# Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

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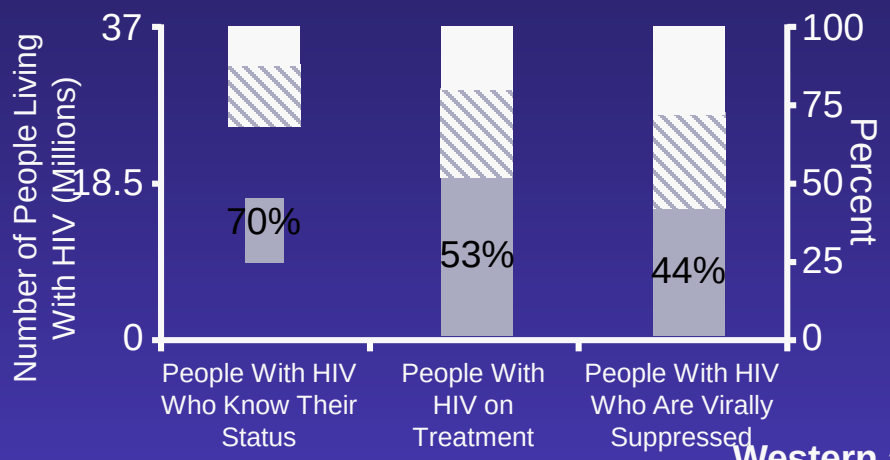
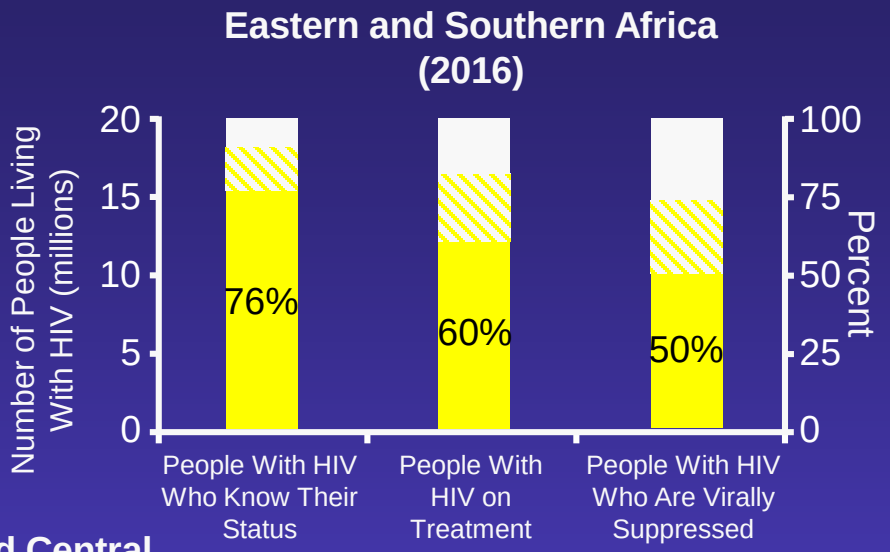
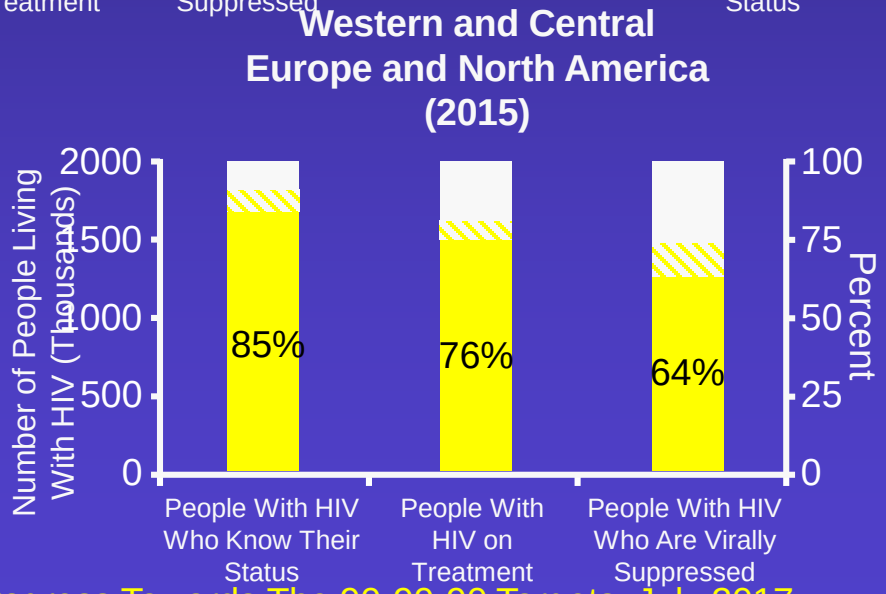
# Program Overview

- Living longer
- Potential impact of persistent inflammation and immune activation during HIV infection
- Age- and HIV-associated non-AIDS comorbidities

# Current Status: 90-90-90 Targets

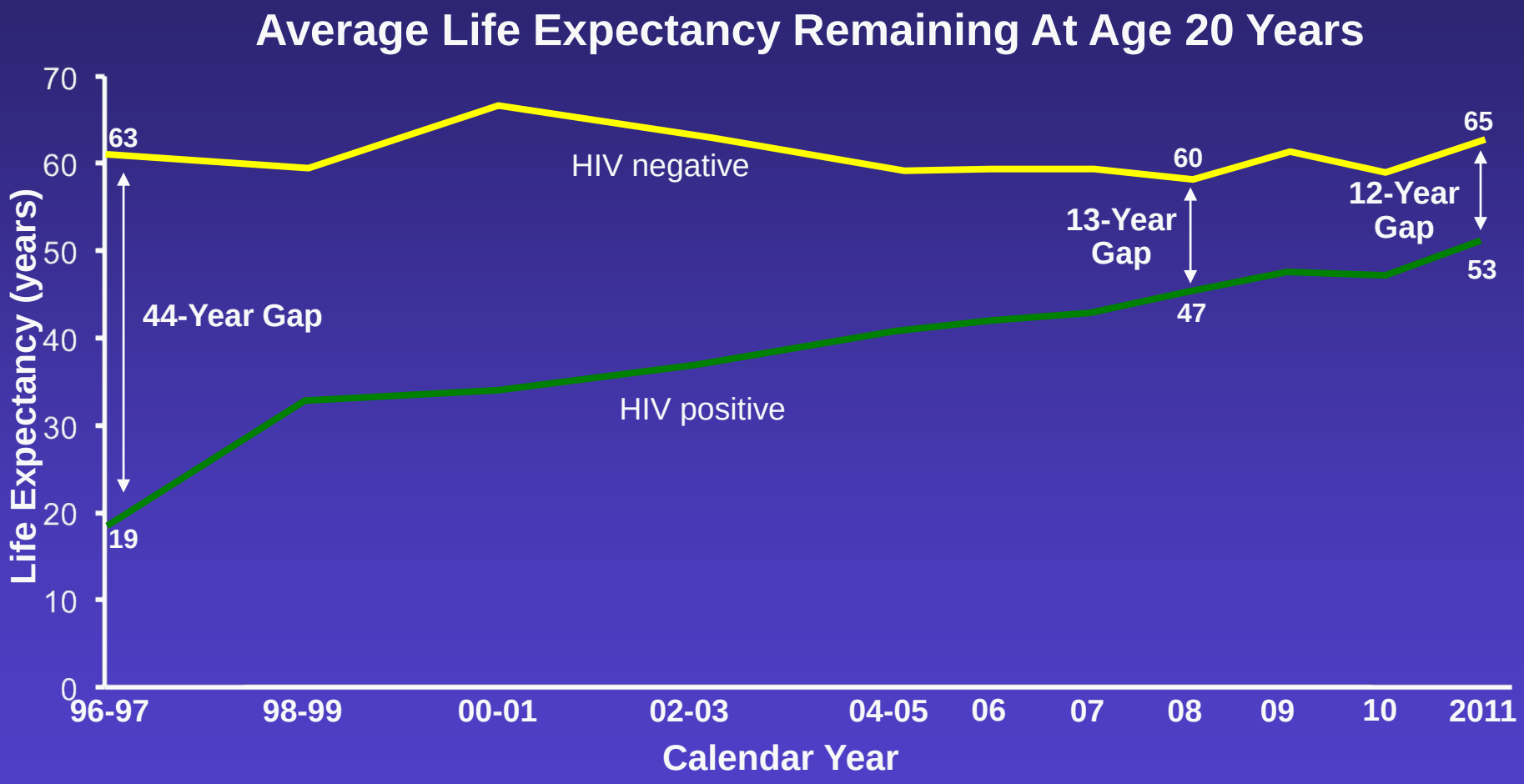



UNAIDS. Ending AIDS: Progress Towards The 90-90-90 Targets. July 2017.

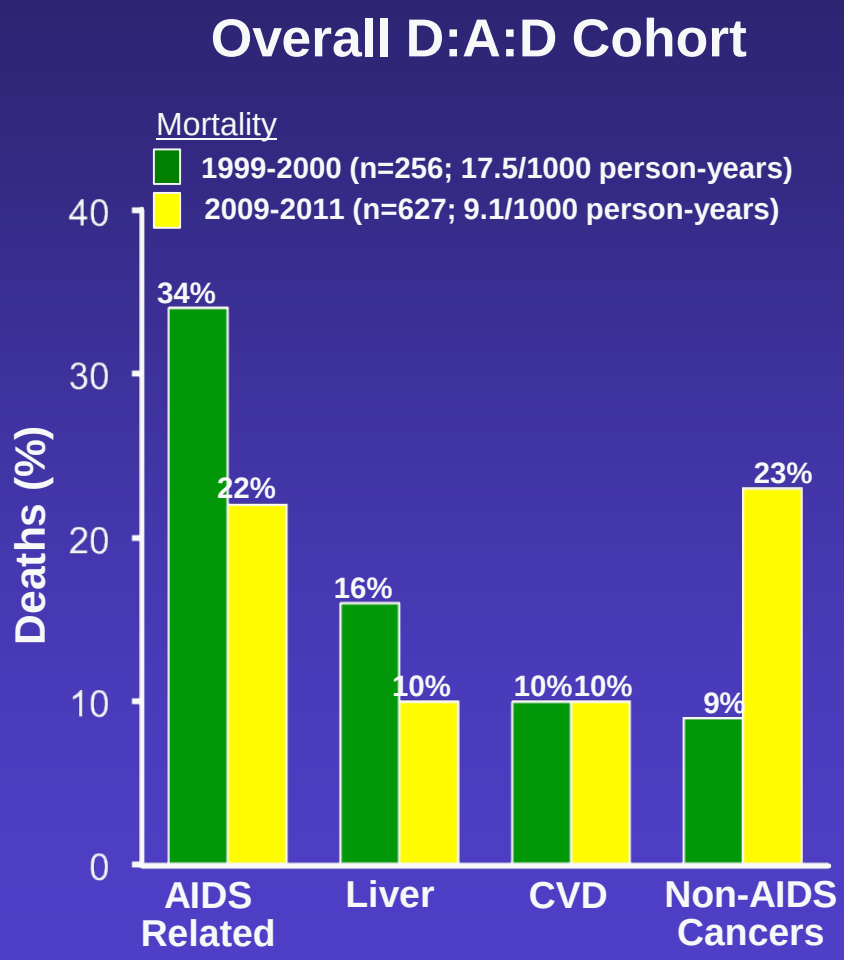
# Narrowing the Gap in Life Expectancy Between HIV-Positive and Uninfected Persons (1996-2011)

