

HIV Management
Hepatitis Management

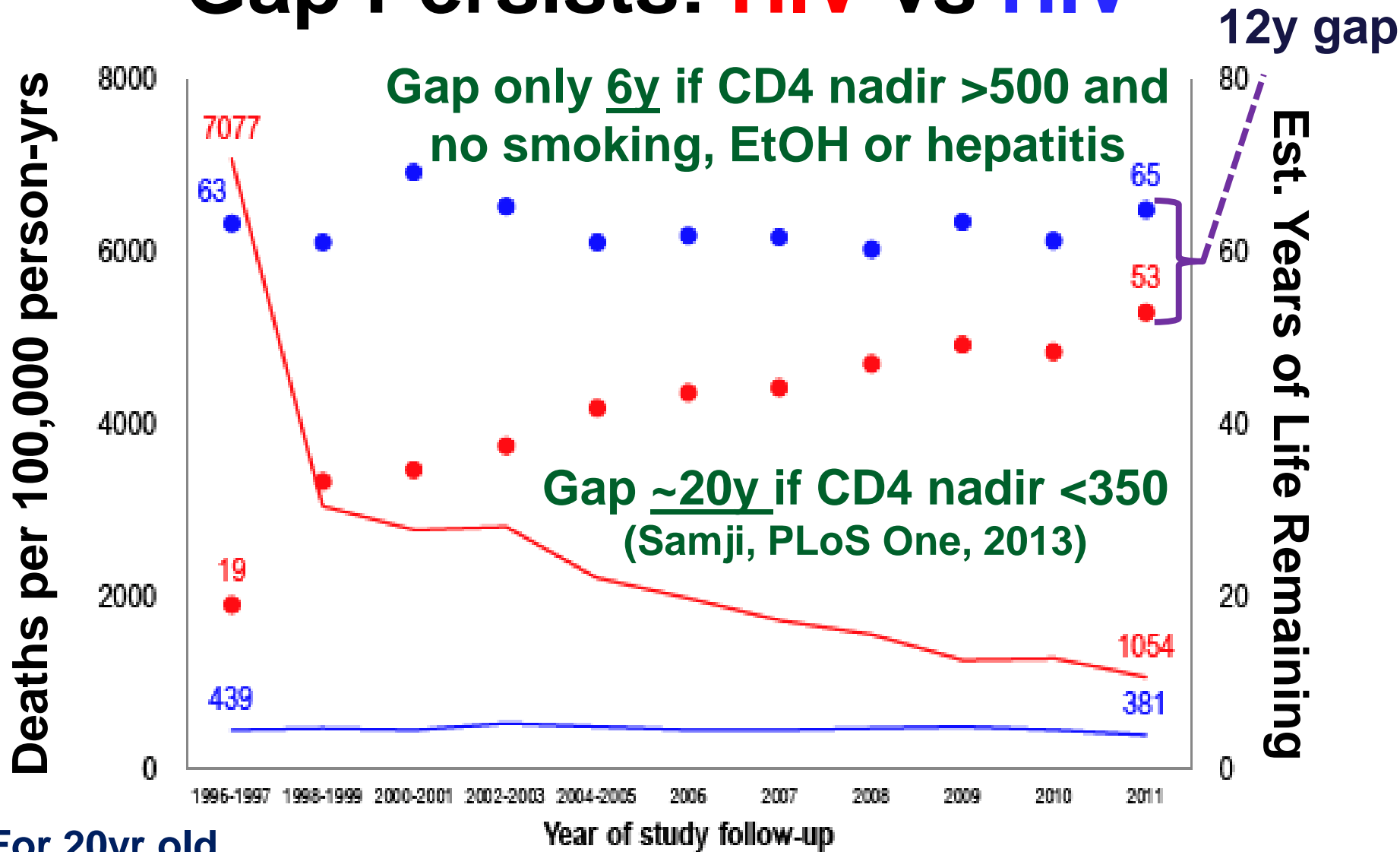
THE NEW YORK COURSE

Immune-based Therapies

Peter W. Hunt, MD

Associate Professor of Medicine
Interim Chief, Division of Experimental Medicine
University of California San Francisco

