HIV Pathogenesis – Virus or Host?

Turner Overton, M.D.
Associate Professor of Medicine
University of Alabama at Birmingham
Goals

• At the conclusion of this presentation, learners should be better able to:

  – Highlight potential mechanisms for persistent inflammation with chronic HIV infection.

  – Demonstrate how chronic inflammation contributes to metabolic comorbidities.
Question 1

• HIV infection is associated with excess cardiovascular disease risk.

  • True
  • False
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-aymi8u
DHHS Recommendations
Initiating ART

ART is recommended for treatment for all HIV-infected individuals, regardless of CD4 lymphocyte count (A1)

- To reduce the morbidity and mortality associated with HIV infection
- Evidence supports starting at high CD4 counts
- Potential decrease in risk of many complications, including:
  - HIV-associated nephropathy
  - Liver disease progression from hepatitis B or C
  - Cardiovascular disease
  - Malignancies (AIDS defining and non-AIDS defining)
  - Neurocognitive decline
  - Blunted immunological response owing to ART initiation at older age
  - Persistent T-cell activation and inflammation

www.aidsetc.org ; www.bhiva.org
**START Study**

**Strategic Timing of Antiretroviral Therapy**

- **Design**: Randomized, open-label study
  - *Immediate* ART initiation vs *Deferred* initiation (initiate CD4⁺ T cell decline to ≤350, AIDS-related event, or another condition that dictated use of ART)
- **Composite Primary Endpoint**: serious AIDS event, serious non-AIDS diagnoses, and all-cause mortality

**Baseline factors, Median (IQR) or %:**
- Age: 36 (IQR 29,44)
- 26.8% Female; 30.1% Black, 13.6% Latino, 44.5% White
- 31.4% current smokers
- Time to HIV diagnosis: 1 yr (IQR 0.4-3.1)
- CD4: 651 cells/mm³ (585-765)
- HIV-1 RNA: 13,000 cps/mL

**HIV+ ART-naïve participants**

- **Immediate ART Group**: N=2,326
- **Deferred ART Group**: until CD4⁺ <350 cells/mm³ or symptoms
  - N=2,359

** NNRTI – 70% **
** PI – 20% **
** INSTI – 8% **
** TDF – 89% **

**Median Follow up**

- 2.8 years (IQR 2.1-3.9)

INSIGHT START Study Group, *NEJM* 15:373(8).
**Interim review May 2015 recommended findings be immediately disseminated and that participants in the deferred-initiation group be offered ART.**

### HIV and CD4 outcomes

<table>
<thead>
<tr>
<th>End Point</th>
<th>Immediate-Initiation Group (N=2326)</th>
<th>Deferred-Initiation Group (N=2359)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary end point</td>
<td>42 no./100 person-yr</td>
<td>96 no./100 person-yr</td>
<td>0.43 (0.30–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Components of the primary end point</td>
<td></td>
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<tr>
<td>Serious AIDS-related event</td>
<td>14 no./100 person-yr</td>
<td>50 no./100 person-yr</td>
<td>0.28 (0.15–0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serious non-AIDS-related event</td>
<td>29 no./100 person-yr</td>
<td>47 no./100 person-yr</td>
<td>0.61 (0.38–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>12 no./100 person-yr</td>
<td>21 no./100 person-yr</td>
<td>0.58 (0.28–1.17)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6 no./100 person-yr</td>
<td>20 no./100 person-yr</td>
<td>0.29 (0.12–0.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1 no./100 person-yr</td>
<td>11 no./100 person-yr</td>
<td>0.09 (0.01–0.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3 no./100 person-yr</td>
<td>10 no./100 person-yr</td>
<td>0.30 (0.08–1.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cancer not related to AIDS</td>
<td>9 no./100 person-yr</td>
<td>18 no./100 person-yr</td>
<td>0.50 (0.22–1.11)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12 no./100 person-yr</td>
<td>14 no./100 person-yr</td>
<td>0.84 (0.39–1.81)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**A** ART Use and HIV RNA Level