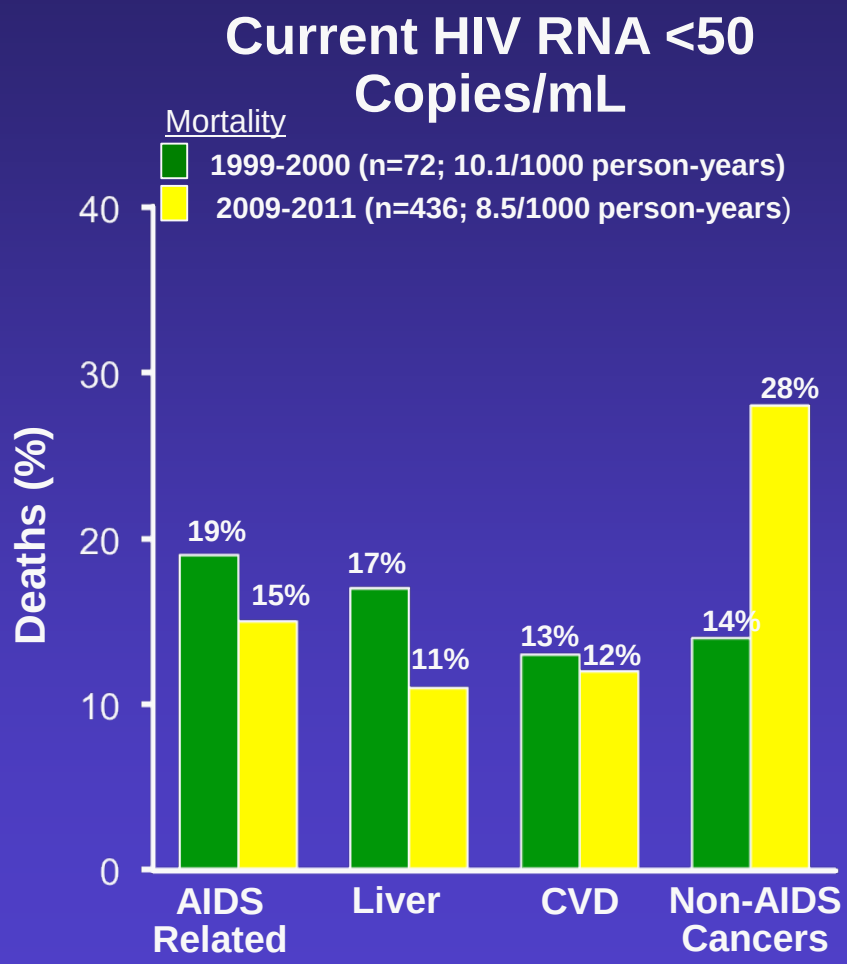



Kaiser Permanente Northern California (1996 to 2011):
HIV-positive (n=25,768) and matched non-HIV-infected adults (n=257,600). Males (91%) and MSM (75%).

Marcus JL, et al. *JAIDS*. 2016;73:39-46.

# D:A:D Study:
# Trends in the Underlying Causes of Death in HIV Patients

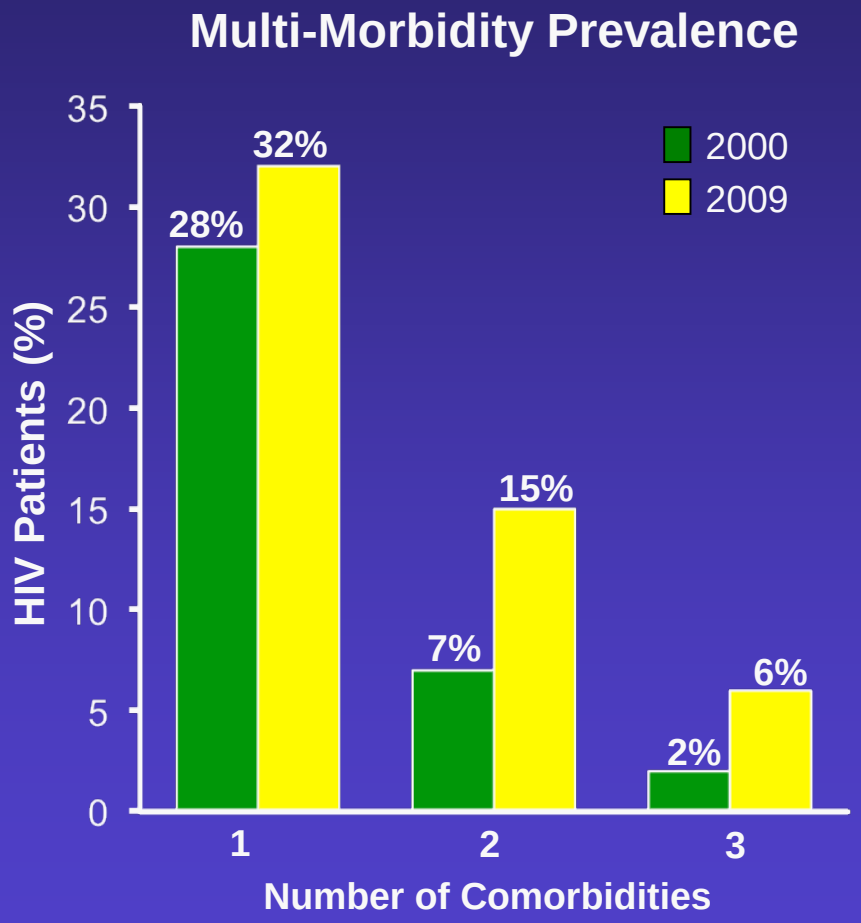



Smith CJ, et al. *Lancet*. 2014;384:241-248.

# NA-ACCORD: Increasing Multi-Morbidity Trends Among HIV Patients Living in the US

- US clinical cohorts of the NA-ACCORD (n=22,969; 2000-2009)
  - Multi-morbidity: ≥2 of hypertension, diabetes mellitus, chronic kidney disease, hypercholesterolemia, end-stage liver disease, non-AIDS-related cancer
- Multi-morbidity prevalence from 2000 to 2009 (38% to 54%)
  - High cholesterol: 18% to 20%
  - Hypertension: 6% to 9%
  - Hypertension with
    - High cholesterol: 4% to 9%
    - Chronic kidney disease: 0.8% to 1.6%
    - High cholesterol and diabetes: 0.8% to 1.6%




Wong C, et al. 24th CROI. Seattle, 2017. Abstract 662.

# NCI and CDC: Excess Burden of Cancer Among HIV-Infected Patients in the US (2010)

Retrospective analysis

- Expected HIV cancer rates: HIV/AIDS Cancer Match study
- General population cancer rates: SEER program

**Excess cancer burden in the US HIV population in 2010: 54%**

- Nearly 65% occurred in MSM
- Largest increase in NHL, Kaposi sarcoma, anal cancer, lung cancer
- Largest excess occurred in those 40 to 49 years of age
  - Largest percentage excess in those 15 to 29 years of age

SEER: Surveillance, Epidemiology, and End Results.

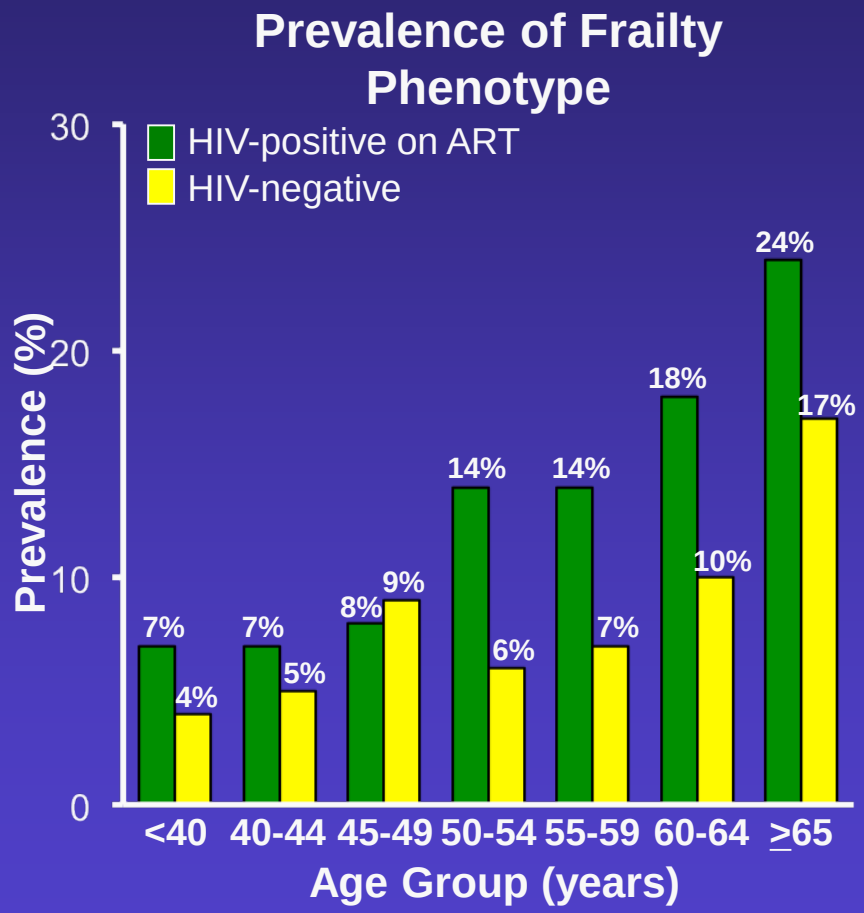
Robbins HA, et al. *J Natl Cancer Inst*. 2015;107(4).

**Excess or Deficit Cancer Cases Among HIV-Infected Patients in the US**

| | Expected Cancers (number) | Excess or Deficit (%) |
|---|---|---|
| NHL (n=1645) | 203 | 87.7 |
| Kaposi sarcoma (n=912) | 2 | 99.8 |
| Lung (n=837) | 401 | 52.0 |
| Anus (n=764) | 20 | 97.4 |
| Prostate (n=574) | 969 | -40.7 |
| Liver (n=389) | 106 | 72.7 |
| Colorectum (n=357) | 379 | -5.8 |
| Hodgkin lymphoma (n=317) | 29 | 90.0 |
| Female breast (n=177) | 303 | -41.6 |

