HOT TOPICS IN HIV

Inflammation, Aging, and HIV

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<th>Consultant</th>
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Learning Objectives

- Describe recent advances in HIV research and clinical practice in the areas of inflammation and aging
- Recognize special concerns for HIV-infected patients with advanced age and risks associated with persistent inflammation
- Implement evidence-based treatment and management strategies to optimize outcomes for HIV-infected patients with advanced age, comorbidities, or safety concerns
Expert Faculty

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Background

- Virus suppressed but present
- Immune dysfunction
- Long-term ART toxicity
- Aging with multimorbidity

HIV+ ART → Aging with HIV

HIV = human immunodeficiency virus; ART = antiretroviral therapy.
Percentage of Adults Living with HIV Aged 50+ By Year and Region

- Western and Central Europe and North America
- Eastern Europe and Central Asia
- Latin America
- Caribbean
- Sub-Saharan Africa
- Asia and the Pacific
- Middle East and North Africa

10-year Decreased Life Expectancy in Older HIV+ Adults in Modern ART Era

Many Age-Associated Morbidities Increased in Treated HIV

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures and osteoporosis
- COPD
- Liver disease
- Kidney disease
- Cognitive decline
- Non-AIDS infections
- Frailty

AIDS = acquired immune deficiency syndrome; COPD = chronic obstructive pulmonary disease.
Why is HIV-1 RNA suppression not enough?
How can we follow our patient’s disease progression?
What can we do to improve outcomes now and in the future?

RNA = ribonucleic acid.
Why Isn’t HIV-1 Suppression Enough?
Does HIV Accelerate Aging? An Important Clue from Nature

Sooty Mangabey
- Infect with SIV
- High levels of viral replication
- No AIDS, normal lifespan
- Minimal immune activation

Rhesus Macaque
- Infect with SIV
- High levels of viral replication
- AIDS and death
- Massive immune activation

SIV = simian immunodeficiency virus.
T-cell Activation Remains Abnormally High During ART-Mediated Viral Suppression

Lower But Persistently Abnormal Immune Activation with Very Early ART (RV254)

- Thai study of HIV+ individuals diagnosed very early during acute HIV infection
- Compared to high-risk HIV- controls and ART-suppressed HIV+ who initiated during chronic HIV infection

Utay NS, et al. CROI 2015; Poster 47.
A Single Measurement of IL-6 or D-dimer Predicts Morbidity/Mortality Over the Next 10 Years

IL-6 = interleukin 6; SNA = serious non-AIDS conditions.
Inflammation Predicts Disease in Treated HIV Infection

- Mortality (Kuller, 2008; Tien, 2010; Justice, 2012; Hunt, 2014)
- Cardiovascular Disease (Duprez, 2009)
- Cancer (Breen, 2010; Borges, 2013)
- Venous Thromboembolism (Musselwhite, 2011)
- Type II Diabetes Mellitus (Brown, 2010)
- COPD (Attia, 2014)
- Renal Disease (Gupta, 2015)
- Bacterial Pneumonia (Bjerk, 2013)
- Cognitive Dysfunction (Burdo, 2013; Letendre, 2012)
- Depression (Martinez, 2014)
- Frailty (Erlandson, 2013)

How Can We Monitor Disease Progression?
Some Markers That Predict Disease Fluctuate Greatly Within Individuals

IL-6

Days

T-cell Activation

Days

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Many Interacting Factors Play A Role

Presenting conditions

Overlapping + Interacting Pathophysiologic Processes

Preclinical + Clinical Organ System Injury

Advanced Clinical Disease

AGING

HIV

Viral Hepatitis

Substance Use

Immune Dysfunction + Senescence

Microbial Translocation “Leaky Gut”