**B** CD4+ Count
START: No Difference in Cardiovascular Outcomes with Early vs. Delayed ART

Cardiovascular Events (Early vs. Delayed):

12 vs. 14 events
HR 0.84 (0.4-1.8)
P=0.65

Small Artery Elasticity (higher is better)

Other comorbidities without effect:
- Neurocognitive dysfunction
- Pulmonary function
- Bone mineral density
- All presented at EACS

START, NEJM, 2015 and Baker, CROI 2016, #41
Why did these comorbidities not improve worsen?

• START trial participants too young or too healthy
  – 7yrs younger than SMART, no interaction by age

• May take time for morbidities to manifest
  – Plausible, but this was not the case in SMART

• The disease process hasn’t started yet
  – i.e., these are “low CD4 nadir” diseases
Question 2

- Starting ART reduces the risk of CV disease to the level reported in HIV negative persons.

A. True
B. False
C. It depends...
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-8yd4dr
Improving Survival
But Still Below General Population

Survival from Age 25 Years  N= 3,990

- Population controls
- HIV: 2000-2005 Current ART
- HIV: 1997-1999 Early ART
- HIV: 1995-1996 Pre-ART

CVD Mortality Higher in HIV-positive, even with Suppressed HIV Virus.

- 145,009 HIV+ subjects reported 2001-2012
  - 71% male, median age 49 yrs
  - CVD mortality 54% ↑increase (7→13%)
    - Decreasing in gen population
    - aHR 1.54 (95% CI: 1.47-1.62)
      - Adjusted for age, sex, race/ethnicity, location, and year

- Rate if VL > 400cp/mL: 7.7/1000pt yr
- Rate if VL suppressed: 3.9/1000pt yr
- General population: 3.2/1000pt yr

Impact of HIV on risk comparable to traditional risk factors including HTN, DM and hyperlipidemia.

Comorbidity in relation to age

HIV-negative

HIV-positive

Mean number of AANCC
- 45-50: 0.68, 0.89
- 50-55: 0.80, 1.35
- 55-60: 1.03, 1.52
- 60-65: 1.15, 1.65
- 65+: 1.47, 2.04

Number of participants
- 45-50: 166, 159
- 50-55: 108, 111
- 55-60: 70, 86
- 60-65: 53, 62
- 65+: 34, 52

Schouten et al. CID 2014.
Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

HIV production
HIV replication

HIV-associated fat
Metabolic syndrome

Loss of regulatory
cells

CMV
Excess pathogens

Hepatic steatosis and
inflammation

Microbial
translocation

Co-morbidities
Aging

Adapted from Steve Deeks.
Persistent Viral Infections are Bad

• The majority of viral infections are cleared but
• **Certain viruses may cause persistent infections.**
• Two flavors of chronic persistent infections:
  
  • **True Latency** - the virus remains completely latent following primary infection e.g. HSV, VZV.
    – Its genome may be integrated into the cellular genome or exists as episomes.
    – Reactivation occurs with immunosenescence or stressor.

  • **Persistence** - the virus replicates continuously in the body at a very low level e.g. HIV, HBV, CMV, EBV.
    – Induces T cell activation and **exhaustion**
    – Indirectly induce end organ disease due to failure of adaptive immune response to clear pathogen
• CD8 T cells can adopt a spectrum of exhausted states
• Key determinants of CD8 exhaustion
  • The levels of viral antigen
  • Availability of CD4 T cells

• CD4 T cells also succumb to exhaustion
• Consequences:
  • Further deterioration of antiviral CD8 responses
  • Enhancement of pro-inflammatory cytokine expression

• **Stepwise Progression**
  • Loss of effector capacity
  • Upregulation of inhibitory receptors
  • Loss of self renewal capacity
  • Compromised viral control