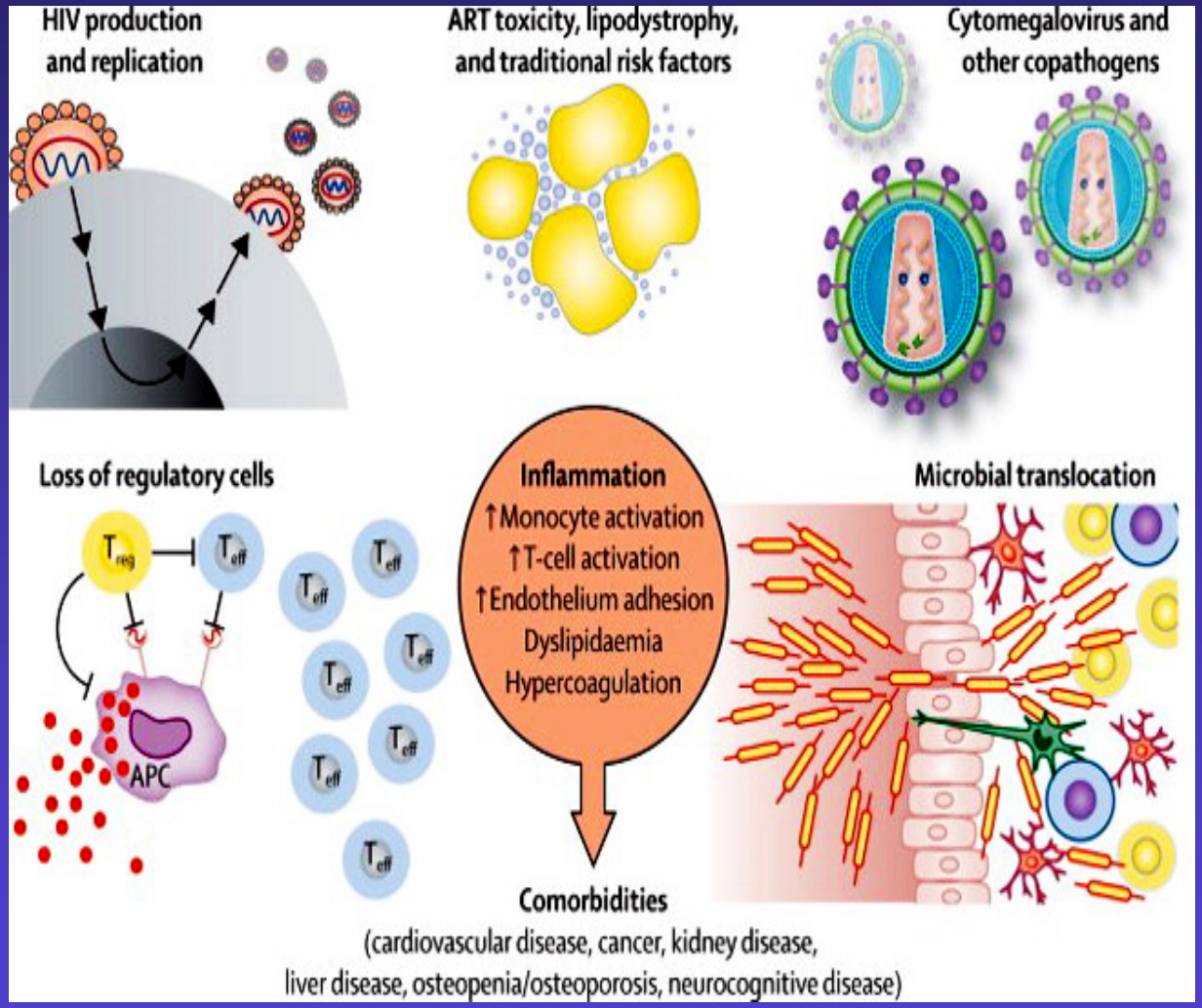
# MACS:
# Frailty Phenotype in HIV-Positive MSM 50 to 70 Years of Age

- Prospective cohort of MSM (2007-2011)
  - 10,571 person-visits
  - HIV positive on ART (n=1946)
  - HIV negative (n=1048)
- Ages 50 to 64 years
  - Frailty phenotype more common in HIV-positive men versus HIV-negative men.
  - May be effect of HIV infection, ART, or both
- Further longitudinal studies are needed




Althoff KN, et al. *J Gerontol A Biol Sci Med Sci*. 2014;69:189-198.

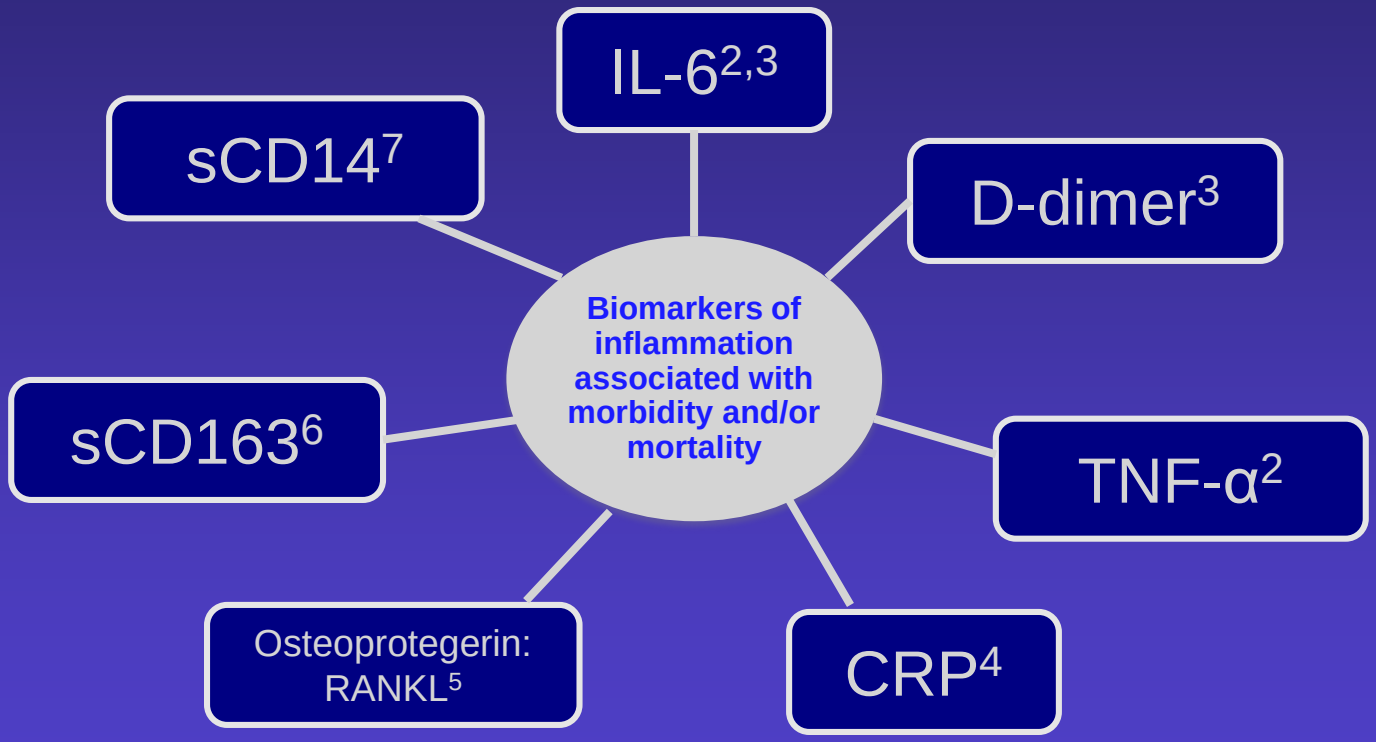
# Persistent Inflammation During ART: Multiple Mechanisms and Consequences




Deeks SG, et al. *Lancet*. 2013;382:1525-1533.

# Biomarkers of Inflammation and Immune Activation

- Recent data demonstrate strong associations between certain biomarkers of inflammation and morbidity and/or mortality in the setting of HIV infection[1]




1. Lundgren JD et al. *Curr Opin HIV AIDS.* 2010;5(6):459-462. 2. McComsey GA et al. *J Acquir Immune Defic Syndr.* 2014;65(2):167-174. 3. Kuller LH et al. *PLoS Med.* 2008;5(10):e203. 4. Lau B et al. *Arch Intern Med.* 2006;166(1):64-70. 5. Hoy J et al. *J Bone Miner Res*. 2013;28(6):1264-1274. 6. Burdo TH et al. *J Infect Dis.* 2011;204(8):1227-1236. 7. Sandler NG et al. *J Infect Dis.* 2011;203(6):780–790.

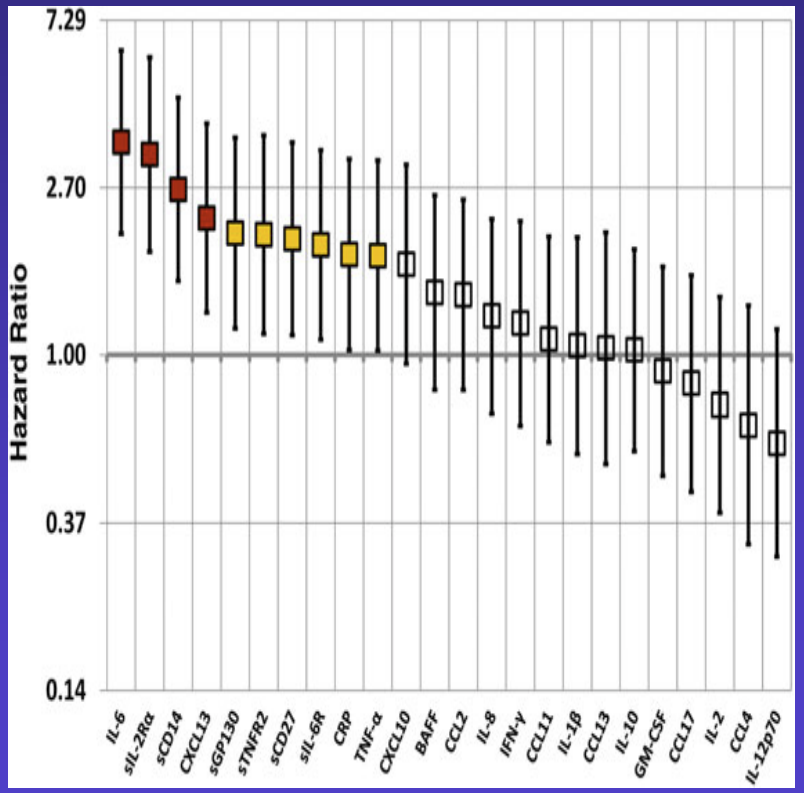
# MACS Cohort: Inflammatory Markers and Mortality Risk Among HIV-Suppressed Men

Prospective cohort study (1996-2014)

HIV suppression (n=670; 54 died)

- Residual inflammation may result from viremia below detectable levels or may represent immunologic processes that continue as a consequence of damage early in the course of infection
- **High concentration of biomarkers associated with increased mortality risk in HIV-suppressed men (adjusted hazard ratio)**
  - **IL-6 (aHR: 3.5; *P*<0.001)**
  - **Soluble IL 2Rα (aHR: 3.3; *P*<0.001)**
  - **Soluble CD14 (aHR: 2.7; *P*<0.001)**
  - **Chemokine ligand 13 (aHR: 2.3; *P*=0.005)**

**Mortality Hazard Ratios for Men**
**(highest quartile of biomarker concentration relative to the lower 3 quartiles)**




aHR: hazard ratio adjusted for age, CD4 count, HBV or HCV infection, and smoking.

Wada NI, et al. *Clin Infect Dis*. 2016;63:984-990.

# Markers of Persistent Innate Immune Activation and Inflammation Predicts Morbidities Among Treated HIV Patients

- Cardiovascular disease
- Osteoporosis
- Type 2 diabetes
- Renal disease
- Lymphoma and non-AIDS-defining cancers
- Chronic obstructive pulmonary disease
- Bacterial pneumonia
- Neurocognitive dysfunction
- Depression
- Frailty


Hunt PW, et al. *J Infect Dis.* 2016;214:S44-S50.
Musselwhite LW, et al. *AIDS.* 2011;25:787-795.
Duprez DA, et al. *PLoS One.* 2012;7:e44454.
Brown TT, et al. *J Inect Dis.* 2015;212:1241-1249.
Brown TT, et al. *Diabetes Care.* 2010;33:2244-2249.
Gupta SK, et al. *HIV Med.* 2015;16:591-598.
Breen EC, et al. *Cancer Epidemiol Biomarkers Prev.* 2011;20:1303-1314.
Borges AH, et al. *AIDS.* 2013;27:1433-14441.
Attia EF, et al. *Chest.* 2014;146:1543-1553.
Bjerk SM, et al. *PLoS One.* 2013;8:e56249.
Burdo TH, et al. *AIDS.* 2013;271387-1395.
Ancuta P, et al. *PLoS One.* 2008;3:e2516.
Lyons JL, et al. *JAIDS.* 2011;57:371-379.
Martinez P, et al. *JAIDS.* 2014;65:456-462.
Erlandson KM, et al. *J Infect Dis.* 2013;208:249-259.