Chronic Inflammation and Platelet Hypercoagulability

HIV + Non HIV Treatment Toxicity

Oxidative Stress

Associated Comorbid Disease

Incremental Depletion in Organ System Reserve

Functional Decline

Organ System Failure

Repeated Hospitalization / Nursing Home Placement

Death

VACS Risk Index

Health Care Outcomes

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# VACS Index Components

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<th>HIV Specific Biomarkers</th>
<th>Score</th>
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<td>Age (years)</td>
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<td>&lt; 50</td>
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<td>50–64</td>
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<td>≥ 65</td>
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<tr>
<td>CD4 cells/mm³</td>
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<tr>
<td>≥ 500</td>
<td>0</td>
</tr>
<tr>
<td>350–499</td>
<td>6</td>
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<td>HIV-1 RNA copies/mL</td>
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<td>500 to 1 x 10⁵</td>
<td>7</td>
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<td>≥ 1 x 10⁵</td>
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<tr>
<td>Hemoglobin g/dL</td>
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<td>12–13.9</td>
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<td>&gt; 3.25</td>
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<td>eGFR mL/min</td>
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<td>45–59.9</td>
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<th>Biomarkers of General Organ System Injury</th>
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<td>Hepatitis C Infection</td>
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Biomarkers of Inflammation Correlated with VACS Index (overall and components)

VACS Index is Accurate in Important Subgroups

NA-ACCORD (N=10,835) VACS (N=5,066) Age < 50 years (N = 11,191) Age > 50 years (N = 4,710)
Men (N=12,785) Women (N=3,116) Black (N = 5,878) White (N = 6,079)
Undetectable VL (N = 8,715) Detectable VL (N = 7,186)

VACS Index Reflects Frailty Indicated By:

- Functional Performance (Erlandson, 2012)
- Sarcopenia (Oursler, 2013)
- Neurocognitive Performance (Marquine, 2014)
- Autonomic Neuropathy (Robinson-Papp, 2013)
- Fragility Fractures (Womack, 2013; Yin, 2016)
- Hospitalizations and ICU Admissions (Akgun, 2013)

ICU = intensive care unit.
Time-updated VACS Index provided better AMI prediction than CD4 count and HIV-1 RNA suggesting that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.

AMI = acute myocardial infection.
**Time-Updated VACS Index for Predicting All-Cause Mortality**

**Referent Category**

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<th>HIV Viral Load (copies/mL)</th>
<th>Baseline</th>
<th>Time-updated</th>
<th>Cumulative time-updated</th>
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<td>1,000-14,999</td>
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<td>1,000+</td>
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<th>Baseline</th>
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<td>265+</td>
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**Time-updated VACS Index provided better mortality prediction than CD4 count and HIV-1 RNA suggesting that current health determines risk more than prior history and that risk assessment can be improved by biomarkers of organ injury.**

What Can We Do?

What can we do now to have the greatest impact?
What potential medications hold promise?
HCV Infection Harms More Than the Liver

HCV = hepatitis C virus; CVD = cardiovascular disease.

HematoLogic and Autoimmune Diseases
- Mixed Cryoglobulinemia
- B-cell Lymphoma
- Autoimmune Thyroiditis
- Membrano-Proliferative Glomerulonephritis
- Sicca Syndrome

CVD/Metabolic Disease
- Atherosclerosis
- Insulin Resistance/Diabetes
- Myocardial Dysfunction

Neurocognitive Diseases
- Cognitive Impairment
- Fibromyalgia

HCV
- Liver: Inflammation, Steatosis, Fibrosis/Cirrhosis, Hepatocellular Carcinoma, Cholangiocarcinoma
- CVD/Metabolic Disease
- HematoLogic and Autoimmune Diseases
- Neurocognitive Diseases
Lifestyle Contributes to Immune Activation in Treated HIV

- Smoking increases monocyte activation (Valiathan, 2014)
- Hazardous EtOH associated with ↑ sCD14 / microbial translocation (Carrico, 2015)
- Methamphetamine use increases immune activation and suppresses T-cell function (Massanella, 2015)
- Obesity associated with increased inflammation (Koethe, 2013)
- Moderate exercise decreases inflammation in pilot trials (Longo, 2014)

