)
- Liver failure\(^7\)
- Kidney failure\(^8\)
- Cognitive decline\(^9\)
- Frailty\(^10\)

Almost two-thirds of deaths in the late ART era are non-AIDS associated.

Non-AIDS events are greater in treated HIV disease than in uninfected people even after adjusting for age, ART, and traditional risk factors.

What Do We Mean by Pathogenesis Today?

What We Talk About When We Talk About Immune Activation

Immune activation occurs early in infection.

- Virus load
- Cytokine

A.R. Stacey et al JV 2009

Normal innate response to viral infection in the acute phase of the infection

As virus load decreases, immune activation persists.

Innate
- Cells: activation of macrophages and dendritic cells
- Cytokines, chemokines: IFN\(\alpha\), TNF, IL-1, IL-6, IL-8, IL-15, IL-10
- Acute-phase proteins: serum amyloid A, C-reactive protein
- Coagulation: D-dimers, tissue factor
- Fibrosis: matrix metalloproteinase activation, collagen deposition
- Microbial sensors: lipopolysaccharide-binding protein, soluble CD14

Adaptive
- T cells: increased turnover, exhaustion, low thymic output, virus reservoir
- B cells: increased turnover, exhaustion, hypergammaglobulinemia

Frequency of activated T cells is a strong predictor of disease progression.
Causes of Chronic Immune Activation

- HIV-induced activation of innate immune system (Bhardwaj)
  - When virus load decreases after acute phase, immune activation remains elevated.
  - Virus load alone is a poor predictor of disease progression (Rodriguez JAMA 2006).
  - Immune activation predicts disease progression independent of viral load (Giongo, Deeks etc).
  - Elite controllers who progress have increased activated CD38+ T cells (Hunt JID 2008).
  - When virus load is suppressed with ART, activation persists and predicts progression.
- Increased antigen load, bacterial overgrowth, herpes viruses (Deeks)
- Defective tryptophan metabolism (McCune, Hunt)
- Immunologic and structural damage to gut, increased mucosal permeability, translocation of inflammatory microbial products into systemic circulation

Consequences of HIV Infection in GI Tract

Healthy Gut
- Tight epithelial junctions, mucus
- Antimicrobial peptides, Abs, cells
- Majority of CD4 T cells in body
- Cross talk between microbes and epithelial and immune cells

HIV-Infected Gut
- Massive loss of CD4 T cells
- Enteropathy
- 2-10x increased permeability
- Translocation of microbial products
- Systemic immune activation

CD4 depletion
enteropathy
microbial translocation
immune activation
immune deficiency
CD4 cell loss
Markers of Inflammation and GI Dysfunction Predict Mortality

Markers of inflammation and gut barrier dysfunction predict mortality independently of CD4 count and virus load.
When Immune Activation Turns to the Dark Side

<table>
<thead>
<tr>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiviral innate immune response</td>
<td>• Target cell generation</td>
</tr>
<tr>
<td>• Restoration of memory CD4 T cells</td>
<td>• HIV replication</td>
</tr>
<tr>
<td></td>
<td>• Thymic dysfunction</td>
</tr>
<tr>
<td></td>
<td>• T- and B-cell exhaustion</td>
</tr>
<tr>
<td></td>
<td>• Macrophage/DC activation</td>
</tr>
<tr>
<td></td>
<td>• Cytokine/chemokine secretion</td>
</tr>
<tr>
<td></td>
<td>• Lymph node fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Generalized tissue fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Coagulation cascade activation</td>
</tr>
</tbody>
</table>

Does inflammation contribute to HIV persistence?

Does HIV replication contribute to persistent inflammation?

Can novel therapies reduce reservoir size?
  - Anti-inflammatory drugs
  - Enhanced HIV-specific immunity

It is difficult to establish cause and effect.

Frequency of HIV DNA-containing resting memory CD4 T cells correlates with frequency of activated CD4 T cells.
IL-7 causes CD4 T-cell proliferation without virus production but with increased HIV-infected CD4 T-cell reservoir.

No association between plasma measures of viral persistence and T-cell activation in blood.

Raltegravir intensification reduces immune activation and virus replication significantly more than conventional therapy.
Raltegravir intensification in nine subjects resulted in decrease in infectious virus and CD8 T-cell activation.

Rapid increase in the level of 2-LTR circles and decrease in D-dimers in some subjects.

Viral replication persists in some individuals even after long-term ART and is associated with inflammatory biomarkers.

Raltegravir intensification reduces immune activation and HIV RNA levels in gut tissue sites.
How Big Is the Reservoir?

It was thought that <1% of HIV sequences in cells are replication competent.

- 88% of HIV sequences in cells have identifiable defects.
- 12% have intact genomes and may be replication competent.

Size of the latent reservoir, and hence the barrier to cure, may be up to 60-fold greater than previously estimated.