# START Study:
# Initiation of ART in Early Asymptomatic HIV Infection

**Multicontinental Study (n=4685)**

**HIV-positive adults**

**Treatment-naive**

**CD4 >500 cells/mm$^3$**

Randomization
1:1

**Immediate ART (n=2326)**

**Deferred ART (n=2359)**
**(CD4 Declined to <350 cells/mm$^3$ or AIDS-related event)**

5/2015: DSMB recommends stopping trial:
Deferred arm offered ART

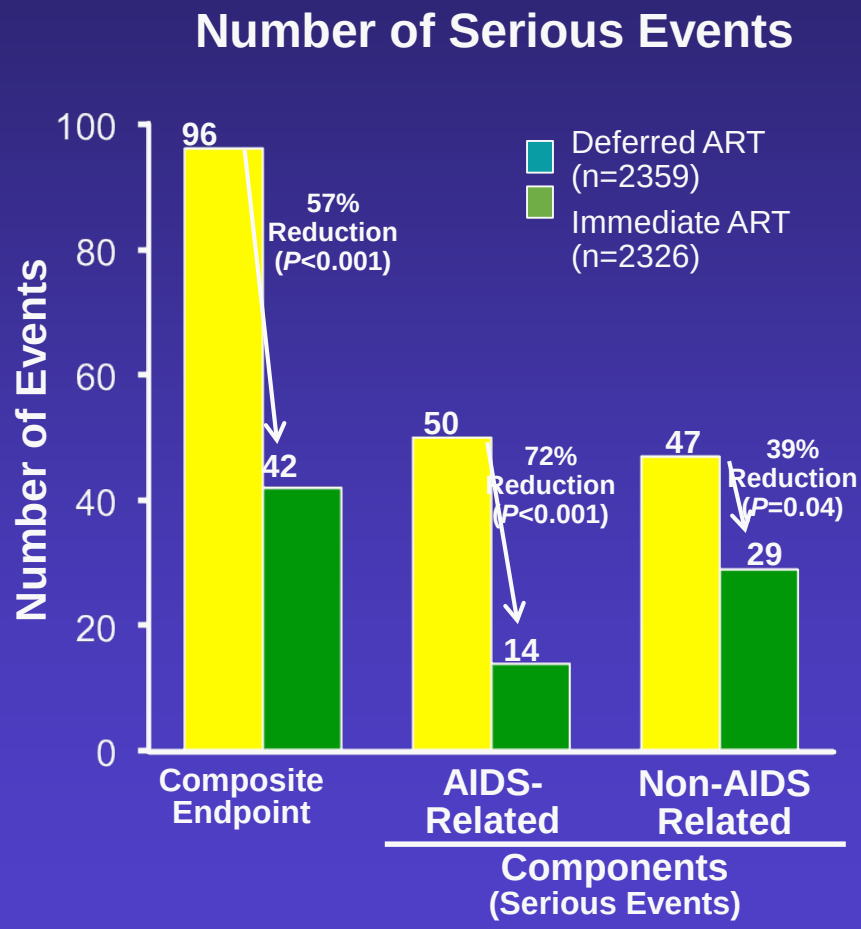
Primary outcome a composite outcome of 2 major components:

- Any serious AIDS-related event
  - Death from AIDS or any AIDS-defining event, Hodgkin's lymphoma
- Any serious non–AIDS-related event
  - CVD (myocardial infarction, stroke, or coronary revascularization) or death from CVD, end-stage renal disease (initiation of dialysis or renal transplantation) or death from renal disease, liver disease (decompensated liver disease) or death from liver disease, non–AIDS-defining cancer (except for basal-cell or squamous cell skin cancer) or death from cancer, and any death not attributable to AIDS

**Molina J-M, et al. *JAIDS*. 2016;19(suppl 5):78-79. Abstract THAB0201.**
**The INSIGHT START Study Group. *N Engl J Med.* 2015;373:795-807.**

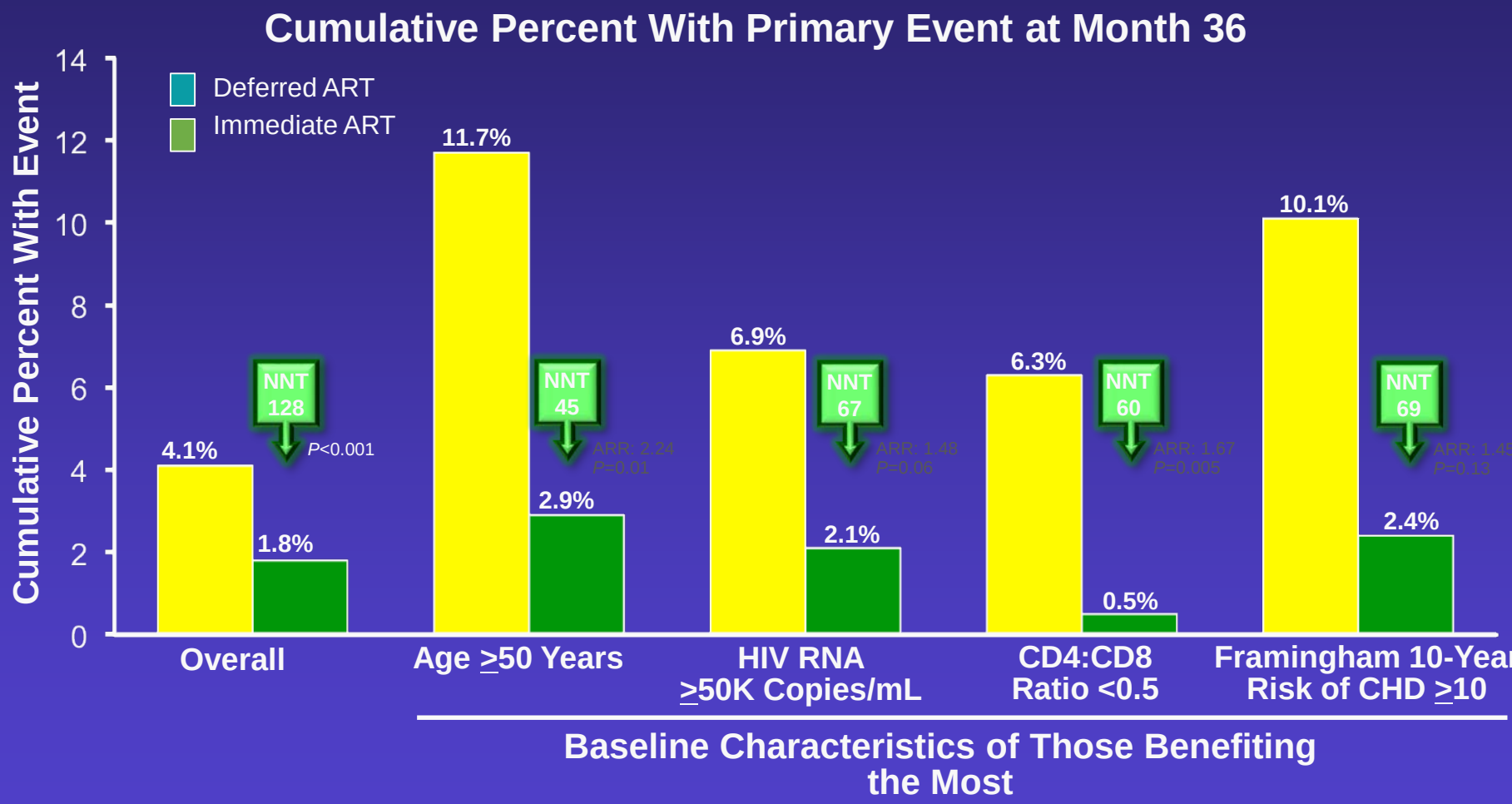
# START Study Outcomes: Composite Primary Endpoint and its Components

- Immediate ART was superior to deferral of ART **both for serious and non-serious AIDS events**
- Majority (68%) of the primary endpoints occurred in patients with a CD4 >500 cells/mm$^3$
- Similar significant reductions were noted across all patient subgroups
- No increase in adverse events associated with immediate versus deferred ART




The INSIGHT START Study Group. *N Engl J Med.* 2015;373:795-807.

# START Study:
# Who Benefited the Most From Immediate ART?




NNT: number needed to treat to prevent 1 primary event.
ARR: adjusted rate ratio (deferred-immediate ART).

Molina J-M, et al. *JAIDS*. 2016;19(suppl 5):78-79. Abstract THAB0201.

# START Study: Who Benefited the Most From Immediate ART?

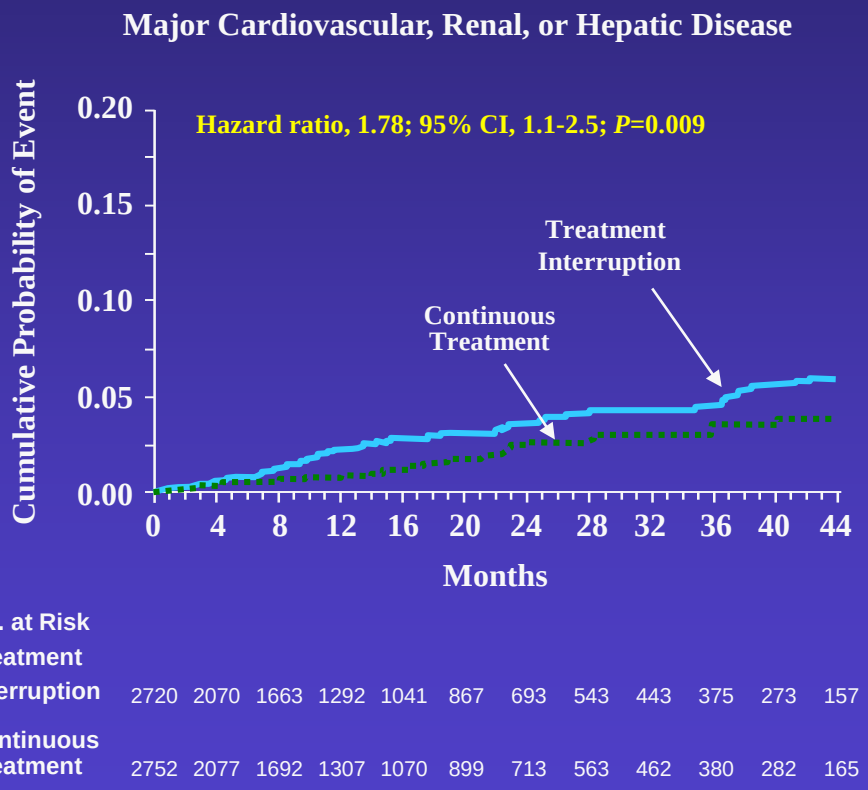
Immediate ART was superior to deferred ART in asymptomatic, treatment-naïve adults with baseline CD4 >500 cells/$mm^3$

- Benefit seen in all subgroups, but not to the same magnitude
- Univariate analysis: Who benefited the most (higher absolute risk reduction and lower NNT)?
- Age: ≥50 years
- HIV RNA: ≥50K copies/mL
- CD4:CD8 ratio: <0.5
- Framingham 10-year CHD risk score: ≥10%

Molina J-M, et al. *JAIDS*. 2016;19(suppl 5):78-79. Abstract THAB0201.

# SMART Study: HIV Viremia Can Contribute to CV Risk

**N=5472 HIV-infected patients with a CD4+ cell count >350mm$^3$**




| Endpoint | Hazard Ratio (95%CI)* | *P* Value |
|---|---|---|
| Death, any cause | 1.8 (1.2-2.9) | 0.007 |
| Major cardiovascular, renal or hepatic disease | 1.7 (1.1-2.5) | 0.009 |
| Fatal or non-fatal CVD | 1.6 (1.0-2.5) | 0.05 |

*Treatment Interruption vs. Continuous Treatment

SMART Study Group. N Eng J Med. 2006;355: 2283-2296.