EtOH = ethyl alcohol; sCD14 = soluble CD14.
Weight Change After ART and Mortality (Normal [N = 2,226] vs Overweight/Obese [N = 1,842])

*Adjusted for VACS Index at ART initiation.
BMI = body mass index.
Alcohol Use More Harmful Among HIV+

Mortality

Physiologic Frailty

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<th>Variable</th>
<th>Overall (N = 64,441)</th>
<th>Uninfected (n = 47,452)</th>
<th>HIV-infected (n = 16,989)</th>
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<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
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<td>1.39 (1.21, 1.60)</td>
<td>&lt; 0.001</td>
<td>1.35 (1.14, 1.61)</td>
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<td>Long-term benzodiazepine receipt</td>
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<td>0.004</td>
<td>1.41 (1.12, 1.78)</td>
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<td>0.0001</td>
<td>1.43 (1.10, 1.86)</td>
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<td>Long-term medication count</td>
<td>1.05 (1.04, 1.07)</td>
<td>&lt; 0.001</td>
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<td>Alcohol use disorder</td>
<td>1.63 (1.39, 1.90)</td>
<td>&lt; 0.001</td>
<td>1.56 (1.30, 1.88)</td>
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<td>Drug use disorder</td>
<td>0.95 (0.81, 1.13)</td>
<td>0.59</td>
<td>0.88 (0.70, 1.11)</td>
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<td>Schizophrenia</td>
<td>1.14 (0.92, 1.40)</td>
<td>0.23</td>
<td>1.09 (0.86, 1.38)</td>
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<td>Bipolar</td>
<td>0.92 (0.74, 1.14)</td>
<td>0.44</td>
<td>0.93 (0.71, 1.22)</td>
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<td>Major depression</td>
<td>0.95 (0.79, 1.15)</td>
<td>0.62</td>
<td>1.07 (0.84, 1.35)</td>
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<td>PTSD</td>
<td>0.79 (0.68, 0.93)</td>
<td>0.004</td>
<td>0.75 (0.63, 0.91)</td>
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<td>Acute pain</td>
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<td>Chronic pain</td>
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<td>0.24</td>
<td>0.93 (0.81, 1.07)</td>
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<td>Black vs white</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
<td>0.81 (0.70, 0.92)</td>
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<td>&lt; 0.001</td>
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<td>Other vs white</td>
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<td>&lt; 0.001</td>
<td>1.23 (1.21, 1.25)</td>
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<td>Current smoking vs never</td>
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<td>Past smoking vs never</td>
<td>1.43 (1.21, 1.70)</td>
<td>&lt; 0.001</td>
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PTSD = post-traumatic stress disorder.
Polypharmacy

• Typically defined as > 5 chronic drugs

• Associated with diminished marginal benefit from additional medication due to:
  - Nonadherence
  - Drug-drug interactions
  - Cumulative toxicity

• Risk of adverse events increases approximately 10% with each additional medication

• Interacts with alcohol, tobacco, or other substances

Chronic Medication Count by Age and HIV Status (VACS)

Daily Long-term Medications

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<th>Age (years)</th>
<th>Uninfected (n=47,613)</th>
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<td>&lt; 40</td>
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<td></td>
</tr>
<tr>
<td>40 - 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 - 60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prescribed Substances
Opioids and Benzodiazepines

• Co-prescribing particularly problematic
• Long-term (> 90 days) requires careful intervention
• Partner with addiction specialists
• Motivational interviewing and cognitive behavioral therapy
• May require medication:
  – Most commonly buprenorphine
Polypharmacy and Substance Use

Complete Medication Reconciliation
- Perform annually and update with medication changes
- Assess medications taken, adherence, and related symptoms
- Include assessment of over-the-counter medications and supplements

