Impact of Persistent Immune Activation in Treated HIV Infection

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Life Expectancy* May Start to Approach General Population with Early ART

By pre-ART CD4 count

- Life expectancy of patients on or starting ART in North America
- ~23,000 person-years FU
- 1,622 deaths
- May overestimate life expectancy
  - Excludes those out of care
  - “Survivorship bias” for older patients who survived 80s and 90s.
- Majority of HIV+ around the world still starting ART <350.

*For 20-year old initiating ART

Many age-associated morbidities also increased in treated HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]
- Frailty [10]

HIV and Aging — Preparing for the Challenges Ahead
Edward J. Mills, Ph.D., Till Bärnighausen, M.D., Sc.D., and Joel Negin, M.I.A.
Many chronic diseases of aging are more common in HIV+’s, even after adjustment for ART use and lifestyle factors

Deeks and Phillips, BMJ, 2009
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**

*Silvestri, Immunity, 2003*
T Cell Activation Declines with ART

But Remains Abnormally High During ART-mediated Viral Suppression

Inflammatory markers remain abnormally high in treated HIV infection

A Single IL-6/D-dimer Measurement Predicts Morbidity and Mortality Over Next 10 Years!

**IL-6**

![Graph showing cumulative percentage of events for IL-6 quartiles](image)

**D-dimer**

![Graph showing cumulative percentage of events for D-dimer quartiles](image)

Grund, CROI 2013, Abstract #60
Increased Arterial Inflammation in HIV

Aortic Inflammation associated with ↑sCD163 levels (monocyte activation)

Subramanian/Grinspoon, JAMA, 2012
Inflammation Predicts Disease in Treated HIV Infection

- **Mortality**  (Kuller, PLoS Med, 2008; Tien, JAIDS, 2010; Justice, CID 2012)
- **Cardiovascular Disease**  (Duprez, Atherosclerosis, 2009)
- **Cancer**  (Breen, Cancer Epi Bio Prev, 2010; Borges, AIDS, 2013)
- **Venous Thromboembolism**  (Musselwhite, AIDS, 2011)
- **Type II Diabetes**  (Brown, Diabetes Care, 2010)
- **Cognitive Dysfunction**  (Burdo, AIDS, 2013; Letendre CROI 2012, Abs#82)
- **Frailty**  (Erlandson, JID, 2013)
What can we do about the inflammatory state in HIV?

ART is important!

Maybe even in “elite” controllers…
Negative Inflammatory Consequences in HIV Controllers

- Controllers also have:
  - ↑ Microbial Translocation (Hunt, JID, 2008)
  - ↑ Monocyte activation (Pereyra, AIDS, 2012)
  - ↑ Atherosclerosis (Hsue, AIDS, 2009; Pereyra, AIDS, 2012)
  - ↑ Lymphoid fibrosis (Sanchez, CROI 2013, #74)

- Treating controllers with ART decreases immune activation (Hatano, CROI 2013, #75LB)

Early ART initiation might also be beneficial.
OPTIONS Cohort: Early vs. Late ART Initiation

- Sx of Acute HIV or Recent Seroconversion
- HIV+ <6mo
  - Early ART Initiate <6 mo of Infxn
- HIV-
  - Late ART Initiate >2 yr of Infxn
Persistently Abnormal Immune Activation When ART Initiated during Chronic Infection

Timing of ART Post-infection: Chronic (~3y)

See also: Burdo, JID, 2011; Vinikoor, CROI 2012, Abstract #554
Early ART Appears to Cause Greater Reduction in Residual T Cell Activation

See also: Burdo, JID, 2011; Vinikoor, CROI 2012, Abstract #554
What about commonly used medications with anti-inflammatory properties?
Rosuvastatin Decreases Both Monocyte and T Cell Activation during Suppressive ART

SATURN Trial (n=147)

Also under study:
Aspirin, ACEI, ARB

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REPRIEVE
Clinical Endpoint Trial of Statins (pitavastatin)
N=6500
Starts Enrolling Next Year

Funderburg, CROI 2014, Abstract #335 (see also: Funderburg, Clin Infect Dis, 2014)
Moderate Exercise Decreases Inflammation in Sedentary ART-suppressed HIV+ Patients (n=49)

3 Days/Wk x 12 Wks
1hr brisk walking (n=29) + strength training (n=20)
71% completed 12 wks

Also improved:
- Weight (-3 kg)
- BMI
- Waist Circumference
- LDL
- Strength studies
- ALT

Longo, CROI 2014, Abstract #763
What if statins, aspirin, and exercise are not enough?