# Biomarkers of Immune Activation: The SMART Study—CRP, IL-6, D-dimer

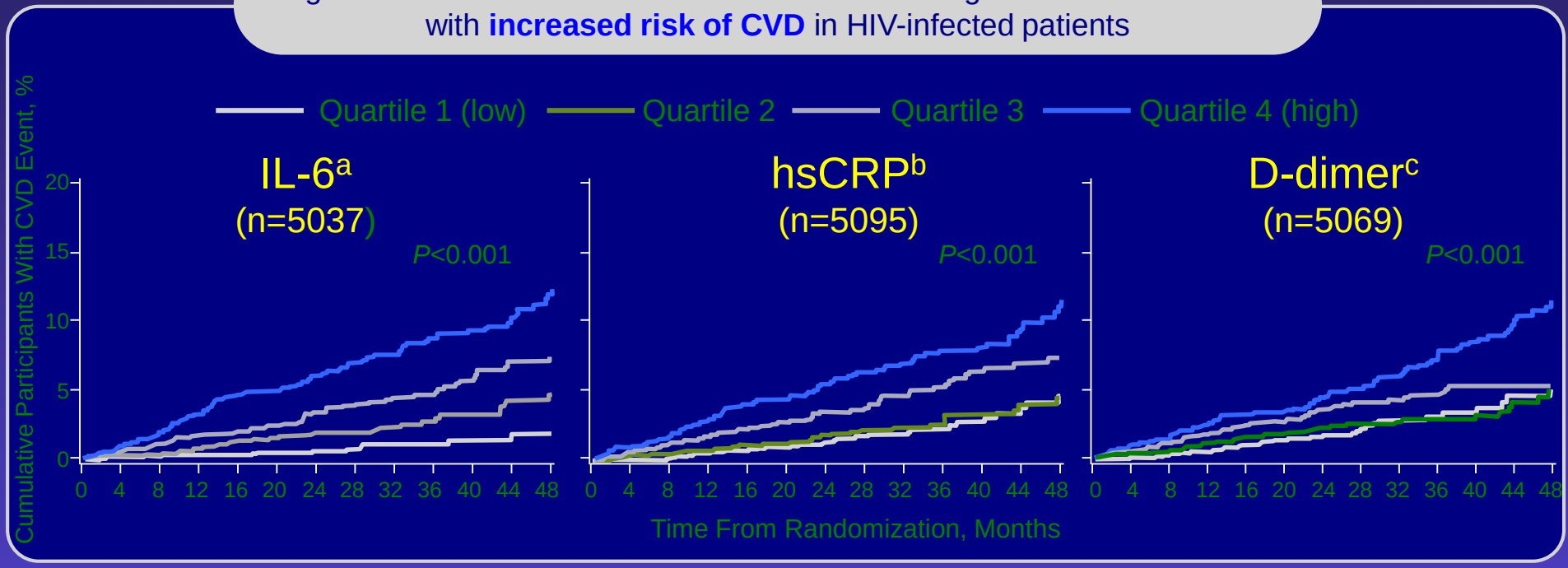
Higher levels of hsCRP, IL-6, and C-dimer were significantly associated with an increased risk of **all-cause mortality**

| | <25th Percentile (Reference) | ≥75th Percentile | |
|---|---|---|---|
| | | OR (95% CI) | *P*-value |
| **hsCRP (µg/mL)** | | | |
| N (cases/controls) | 16/45 | 40/55 | |
| Univariate | 1.0 | **2.0 (1.0-4.1)** | **0.05** |
| **IL-6 (pg/mL)** | | | |
| N (cases/controls) | 8/48 | 40/29 | |
| Univariate | 1.0 | **8.3 (3.3-20.8)** | **<0.0001** |
| **D-dimer (µg/mL)** | | | |
| N (cases/controls) | 8/51 | 37/25 | |
| Univariate | 1.0 | **12.4 (4.2-37.0)** | **<0.0001** |

Kuller LH et al. *PLoS Med*. 2008;5(10):e203.

# Biomarkers of Immune Activation: The SMART Study—CRP, IL-6, D-dimer

High levels of biomarkers for inflammation and coagulation are associated with **increased risk of CVD** in HIV-infected patients




- **Time-to-event methods were used to study associations of the baseline level of IL-6, hsCRP, and D-dimer with a CVD event**

[a] IL-6 quartiles are <1.10, 1.10-1.76, 1.77-3.01, >3.01 pg/mL.
[b] hsCRP quartiles are <0.72, 0.72-1.71, 1.72-4.17, >4.17 µg/mL.
[c] D-dimer quartiles are <0.13, 0.13-0.21, 0.22-0.37, >0.37 µg/mL.

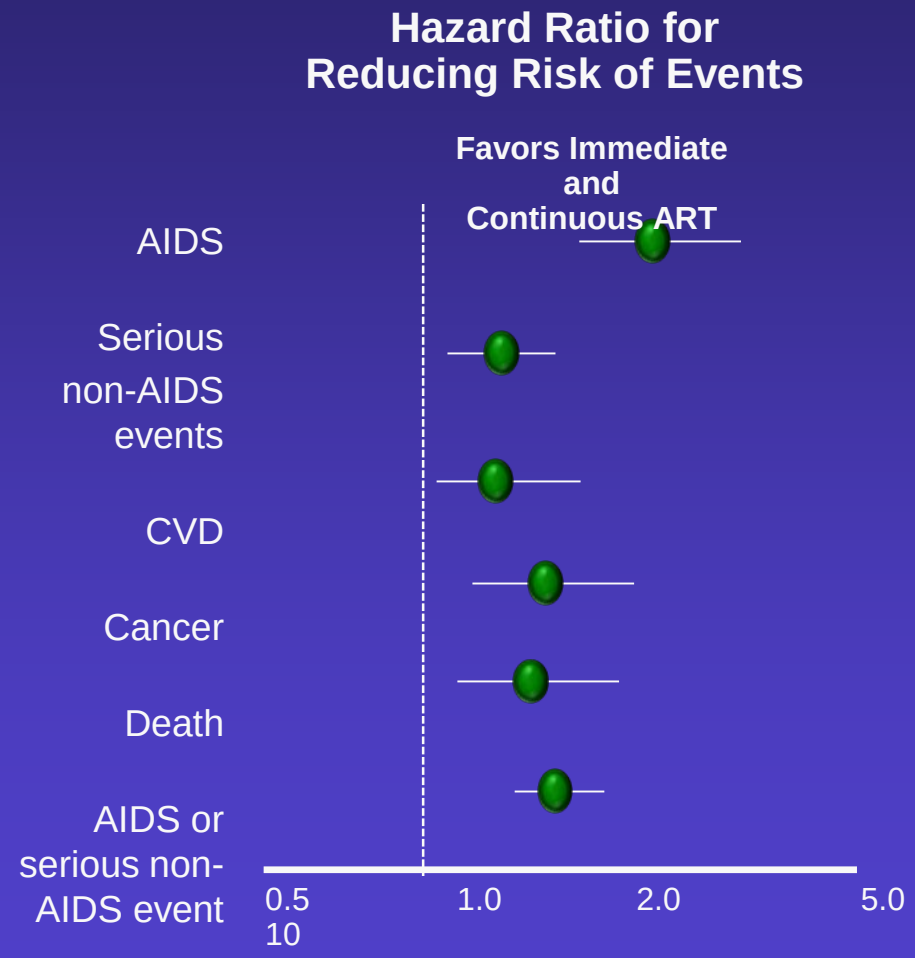
Duprez DA et al. *PLoS One*. 2012;7(9):e44454.

# SMART and START Studies: Benefit of Immediate/Continuous ART on Disease Risk

**Combined analysis of SMART and START studies (n=10,157)**

- **AIDS events (n=123)**
- **Serious non-AIDS events (n=244)**
- **CVD (n=103)**
- **Cancer (n=117)**
- **Death (n=118)**
- **AIDS and serious non-AIDS events (n=359)**
- **Cancer risk reduction did not vary by type of cancer**

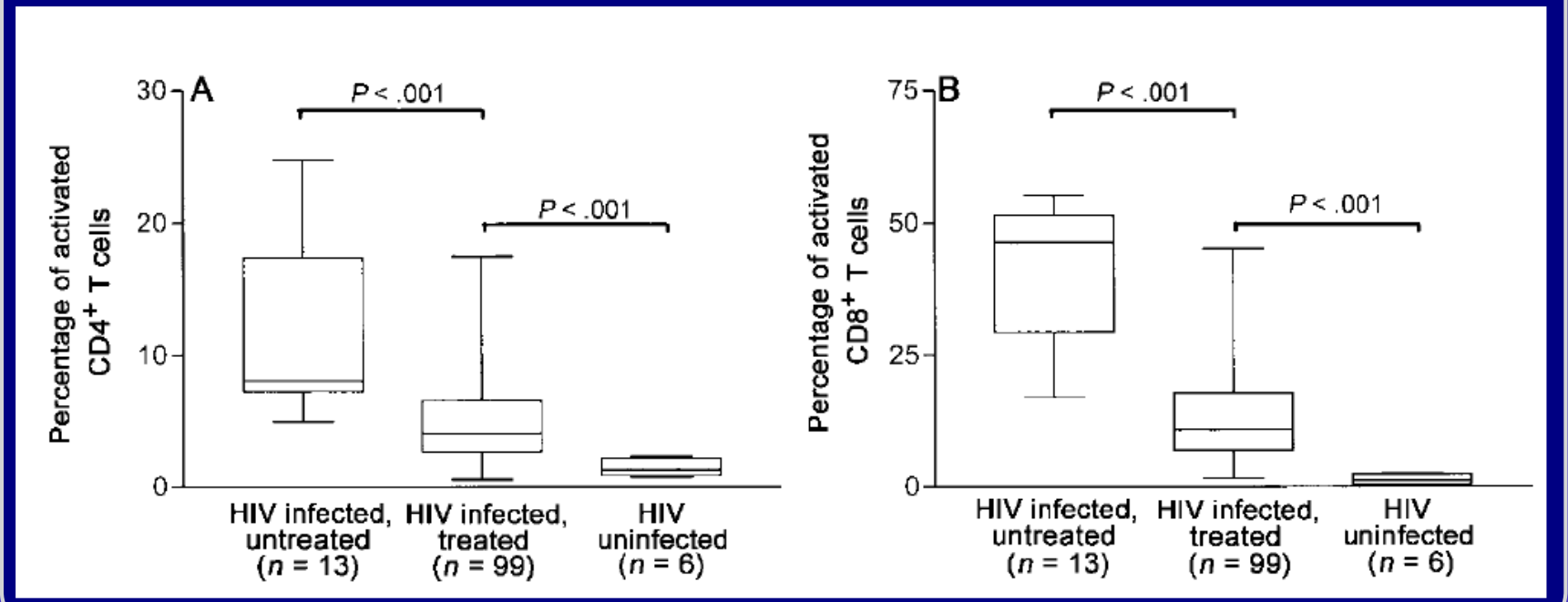
**Immune preservation through immediate and continuous ART significantly reduces the risk of AIDS and non-AIDS events**




Borges AH, et al. 24th CROI. Seattle, 2017. Abstract 474.