Assess for Tobacco, Alcohol, and Substance Use
- Use standardized instruments

Assess and Rank Each Medication According to Risks and Benefits
- Prioritize ART and pharmacotherapy for alcohol/substance use disorders
- Use risk index, such as VACS index, to assess mortality

Prioritize and Plan with Patient
- Incorporate goals and criteria for stopping treatment
- Develop strategies to monitor for medication-induced symptoms and other adverse events
- Incorporate patient preferences

Compared to less active adults, greater activity:

- Lowers mortality, CAD/CVD, HTN, diabetes, colon/breast cancer, and depression
- Decreases hip and vertebral fracture
- Improves weight maintenance

WHO recommendations for adults:

- Perform 150 mins of moderate (75 mins of vigorous) aerobic/wk:
  - In bouts of 10+ mins each
  - Increase to 300 mins of moderate (150 mins of vigorous)/wk
- Muscle strengthening (resistance) 2+ days/wk

Inactive people: start small and increase over time

Exercise prescriptions, apps, and partnering with a friend help

CAD = coronary artery disease; HTN = hypertension; WHO = World Health Organization.
What Medications Hold Promise?
Statins Reduce Vascular Events in Non-HIV Patients with Low LDL and Increased CRP

- LDL was reduced 47 mg/dL ... and should have resulted in a HR of 0.73 based on LDL lowering alone, according to CTTC meta-analysis
- Instead, JUPITER showed a HR of 0.56, greater than expected based on LDL lowering alone

* Nonfatal myocardial infarction, nonfatal stroke, arterial stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes

Screening for a population with increased inflammation (CRP) in Jupiter trial resulted in a greater reduction in CAD events from statins than would have been expected based on the extent of LDL reduction.

CRP = C-reactive protein; LDL = low-density lipoprotein.
Statins Decrease Immune Activation and Aortic Plaque in Treated HIV Infection

sCD14 Declines with Rosuvastatin

Plaque Regression with Atorvastatin


REPRIEVE Trial of Pitavastatin (N = 6,500) Now Enrolling!
Aspirin Fails to Reduce Immune Activation or Improve Vascular Function (A5331)

Serum Thromboxane (cyclooxygenase inhibition)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>300 mg ASA</th>
<th>100 mg ASA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>12</td>
<td>37</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>16</td>
<td>33</td>
<td>39</td>
<td>36</td>
</tr>
</tbody>
</table>

Mean Fold Change (95% CI)

Overall

Number of Participants

300 mg ASA: 37
100 mg ASA: 37
Placebo: 33

sCD14

Overall

Number of Participants

300 mg ASA: 38
100 mg ASA: 38
Placebo: 36

Overall

Mean Fold Change (95% CI)

O’Brien M, et al. CROI. 2016; Abstract 44LB.
HIV-Mediated Immune Activation and Aging Current Paradigm

- HIV-1 Infection
  - Immunodeficiency
    - Viral Reactivation (eg, CMV)
  - Microbial Translocation
  - TLR 7,8 Nef, gp120

Innate Immune Activation (MØ/DC)

- Increased Cell Turnover and Lymphoid Fibrosis
- Immune Exhaustion
- Malignancy, Infections
- Increased TF Expression and Clotting
- CAD/Stroke, Thrombosis
- Cytokine Secretion (eg, IL-6, TNFL)
- “Inflam-Aging” (eg, atherosclerosis, osteoporosis, T2DM)

Can We Find the Tree Trunk?