Improving Life Expectancy*, but Gap Persists: **HIV** vs **HIV-**



*For 20yr old

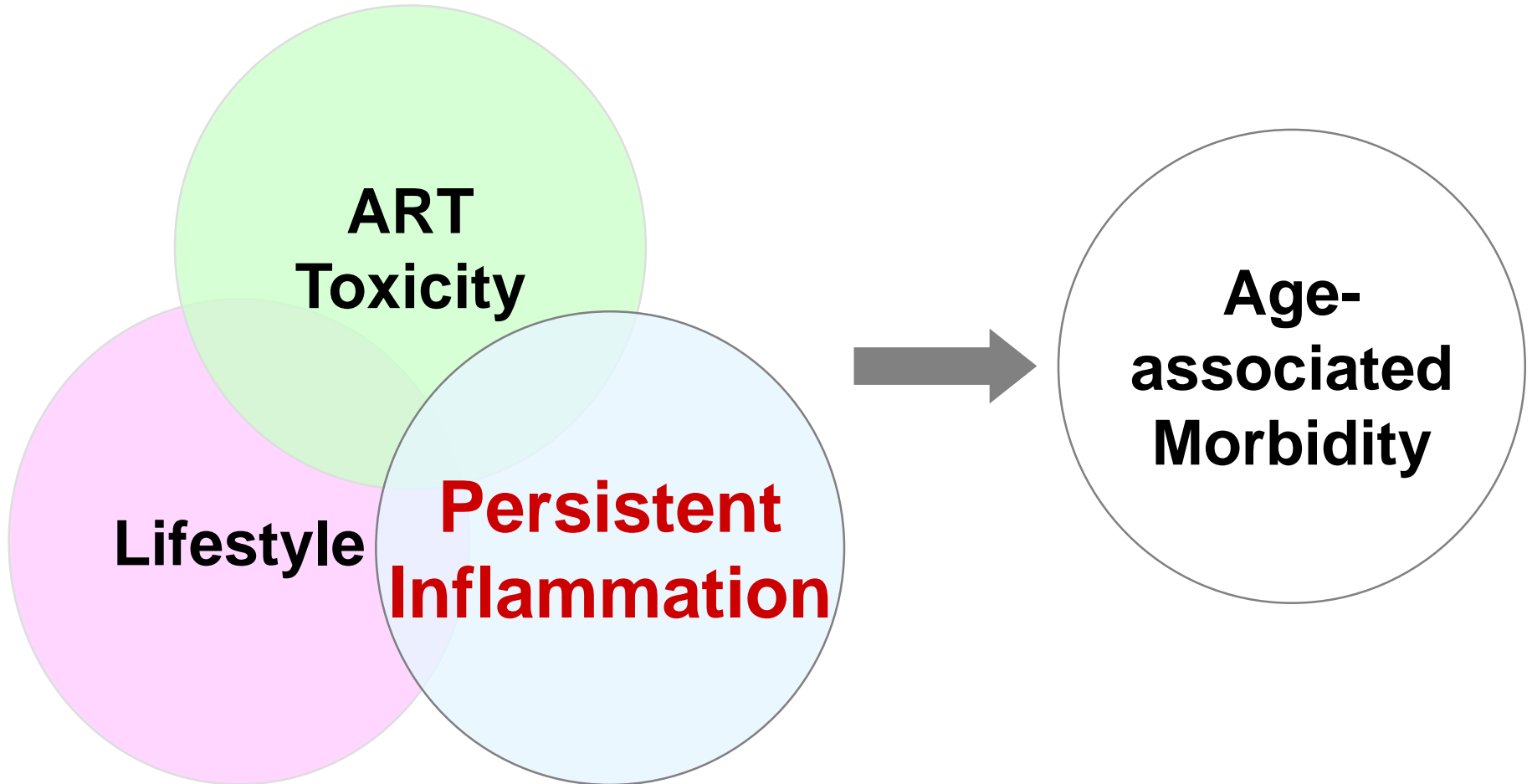
Marcus JAIDS, 2016 (see also: Legarth/Obel, JAIDS, 2016; Samji for NA-ACCORD, PLoS One, 2013)