# Patients with Sustained ART-Induced Viral Suppression had Lower levels of T-Cell Activation than Untreated Persons but Higher Levels than HIV-Uninfected Cntrols

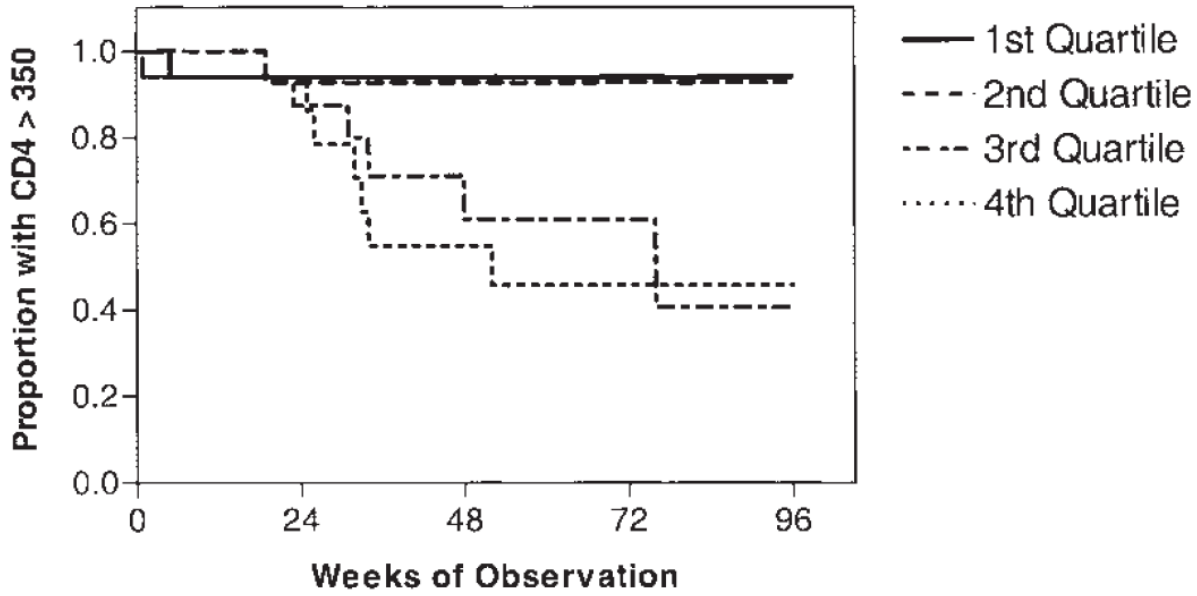
- T-cell activation persists despite viral suppression with ART




Hunt PW et al. *J Infect Dis.* 2003;187(10):1534-1543.

# Immune activation during early infection predicts CD4 cell decline

- **Early immune activation after HIV infection has a strong impact on subsequent disease progression**



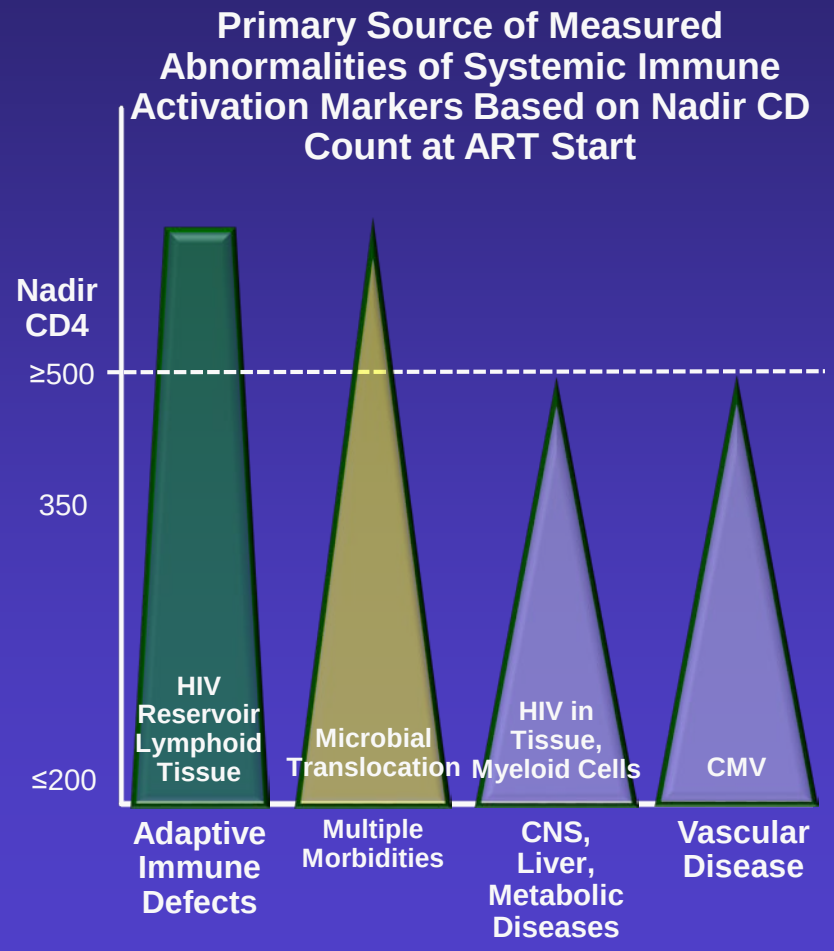

**Time to a CD4+ T-cell count <350 cells/mm$^3$ in 68 recently HIV-infected adults who did not receive antiretroviral therapy immediately after study entry.**

Deeks SG et al. *Blood*. 2004;104(4):942-947.

# Theoretical Model: Impact of Nadir CD4 Count on the Root Drivers of Immune Activation in Treated HIV and Disease Manifestations

- Not all putative root drivers of the inflammatory state in treated HIV infection are likely to be active in those who initiate ART at early disease stages
- Many preferentially drive inflammation in distinct anatomic compartments
- **Primary source of measured abnormalities of systemic immune activation markers:**
  1. Nadir CD4 count at ART start
  2. HIV reservoirs in lymphoid tissues and, potentially, microbial translocation (both do not need significant pre-ART immunodeficiency to be established)
  3. Much greater diversity of sources and anatomic sites likely contributes to any elevations observed in those with very low nadir CD4 count at ART start

**Further research needed**




Hunt PW, et al. *J Infect Dis.* 2016;214(suppl 2):S44-S50.

# Other Contributors of Persistent Immune Activation in Treated HIV Infection

- **Lifestyle factors**
  - **Smoking**
  - **Alcohol/drug abuse**
  - **Obesity**
- **Coinfections**

Hunt PW, et al. *J Infect Dis.* 2016;214(suppl 2):S44-S50.

# AGEhIV Cohort Study: Cigarette Smoking and Immune Activation in Treated HIV Patients

Prospective cohort study (n=1042; 2010-2012)

- **HIV-infected and uninfected** ≥45 years of age
- Male (87%), MSM (72%)
- Smokers
  - Current: 32% (median 15 cigarettes/day per smoker)
  - Former: 37%
- HIV RNA <200 copies/mL in year before enrollment (94%)

Smoking was independently associated with :

- •higher hsCRP levels
- •lower sCD163 levels
- •(borderline significance for higher sCD14 and D-dimer levels
- •No differential effect between HIV-infected and uninfected persons

*Adjusted for age, sex, HCV infection, use of alcohol and recreational drugs, and waist to hip ratio.

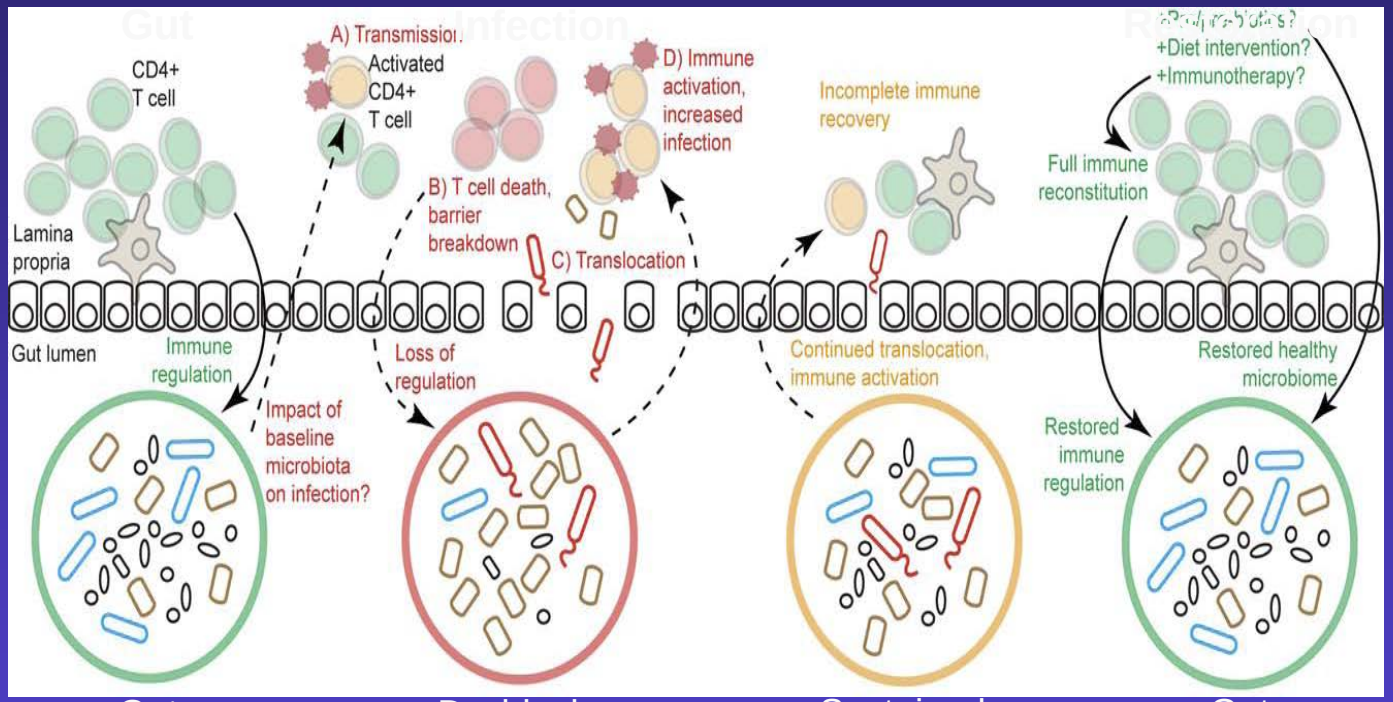
**Smoking and HIV Status: Association With Biomarker Levels in the Highest Quartile (adjusted OR*)**

| | hsCRP | sCD14 | sCD163 | D-Dimer |
|---|---|---|---|---|
| All subjects | | | | |
| Smoking status | | | | |
| (ref. never smoke) | 1.04 | 1.16 | 0.84 | 0.92 |
| Former | 1.57* | 1.34† | 0.62* | 1.36† |
| Current | 1.44* | 2.11‡ | 1.40¶ | 0.64‡ |
| HIV-positive | | | | |
| Current smokers only | 1.49‡ | 1.27† | 0.78† | 1.30† |
| Cigarette smoked per day (per 10) | 1.24 | 2.08* | 1.42 | 0.52¶ |
| HIV-positive | | | | |

*$P$<0.005; †$P$<0.05; ‡$P$≤0.001; ¶$P$<0.01.

Kooij KW, et al. *J Infect Dis.* 2016;214:1817-1821.