T Cell Activation Remains Abnormally High During ART-mediated Viral Suppression

% CD38+ HLA-DR+ CD8+ T Cells

HIV-  ART+ VL<75  ART- VL>10K

P<0.001

Inflammatory markers remain elevated in treated HIV infection

- 4781 HIV-infected persons (SMART)
- 9617 Controls from MESA Study and CARDIA Study

Proportions of monocyte subsets are altered in HIV-1

-Monocyte populations are altered with HIV infection

- Decreased classic monocytes (CD14++CD16-)
- Increased CD16+ monocytes (elevated inflammation)

-While HAART and virologic control shift monocyte populations towards normal, they remain altered compared with healthy non-HIV infected individuals.

Funderburg N T et al. Blood 2012;120:4599-4608
How is HIV Unique?

Unique Features of HIV:
- Depletion of key regulatory T cell populations
- Changes in gut mucosal integrity
- Excess bacterial translocation
- Promotion of systemic inflammation
  - Lymphocyte activation
  - Monocyte activation
  - Elevated circulating inflammatory biomarkers
  - Neutrophil activation
  - Hypercoagulable state
  - Pro-atherogenic lipid profile

An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia

SM Dillon¹, EJ Lee¹, CV Kotter¹, GL Austin¹, Z Dong¹, DK Hecht¹, S Gianella², B Siewe³, DM Smith², AL Landay³, CE Robertson⁴, DN Frank¹,⁵ and CC Wilson¹
Dysbiosis in HIV infection

HIV Negative

Lamina Propria

Mucosa

Lumen

Homeostatic leukocytes

Butyrate Vit K/B

Protective IgA

Macrophages

Activated Dendritic Cell

Quiescent Dendritic Cell

Neutrophils

Activated T Lymphocytes

Homeostatic T Lymphocytes

Secretory IgA

Proinflammatory Cytokines

Clostridia

Bacteroides

Lactobacillus

Prevotella

Proteobacteria

Neutrophil Proteases

Bacterial ectoenzymes

Zevin, McKinnon, Burgener, Klatt; Curr Opinion HIV/AIDS 2016
Dysfunctional Gut-Liver Axis Induces Systemic Inflammation

**HIV Infection Induced Changes in the GI Tract**
- Depletion of Th17, Th22 CD4 cells
- Dysbiotic intestinal flora
- Increased mucosal permeability

Consequent bacterial translocation via portal vein

- Activation of Innate Immune System
  - Intrahepatic inflammation

**Intrahepatic Complications**
- Recruitment of Monocytes and Neutrophils
- Activation of Kupffer Cells
- Fibrogenesis

**Systemic Complications**
- Pro-inflammatory Lipids
- Insulin Resistance
- Activated Monocytes

**Inflammasome Activation**
- Metabolic Stress
- Inflammatory Cytokine Production
Atherosclerosis
The Role of Circulating Monocytes

Excess CV Disease Risk With Suppressed Viremia

- Vascular inflammation is greater with HIV infection
  - Increased metabolically active macrophages
  - Greater non-calcified, metabolically active, rupture-prone plaque

Question 3

• A 40 yo male presents for care.
  – CD4 count is 325 c/mm³ (16%)
  – Plasma HIV RNA of 42,000 cp/mL.
  – Total cholesterol 196 mg/dL
  – LDL 155 mg/dL
  – HDL 25 mg/dL
  – TG 175 mg/dL.
  – BP is 145/80
  – BMI of 24.5 kg/m²
  – He smokes 1ppd
  – He does not exercise
  – His parents are alive and healthy

• What is the most important intervention to reduce cardiovascular disease risk?
Question 3

• The most important measure to prevent non-AIDS events:

A. ART initiation

B. Smoking cessation

C. Statin initiation

D. Exercise
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-17puoj
How to Beat Inflammation

• Treat early!
• Continue ART.
  – Maintain undetectable viremia
• Stop smoking
• Maintain normal weight
• If overweight, lose at least 5-10% of body weight
• Exercise
• Have a healthy diet
• Cut down on alcohol, avoid drugs
• Consider lipid lowering therapy (aka statins)
CD4+ T cells in the Colonic Mucosa in Early HIV Infection

Acute/Early HIV Cohort

a) CD4 cells in the sigmoid colon mucosa decrease with longer time till diagnosis

b) CD4 cells correlated with colonic HIV RNA

c) CD4 cells correlated with plasma HIV RNA

d) Increased HIV-infected cells with later HIV stage

e) Decreased CD4 T cells (brown) and increased macrophages (red) with later stages of HIV infection.

Therapeutic Options in Development

- **Chemokine receptor inhibitors**: maraviroc, cenicriviroc
- **Anti-infective therapy**: CMV, EBV, HSV, HCV/HBV
- **Microbial translocation**: sevelamer, colostrum, rifaximin, prebiotics, probiotics, isotretinoin
- **Enhance T cell renewal**: growth hormone, IL-7
- **Anti-fibrotic drugs**: pirfenidone, ACE inhibitors, ARBs
- **Anti-aging**: caloric restriction, sirtuin activators, vitamin D, omega-3 fatty acids, sirolimus, diet, exercise

- **Anti-inflammatory drugs**
  - Chloroquine, hydroxychloroquine
  - Minocycline
  - NSAIDs (COX-2 inhibitors), aspirin
  - Statins
  - Methotrexate (low-dose; CIRT)
  - Thalidomide, lenalidomide, pentoxifylline
  - Biologics (e.g., TNF inhibitors, IL-6 inhibitors, anti-INF-alpha)

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

Adapted from Daniel Douek.
A5350: Effect of Probiotics on Gut Microbiome and Immune Activation Markers
Protocol Co-Chairs: Turner Overton and Adriana Andrade

The trial will randomize 90 HIV-infected adults 18 years of age and older on ART, with CD4 count >200 c/mm³, and HIV VL < 50 cp/mL

Followed for an additional 12 weeks off study therapy after completion of probiotic/placebo

45 participants on ART + probiotic X 24 weeks
45 participants on ART + placebo X 24 weeks

ClinicalTrials.gov Identifier: NCT02706717

Key Study Objectives
– Assess changes in inflammatory biomarkers
– Assess changes in microbial translocation markers
– Assess changes in T cell phenotypes
– Assess changes in monocyte phenotypes
– Assess changes in microbial diversity
– Assess changes in gut permeability

Relevance to HIV Pathogenesis?
– Potential to increase Th17 T cell population in gut
– Potential to shift monocyte population
– Mediated through improved gut permeability

Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Microbial translocation

↑ Inflammation

↑ Monocyte activation

↑ T cell activation

Dyslipidemia

Hypercoagulation
Randomized Trial to Prevent Vascular Events in HIV
REPRIEVE (A5332)

Asymptomatic HIV+ patients with no history of CVD

Placebo
Pitavastatin 4mg/day

Coronary plaque, vascular inflammation, immune activation

CV Death, MI, Unstable Angina, Stroke, Arterial Revasc

Individual components of primary endpoint

All cause death
Incidence/Progression of noncalcified plaque; High-risk plaque
Inflammatory, immunological, metabolic biomarkers
Predictors of statin effects
Statin safety and non AIDS comorbidities: DM, Infections, Cancer

Secondary Endpoints

Funded by NHLBI and NIAID. Supported by KOWA Pharmaceuticals.

ClinicalTrials.gov Identifier: NCT02344290

Principal Investigators:
Steven Grinspoon, MD
Pamela S Douglas, MD
Udo Hoffmann, MD, MPH
Heather Ribaudo, PhD
It Takes Two to Tango!

Persistent Viral Infection

Aberrant Host Response
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