What is causing inflammation during suppressive ART?
Low-level Viremia <75 copies/ml is Common During Apparent Viral Suppression on HAART

Mostly reflects release of virus from infected cells without productive replication

We lack interventions that block HIV expression.

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

Veazey, Science, 1998;
Brenchley, J Exp Med, 2004;
Guadalupe, J Virol, 2003;
Mehandru, J Exp Med, 2004

Brenchley et al,
Nat Med, 2006
Gut Barrier Dysfunction Predicts Mortality during ART-mediated Viral Suppression

SOCA cohort

- Microbial translocation
- Inflammation / Coagulation

- sCD14
- IL-6
- D-dimer

Hunt, JID, 2014 (see also: Sandler, JID, 2011)
Interventions to Reduce Microbial Translocation Unsuccessful to Date (CROI 2014)

- Sevelamer (Sandler et al, JID in press)
- Mesalamine (Somsouk et al, Poster #341)
- Rifaximin (Tenorio et al, JID in press)
- Probiotics (Stiksrud et al, Poster #342)

Target epithelial barrier itself? Longer and/or combination interventions?
Do chronic co-infections also contribute to immune activation during ART?
Blocking Asymptomatic CMV Replication with Valganciclovir ↓ Immune Activation in HIV+ Patients with CD4<350 despite ART

-4.4%

Hunt et al, JID, 2011

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

We need larger studies of safer CMV drugs to see if this is clinically meaningful...
HIV-Mediated Immune Activation and Aging

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

Innate Immune Activation (MØ/DC)

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

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IDO-1-induced Tryptophan Catabolism

- IFN-γ/IFN-α and LPS induce Indoleamine 2,3-dioxygenase-1 (IDO-1) production in DCs/MØ
- Causes tryptophan catabolism
- Kynurenine and Picolinic Acid may impair T cell proliferation
  - Maternal tolerance of fetal antigens
  - Cancer evasion of immune response
- Catabolites may be neurotoxic
  - Neurodegenerative diseases, ADC
- 3-Hydroxyanthranilic Acid (HAA) causes Th17 depletion, ↑Tregs

Kynurenine (K/T Ratio) = Marker of Tryptophan Catabolism

Favre, Mold et al, Science TM, 2010
(see also: Munn, Science, 1998; Boasso, Blood, 2007)
IDO-1 Pathway and HIV Pathogenesis
(Indoleamine 2,3-dioxygenase-1)

↑Microbial Translocation (I-FABP, LPS)

MØ / DC Activation (sCD14, sCD163)

Inflammation (IL-6, sTNFR)
T Cell Activation (CD38+DR+)
Coagulation (D-dimer)

↑IDO Induction (KT ratio)

↓Th17/Treg Ratio

↑3-HAA

↓T Cell Proliferation

Morbidity & Mortality

Favre, Science Transl Med, 2010 (see also Boasso, Blood, 2007)
Higher Kynurenine Pathway Activity (K/T ratio) Predicts ↑ Mortality during ART

Each tertile increase in baseline K/T ratio associated with a 2.1-fold greater hazard of death after adjustment for pre-ART BMI and CD4 count (P=0.01).

Byakwaga, JID, 2014
Summary

- Despite ART, HIV decreases life expectancy and increases several age-associated morbidities.
- Immune activation / inflammation persist despite ART and may predict these morbidities.
- Earlier initiation of ART may decrease the degree of persistent immune activation.
- Statins, ASA, diet, and exercise may hold promise and are being studied.
- Need more effective targeted interventions directed at the underlying causes of inflammation (i.e., HIV reservoirs, co-infections/CMV, microbial translocation).
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