# Microbiome During Health and HIV




**Gut Homeostasis**

Homeostasis between immune system and microbiome

**Dysbiosis**

Gut microbes could impact HIV transmission, which leads to CD4 cell death and immune depletion, and loss of immune regulation of gut bacteria (dysbiosis); translocation of dysbiotic bacteria leads to immune activation and further HIV infection of activated CD4 cells

**Sustained Dysbiosis**

ART suppresses viral replication but does not fully restore gut immunity; dysbiosis is sustained during ART and microbial translocation continues to cause chronic immune activation

**Gut Homeostasis**

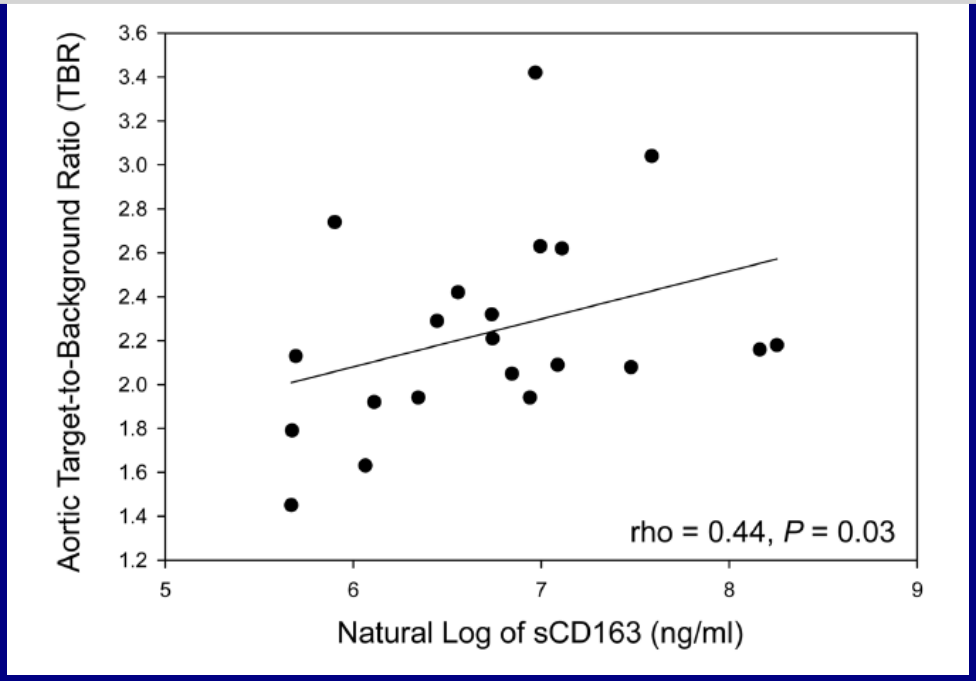
Restoring to a healthy gut may help reconstitute gut immunity and restore immune regulation of the microbiome


Li SX, et al. *Clin Pharmacol Ther.* 2016;99:600-611.
Lynch SV, et al. *N Engl J Med.* 2016;375:2369-2379.

# HIV Is Associated With Increased Arterial Inflammation

- HIV+ individuals had signs of increased arterial inflammation, compared with noninfected controls with similar cardiac risk factors
- Aortic inflammation in HIV+ individuals was associated with the soluble inflammatory marker, sCD163

Arterial inflammation was significantly correlated with sCD163 levels




Subramanian S et al. *JAMA*. 2012;308(4):379-386.

# HIV: Mechanisms of Atherosclerosis/MI

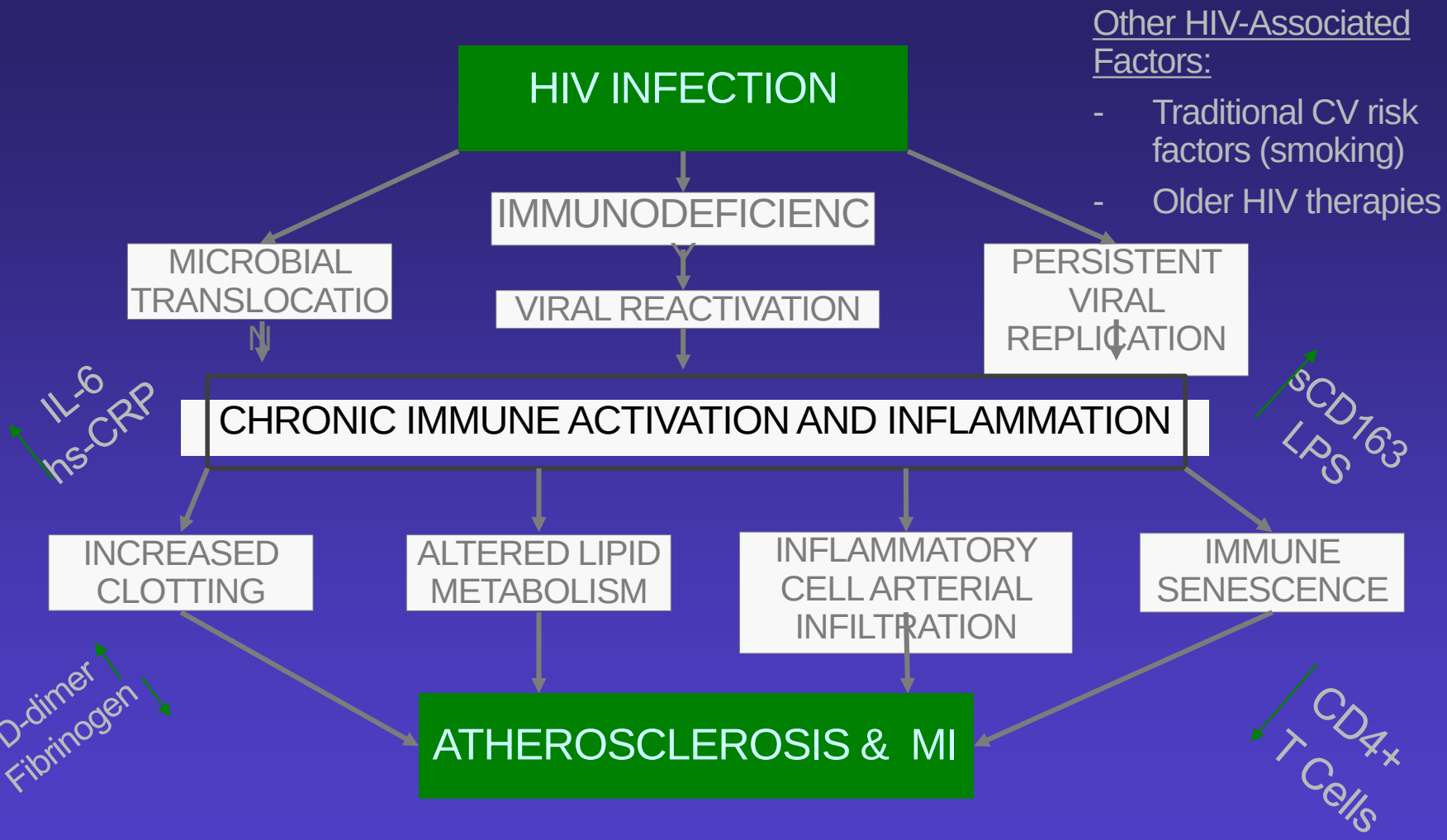



Figure adapted from: Hsue PY, et al. *J infect dis*. 2012;205 Suppl 3:S375-382
Currier JS. *Top HIV Med* 2009;17(3): 98-103.
Post WS, et al. *Ann Intern Med*. 2014;160:458-467.

# HIV and the Risk of Acute Myocardial Infarction

Rates of AMI were significantly higher for HIV-positive vs uninfected veterans across 3 decades of age

| | Age Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Status** | **<30** | **30-39** | **40-49** | **50-59** | **60-69** | **70-79** | **80-89** | **>89** |
| | | | | **Uninfected** | | | | |
| **N** | 1,175 | 6,783 | 21,866 | 19,805 | 4,209 | 1,120 | 148 | 3 |
| **AMI rates per 1000 person-years (95% CI)** | … | 0.3 (0.2-0.6) | 1.5* (1.3-1.7) | 2.2* (1.9-2.5) | 3.3* (2.6-4.2) | 6.7 (4.8-9.2) | 21.5 (12.7-36.4) | … |
| | | | | **Infected** | | | | |
| **N** | 725 | 3,848 | 10,575 | 9,342 | 2,065 | 557 | 56 | 0 |
| **AMI rates per 1000 person-years (95% CI)** | … | 0.7 (0.4-1.2) | 2.0* (1.6-2.4) | 3.9* (3.3-4.5) | 5.0* (3.8-6.7) | 10.0 (6.7-14.7) | 13.5 (4.3-42.0) | … |

***p*<0.05 for HIV-infected vs uninfected veterans.**

Freiberg MS et al. *JAMA Intern Med.* 2013;173(8):614-622.

Annals of Internal Medicine

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# Associations Between HIV Infection and Subclinical Coronary Atherosclerosis

Wendy S. Post, MD, MS; Matthew Budoff, MD; Lawrence Kingsley, PhD; Frank J. Palella Jr., MD; Mallory D. Witt, MD; Xiuhong Li, MS; Richard T. George, MD; Todd T. Brown, MD, PhD; and Lisa P. Jacobson, ScD

**Background:** Coronary artery disease (CAD) has been associated with HIV infection, but data are not consistent.

**Objective:** To determine whether HIV-infected men have more coronary atherosclerosis than uninfected men.

**Design:** Cross-sectional study.

**Setting:** Multicenter AIDS Cohort Study.

**Participants:** HIV-infected ($n = 618$) and uninfected ($n = 383$) men who have sex with men who were aged 40 to 70 years, weighed less than 136 kg (200 lb), and had no history of coronary revascularization.

**Measurements:** Presence and extent of coronary artery calcium (CAC) on noncontrast cardiac computed tomography (CT) and of any plaque; noncalcified, mixed, or calcified plaque; or stenosis on coronary CT angiography.

**Results:** 1001 men had noncontrast CT, of whom 759 had coronary CT angiography. After adjustment for age, race, CT scanning center, and cohort, HIV-infected men had a greater prevalence of CAC (prevalence ratio [PR], 1.21 [95% CI, 1.08 to 1.35]; $P = 0.001$) and any plaque (PR, 1.14 [CI, 1.05 to 1.24]; $P = 0.001$), including noncalcified (PR, 1.28 [CI, 1.13 to 1.45]; $P < 0.001$) and mixed (PR, 1.35 [CI, 1.10 to 1.65]; $P = 0.004$) plaque, than uninfected men. Associations between HIV infection and any plaque or noncalcified plaque remained significant ($P < 0.005$) after CAD risk factor adjustment. HIV-infected men had a greater extent of noncalcified plaque after CAD risk factor adjustment ($P = 0.026$). They also had a greater prevalence of coronary artery stenosis greater than 50% (PR, 1.48 [CI, 1.06 to 2.07]; $P = 0.020$), but not after CAD risk factor adjustment. Longer duration of highly active antiretroviral therapy (PR, 1.09 [CI, 1.02 to 1.17]; $P = 0.007$) and lower nadir $CD4^+$ T-cell count (PR, 0.80 [CI, 0.69 to 0.94]; $P = 0.005$) were associated with coronary stenosis greater than 50%.

**Limitation:** Cross-sectional observational study design and inclusion of only men.

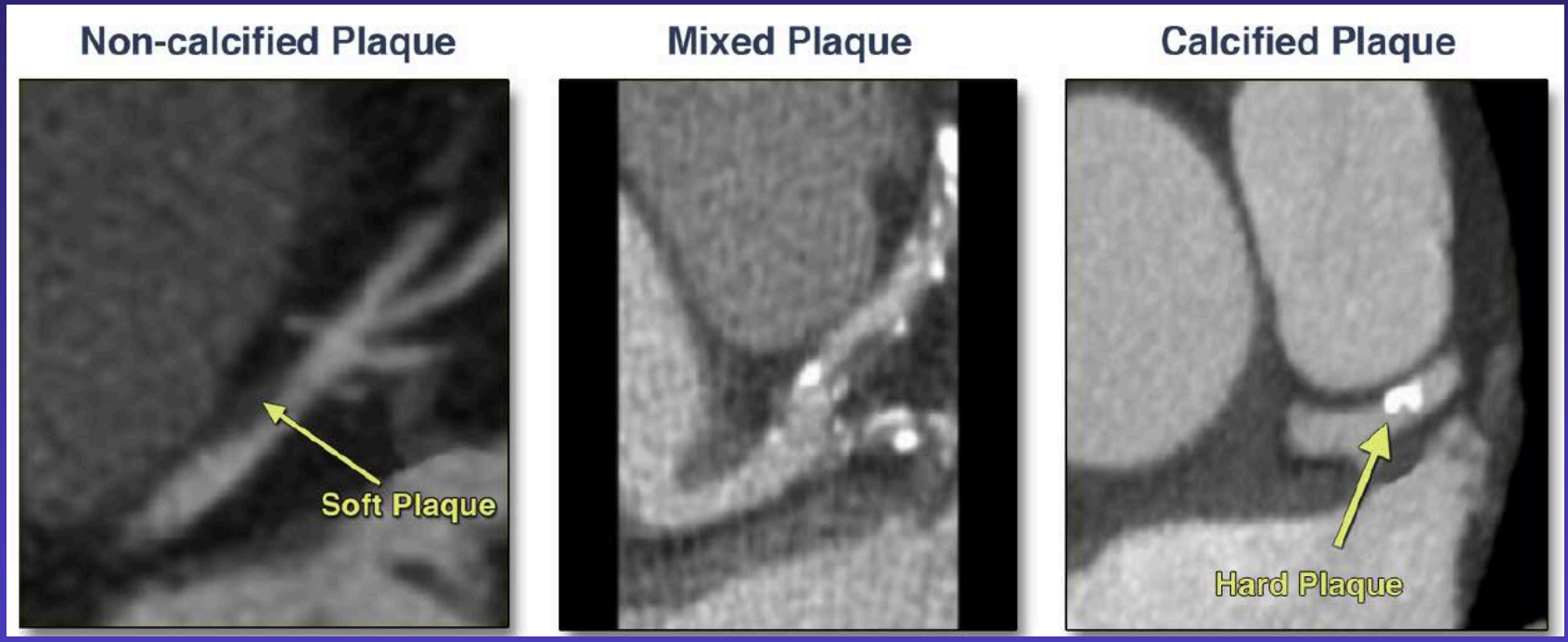
**Conclusion:** Coronary artery plaque, especially noncalcified plaque, is more prevalent and extensive in HIV-infected men, independent of CAD risk factors.