**Branches**
- IL-6
- D-dimer
- TNFa

**Trunk**
- IL-1β
- Jak/Stat
- IDO-1?

**Roots**
- HIV Reservoirs
- CMV
- Microbial Translocation

www.ulead.org
Upcoming HIV Webinars

PEP and PrEP Updates
Tuesday, October 18th at 2pm EST

Case Studies in HIV/HCV Co-Management
Tuesday, November 29th at 2pm EST

Register today at: primeinc.org/webinars/1253
On-Demand HIV Activities

Available now at: www.primeinc.org/hiv
Credit Center

To receive credit please visit

www.primeinc.org/credit

and enter program code

54WC169
EXTRA SLIDES
Delayed Treatment by Age

*Among individuals in NA-ACCORD.
Reduced but Persistently High Risk of TB with Early ART: Temprano Trial

CD4 > 500

30-month Probability

- Deferred ART: 12.4%
- Deferred ART + IPT: 7.4%
- Early ART: 6.9%
- Early ART + IPT: 4.6%

Cumulative Probability of Death or Severe HIV-Related Illness (%)

Time (months since randomization)
Reduced but Persistently High Risk of Infections and Cancer with Early ART: START Trial

**AIDS Events**

~ 1% of Immediate ART arm had an AIDS Event by Year 5

**Non-AIDS Events**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>0.29</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>0.38</td>
</tr>
<tr>
<td>KS</td>
<td>0.09</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.30</td>
</tr>
<tr>
<td>Non-AIDS Cancer</td>
<td>0.50</td>
</tr>
</tbody>
</table>

INSIGHT START Study Group, et al.


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Cardiovascular Complications Much Lower in START than SMART

Role of CD4 Nadir

Some complications are “low CD4 Nadir diseases”

Event Rate (per 100 person-years)

Nadir CD4+ T-cell count (cells/μL)

SMART Study
Interrupted ART

Continuous ART

START Study
Delayed ART

Theoretical Model for Drivers of Immune Activation During Suppressive ART

A New Paradigm?

CD4 Nadir

500

350

200

HIV Reservoir in Lymphoid Tissues

Microbial Transl.

HIV in Myeloid Cells

CMV

Adaptive Immune Defects

Multiple Morbidities

CNS, Liver, Metabolic Dz

Vascular Dz

HIV in Reservoir in Lymphoid Tissues

Multiple Morbidities

CNS, Liver, Metabolic Dz

Vascular Dz
HIV Reservoirs Established in First Week of Infection and Continue to Release Virus on ART

Mostly reflects release of virus from infected cells without productive replication

We lack interventions that block HIV expression

Inflammation and Immune Activation Pre- and Post-ART (MACS 1984–2009)

- Generalized gamma models adjusted for age, race, smoking, HCV, obesity, diabetes, and site
- Median ages (years): 42 uninfected, 38 ART-naïve, and 48 suppressed
- 13 biomarkers “normalized” in 1 year, 12 remained distinct from uninfected
- After 1 year, values stabilized

HIV-1 RNA Suppression and Cancer

Valacyclovir, which has strong anti-HSV1/2 but minimal anti-CMV activity, failed to decrease immune activation (Yi, CID, 2013).

CMV Sero-Status Predicts non-AIDS Events (and less so AIDS...): ICONA Cohort

CMV replicates in vascular endothelium and contributes to transplant vasculopathy

Likely plays a greater role in individuals with lower CD4 Nadir

Strongest effect for CAD (HR 2.3)

Microbial Translocation ("Leaky Gut") as a Cause of Immune Activation in HIV

Disrupted Gut Epithelial Barrier

↑EC Apoptosis
  (Li, JID, 2008)

↓Tight Junctions
  (Epple, Gut, 2009)

Loss of Mucosal Immunity

↓CD4+ T cells
↓Th17 cells


Brenchley JM, et al.
Microbial Translocation Persists on ART

Particularly in those with low CD4 Nadirs and poor CD4 recovery

HIV-  
HIV+ ART+ CD4 > 500  
HIV+ ART+ CD4 < 350

Persistent neutrophil infiltration in rectal mucosa during treated HIV infection in response to mucosal barrier breach

Chronic Immune Activation May Also Cause Lymphoid Tissue Fibrosis

• Associated with low % naïve T cells and poor CD4+ T-cell recovery
• May impair functional immune responses