Ongoing HIV Replication During ART?

Although complete inhibition of viral replication is unlikely to be curative, all cure strategies are based on first having achieved complete suppression.

- Evidence against ongoing HIV replication on ART.
- *Increasing* evidence in favor of ongoing replication.
- Evidence it is associated with immune activation.
- The source of the sample is key (blood vs tissues).
- The assay used to measure virus is critical.

Virus Persistence on cART: A5276

- Virus persistence by single copy assay (SCA) of plasma virus
- SCA on patients at ~4, 7, and 11 years on suppressive ART (n=64)

<table>
<thead>
<tr>
<th></th>
<th>Yr 4: N (%)</th>
<th>Yr 7: RNA &gt; 1 c/mL</th>
<th>Yr 10: RNA &gt; 1 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+ (persistent)</td>
<td>17 (27)</td>
<td>65%</td>
<td>56%</td>
</tr>
<tr>
<td>+/- (intermittent)</td>
<td>25 (39)</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>-/- (negative)</td>
<td>22 (34)</td>
<td>14%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Persistent viremia at year 4 often still positive at years 7 and 10
- Absence of viremia at year 4 often still negative at years 7 and 10
- No change in pVL over time if persistent viremia (median ~ 1.4 c/mL)
Persistent virus replication in lymph nodes during ART is associated with lower levels of ARVs in tissues.

**Ongoing HIV Replication During ART?**

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues.

**Immune Activation and HIV Persistence**

A. What mechanisms associate immune activation with HIV persistence?

B. How may they direct therapeutic interventions?
HIV Disease Pathogenesis

Daniel C. Douek, MD, PhD

Therapeutic Interventions in Development

- Chemokine receptor inhibitors:
  - maraviroc, TB-652
- Anti-infective therapy:
  - CMV, EBV, HSV, HCV/HBV
- Microbial translocation:
  - sevelamer, colostrum, rifaximin
- Enhance T-cell renewal:
  - growth hormone, IL-7
- Antifibrotic drugs:
  - pirfenidone, ACEI, ARBs, KGF
- Anti-aging:
  - caloric restriction, sirtuin activators, vit. D, omega-3 fatty acids, rapamycin, diet, exercise (not recommended by me)
- Anti-inflammatory drugs:
  - chloroquine, hydroxychloroquine
  - minocycline
  - NSAIDs (COX-2, aspirin)
  - statins
  - methotrexate
  - anakinra (IL-1Ra)
  - thalidomide, lenalidomide, pentoxifylline (weak TNF inhibitors)
  - biologics (TNFi, IL-6i, anti-IFNa, anti-PD1, anti-PDL1, JAKi, IDOi, Casp-11)
- Anticoagulants:
  - warfarin, dabigatran, aspirin, clopidogrel

Combination therapy may be necessary.

Therapeutic Interventions in Studies

- Sevelamer: Pandrea, CROI 2013
- Probiotics: Klatt et al. JCI 2013
- Bovine colostrum: Asmuth, Douek et al. AIDS 2013
- IL-7: Sereti et al. PLoS Path 2014
**HIV Disease Pathogenesis**

**Daniel C. Douek, MD, PhD**

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### In the Context of the Cure

- Multiple mechanisms account for HIV persistence, all of which are being addressed therapeutically.
- The unifying theme is to reduce HIV reservoir size.
  - Reduce inflammation.
  - Increase immune function.
  - Vaccines may enhance host-clearance mechanisms.
  - Early ART and ART intensification.
  - Drugs with biologic activity against latent virus exist.
  - Gene therapy to reduce reservoir size.
  - Stem cell transplants can reduce reservoir size.

Combination therapy may be necessary.

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### Berlin and Boston Patients

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<tr>
<th>HSC/T Patient Factor</th>
<th>Berlin Patient</th>
<th>Boston Patient A</th>
<th>Boston Patient B</th>
</tr>
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<tbody>
<tr>
<td>Cancer</td>
<td>AML</td>
<td>Hodgkin's lymphoma</td>
<td>Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Mode of acquisition</td>
<td>Sexual (adult)</td>
<td>Pernatal</td>
<td>Sexual (adult)</td>
</tr>
<tr>
<td>Favorable HLA alleles?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type of HSC</td>
<td>HLA identical (“10 of 10 match”)</td>
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<td>TDF/FTC/Ral</td>
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<tr>
<td>Length of ART post-HSCT</td>
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<td>Pre-HSCT HIV-1 DNA</td>
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Adapted from Heinrich CROI 2014

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### Patient A: Where Did the Virus Come From?

HIV-1 DNA pre-HSCT

Consensus B

Plasma RNA 5 days after rebound

A single virus accounts for recrudescence

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### The Importance of Target Cell Availability

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### Thanks for the Memories

- Netanya Sander
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