**Primary Funding Source:** National Heart, Lung, and Blood Institute and National Institute of Allergy and Infectious Diseases.

*Ann Intern Med.* 2014;160:458-467. www.annals.org

For author affiliations, see end of text.

# Imaging Atherosclerosis in HIV




759 men: 2/3 HIV+, 1/3 HIV- controls

- **Noncalcified plaque (PR 1.28, CI 1.13-1.45) and coronary calcium (PR** 1.13, CI 1.04-1.23) both significantly more likely for HIV+ patients

Post, W.S., et al. Associations Between HIV Infection and Subclinical Coronary Atherosclerosis. Ann Intern Med 2014; 160(7):458-467.

# Summary/Conclusions

- Non-calcified plaque is more prevalent and extensive in HIV-infected men, suggesting increased risk for cardiovascular events.
- Men with more advanced HIV infection, as demonstrated by low nadir CD4+ T cell count and a greater number of years on HAART have a higher prevalence of clinically significant coronary stenosis > 50%.
- Additional studies are needed to identify how best to prevent progression of atherosclerosis in this unique population and correlation with future events.
- Although coronary CT angiography is not indicated as a screening test in asymptomatic individuals, these results emphasize the importance of assessing and modifying traditional cardiovascular risk factors in this population, especially in men with a history of a low nadir CD4+ T cell count.

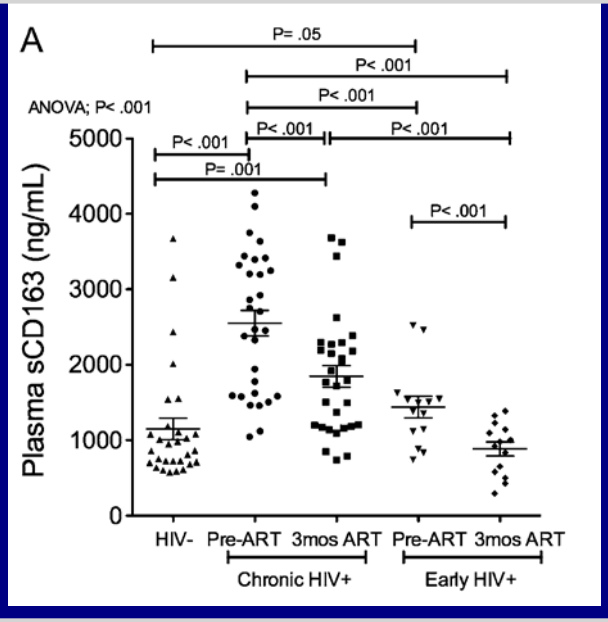
# Biomarkers of Immune Activation: sCD163

- CD163 is a scavenger receptor expressed exclusively on monocytes/macrophages
  - Mediates uptake of hemoglobin-haptoglobin complexes for the removal and metabolism of hemoglobin, a potent oxidant molecule
  - CD163+ macrophages have been identified in atherosclerotic lesions
  - Soluble CD163 (sCD163) levels are increased in association with macrophage proliferation and activation

# Biomarkers of Immune Activation: sCD163

- **sCD163 levels are significantly increased in plasma during chronic and early HIV infection[1]**
  - **sCD163 decrease after receipt of ART, but do not completely "normalize"**

sCD163 levels are increased in chronic and early HIV infection and are decreased after ART[1]




**Elevated sCD163 levels have been associated with noncalcified coronary plaque and neurocognitive impairment in HIV+ persons[2,3]**

1. Burdo TH et al. *J Infect Dis*. 2011;204(1):154-163. 2. Burdo TH et al. *J Infect Dis*. 2011;204(8):1227-1236. 3. Burdo TH et al. *AIDS*. 2013;27(9):1387-1395.

- **sCD14**
  - **Correlates with HIV infection and mortality**
  - **Associated with carotid atherosclerosis in HIV-infected populations**

- **Monocyte chemoattractant protein-1 (MCP-1)**
  - **Associated with HIV infection and carotid atherosclerosis in HIV-infected individuals**
  - **Expression is genetically determined**

Sandler NG et al. *J Infect Dis* 2011; 203: 780-90.
Kelesidis T et al. *J Infect Dis* 2012; 206: 1558-67.
Floris-Moore M et al. *AIDS* 2009; 23: 941-9.
Joven J et al. *Clinica Chimica Acta* 2006; 368: 114-9.

# Elevated Levels of Monocyte Activation Markers, soluble CD14 and CD163, are associated with Subclinical Atherosclerosis in the MACS

**Rebeccah A McKibben, Stephen Grinspoon, Xiuhong Li, Frank Palella, Lawrence A Kingsley, Mallory D Witt, Todd T Brown, Lisa P Jacobson, Matthew Budoff, Wendy S Post**

J Infect Dis. 2015 Apr 15;211(8):1219-28. doi: 10.1093/infdis/jiu594. Epub 2014 Oct 30.
PubMed PMID: 25362192; PubMed Central PMCID: PMC4402336.

# Elevated Levels of Monocyte Activation Markers, soluble CD14 and CD163, are associated with Subclinical Atherosclerosis in the MACS

## Conclusions

- Monocyte activation marker (sCD163, sCD14 and MCP-1) levels were higher among HIV-infected men, and associated with subclinical coronary atherosclerosis.
- Monocyte activation may contribute to the burden of CVD among HIV-infected men despite viral suppression.

J Infect Dis. 2015 Apr 15;211(8):1219-28. doi: 10.1093/infdis/jiu594. Epub 2014 Oct 30.
PubMed PMID: 25362192; PubMed Central PMCID: PMC4402336.

# Developmental Considerations for Reducing Persistent Immune Activation in HIV

| | Potential Investigative Options |
|---|---|
| Biologics | Anti-PD-1 antibodies, anti-IFN-alfa antibodies<br>TNF inhibitors, IL-6 inhibitors |
| Enhance T-cell renewal | Gamma-chain cytokines (IL-2, IL-7, IL-15), growth hormone |
| Microbial translocation | Rifaximin, sevelamer, prebiotics/probiotics, colostrum |
| Chemokine receptor inhibitor | Maraviroc, cenicriviroc |
| Anti-fibrotic agents | Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, keratinocyte growth factor, pirfenidone |
| Anti-coagulants | Low-dose warfarin, dabigatran, aspirin, clopidogrel |
| Anti-infective therapy | CMV, HCV/HBV, HSV, EBV |
| Anti-inflammatory agents | Chloroquine, hydroxychloroquine<br>NSAIDs (aspirin, mesalamine, COX-2 inhibitors)<br>**Statins**<br>Minocycline<br>Methotrexate<br>Thalidomide, lenalidomide, pentoxifylline |
| Anti-aging | Sirolimus, caloric restriction, omega-3 fatty acids, diet, exercise |

Douek DC. *Top Antivir Med*. 2013;21:128-132.

# Impact of Aspirin and Statin Use on Inflammation and Immune Activation

## ACTG A5331

- Prospective, double-blind study, healthy HIV adults on suppressive ART (n=113)
  - Aspirin 100 or 300 mg/day or placebo for 12 weeks
  - Primary outcome: change in sCD14
- Aspirin had no impact on immune activation or endothelial function

## Statin use and liver

- Dose-dependent reduction in hepatic fibrosis progression in HCV monoinfected patients
- Significant protective effect against development of cirrhosis in less severe liver disease (ALT <40 IU/L) in HIV/HCV coinfection
- Reduced hepatosteatosis in HIV patients with NAFLD

## Statin use and renal function

- SATURN-HIV
  - Prospective, double-blind study, healthy HIV adults on suppressive ART with normal lipid levels
  - Rosuvastatin for 24 weeks reduced plasma cystatin C and slowed kidney function decline


O'Brian MK, et al. 23rd CROI. Boston, 2016. Abstract 44LB.
Simon T, et al. *Hepatology*. 2016;64:47-57..
Oliver N, et al. *AIDS*. 2016;30:2469-2476..
Lo J, et al. 23rd CROI. Boston, 2016. Abstract 553.
Longenecker CT, et al. *Clin Infect Dis.* 2014;59:1148-1156.

# Modulating Immune Activation With Statins SATURN Trial (cont'd)

- 24 weeks of rosuvastatin treatment significantly reduced levels of a vascular-specific inflammatory enzyme, Lp-$PLA_2$
  - Lp-$PLA_2$ is a predictive marker for primary and recurrent CV events in the general population

| Marker | Statin, Percentage Change (n=72) | Placebo, Percentage Change (n=75) | *P* |
|---|---|---|---|
| Lp-$PLA_2$ level | −9.9 (−20.1 to −1.0) | −1.9 (−8.6 to 13.3) | <.01 |
| LDL cholesterol level | −28 (−43 to −16) | 3.8 (−0.7 to 17.2) | <.01 |

- Conclusions: 48 weeks of rosuvastatin treatment reduced significantly several markers of inflammation and lymphocyte and monocyte activation in ART-treated subjects. Whether these favorable changes translate to a clinical benefit remains to be elucidated.

Eckard AR et al. *J Infect Dis.* 2014;209(8):1156-1164.

# Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

## Conclusions

- Inflammation is bad:
- Many types of immune activation are bad
- HIV-infected persons have more of both compared to HIV-uninfected persons, even when they are virally suppressed with cART
- It is important to isolate the effects of these from other traditional risk factors and HIV itself
- Chronic inflammation and immune activation are contributors to the risk of morbidity and mortality in HIV-infected individuals

# Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

## Conclusions (cont'd)

- Paradigm shift: need to go beyond CD4 count, viral load, and AIDS-defining conditions to guide clinical care and research
- Risk assessment for important non-infectious comorbidities that are likely driven by excess inflammation and immune activation (eg cardiovascular disease) should be a part of routine HIV care
- Should screening for CVD risk among HIV-infected persons include selected biomarker assessment? If so, which ones?

# Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

## Conclusions

- Should interventions aimed at reducing morbidity and mortality risk in HIV target inflammation and immune activation? We already know that ASA, statins work in the general population to reduce CVD events.
- If yes to above, how do we know that interventions aimed at reducing biomarker levels will also reduce CVD clinical events?
  - One currently-enrolling NIH-funded study seeking to answer someof these questions: REPRIEVE