HIV Pathogenesis – Virus or Host?

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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
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

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**HIV+ ART-naïve participants with CD4 >500 cells/mm³**

- **N=4,685**

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>20%</td>
</tr>
<tr>
<td>INSTI</td>
<td>8%</td>
</tr>
<tr>
<td>TDF</td>
<td>89%</td>
</tr>
</tbody>
</table>

**Immediate ART Group**: 

- **N=2,326**

**Deferred ART Group**: 

- until CD4+ <350 cells/mm³ or symptoms 
- **n=2,359**

**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

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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>42/100 person-yrs</td>
<td>96/100 person-yrs</td>
<td>0.43 (0.30–0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Components of the primary end point</td>
<td></td>
<td></td>
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<tr>
<td>Serious AIDS-related event</td>
<td>14/100 person-yrs</td>
<td>50/100 person-yrs</td>
<td>0.28 (0.15–0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serious non-AIDS-related event</td>
<td>29/100 person-yrs</td>
<td>47/100 person-yrs</td>
<td>0.61 (0.38–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>12/100 person-yrs</td>
<td>21/100 person-yrs</td>
<td>0.58 (0.28–1.17)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6/100 person-yrs</td>
<td>20/100 person-yrs</td>
<td>0.29 (0.12–0.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1/100 person-yrs</td>
<td>11/100 person-yrs</td>
<td>0.09 (0.01–0.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3/100 person-yrs</td>
<td>10/100 person-yrs</td>
<td>0.30 (0.08–1.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cancer not related to AIDS</td>
<td>9/100 person-yrs</td>
<td>18/100 person-yrs</td>
<td>0.50 (0.22–1.11)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12/100 person-yrs</td>
<td>14/100 person-yrs</td>
<td>0.84 (0.39–1.81)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
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...
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.

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

Co-morbidities
Aging

Microbial translocation

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
**T cell exhaustion during persistent viral infections**

- 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

![CD8 T Cell Exhaustion Diagram](image)

- **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

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

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**c**

<table>
<thead>
<tr>
<th>Bacteroidetes phylum</th>
<th>Firmicutes phylum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroidaceae⁶</td>
<td>Lachnospiraceae⁶</td>
</tr>
<tr>
<td>Porphyromonadaceae⁶</td>
<td>Ruminococcaceae⁶</td>
</tr>
<tr>
<td>Prevotellaceae⁶</td>
<td>Veillonellaceae</td>
</tr>
</tbody>
</table>

Proteobacteria phylum
- Comamonadaceae
- Campylobacteraceae
- Helicobacteraceae
- Moraxellaceae
- Other

**d**

- **Prevent**l
  - Relative abundance (% of total bacteria)
  - Uninfected: 0-50
  - HIV infected: 0-80
  - P = 0.01

- **Bacteroides**
  - Relative abundance (% of total bacteria)
  - Uninfected: 0-50
  - HIV infected: 0-50
  - P = 0.04

- **Ratio of abundance of bacteroides to prevent**l
  - Uninfected: 0-10000
  - HIV infected: 0.001-10000
  - P = 0.004
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 Kuppfer Cells
- Fibrogenesis

Systemic Complications

- Pro-inflammatory Lipids
- Insulin Resistance
- Activated Monocytes
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

Inflammation predicts disease in treated HIV infection


- **Cardiovascular Disease** (Baker, AIDS 2014)

- **Lymphoma** (Breen, Cancer Epi Bio Prev, 2010)

- **Venous Thromboembolism** (Musselwhite, AIDS, 2011)

- **Type II Diabetes** (Brown, Diabetes Care, 2010)

- **Cognitive Dysfunction** (Burdo AIDS 2012)

- **Frailty** (Erlandson, JID 2013)
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

Options marked as:
- ART initiation: ✔️
- Smoking cessation: ❌
- Statin initiation: ✔️
- Exercise: ✗
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.
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 < 50cp/mL

45 participants on ART + probiotic X 24 weeks

45 participants on ART + placebo X 24 weeks

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

ClinicalTrials.gov Identifier: NCT02706717
Randomized Trial to Prevent Vascular Events in HIV
REPRIEVE (A5332)

Principal Investigators:
Steven Grinspoon, MD
Pamela S Douglas, MD
Udo Hoffmann, MD, MPH
Heather Ribaudo, PhD

ClinicalTrials.gov Identifier:
NCT02344290

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It Takes Two to Tango!

Persistent Viral Infection

Aberrant Host Response
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