Many age-associated morbidities also increased in treated HIV

- **Cardiovascular disease** [1-3]
- **Cancer (non-AIDS)** [4]
- **Bone fractures / osteoporosis** [5,6]
- **COPD** [12]
- **Liver disease** [7]
- **Kidney disease** [8]
- **Cognitive decline** [9]
- **Non-AIDS infections** [10]
- **Macular Degeneration**[13]
- **Frailty** [11]

1. Freiberg, M., et al. JAMA Int Med. 2013;173(8):614-22. 2; Tseng, Z, et al. JACC. 2012;59(21):1891-6. 3. Grinspoon SK, et al. Circulation. 2008;118:198-210. 4. Silverberg, M., et al. AIDS, 2009;23(17):2337-45. 5. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504. 6. Arnsten JH, et al. AIDS. 2007 ;21:617-623. 7. Odden MC, et al. Arch Intern Med. 2007;167:2213-2219. 8. Choi A, et al. AIDS, 2009;23(16):2143-49. 9. McCutchan JA, et a. AIDS. 2007 ;21:1109-1117. 10. Sogaard, CID, 2008; 47(10): 1345-53. 11. Desquilbet L, et al. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286; ¹² Attia, Chest,2014; ¹³ Jabs, Am J Ophthal, 2015

Potential Role of Inflammation in Driving Morbidity in Older HIV+ Individuals



Inflammation Predicts Disease in Treated HIV Infection

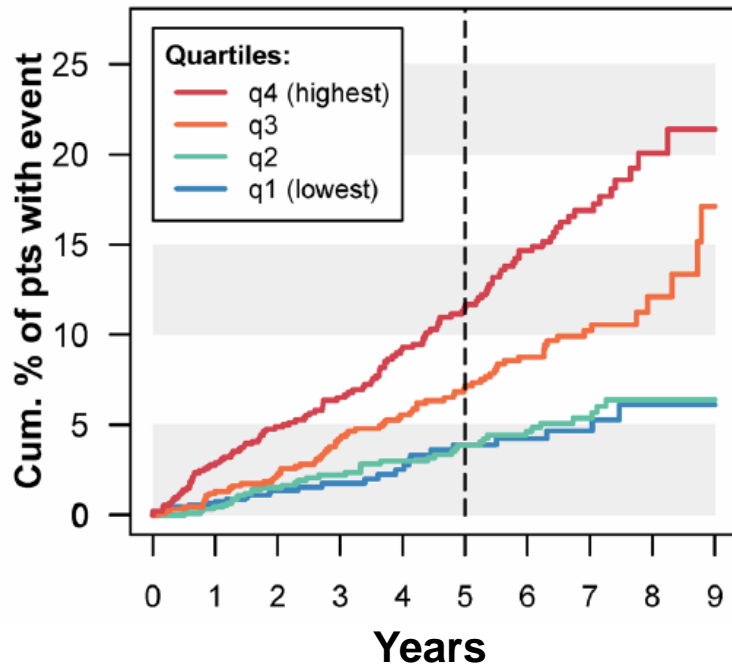
- **Mortality** (Kuller, PLoS Med, '08; Tien, JAIDS, '10; Tenorio, JID '14; Hunt, JID '14)
- **Cardiovascular Disease** (Duprez, Atherosclerosis, 2009)
- **Cancer** (Breen, Cancer Epi Bio Prev, 2010; Borges, AIDS, 2013)
- **Venous thromboembolism** (Musselwhite, AIDS, 2011)
- **Type II diabetes** (Brown, Diabetes Care, 2010)
- **COPD** (Attia, Chest, 2014)
- **Renal disease** (Gupta, HIV Med, 2015)
- **Bacterial pneumonia** (Bjerk, PLoS One, 2014)
- **Cognitive dysfunction** (Burdo, AIDS, 2013; Letendre CROI 2012)
- **Depression** (Martinez, JAIDS, 2014)
- **Frailty** (Erlandson, JID, 2013; Piggott, CROI 2017, #133)

Inflammation Strongly and Durably Predicts Morbidity / Mortality in Treated HIV Infection (IL-6 + D-dimer Score)

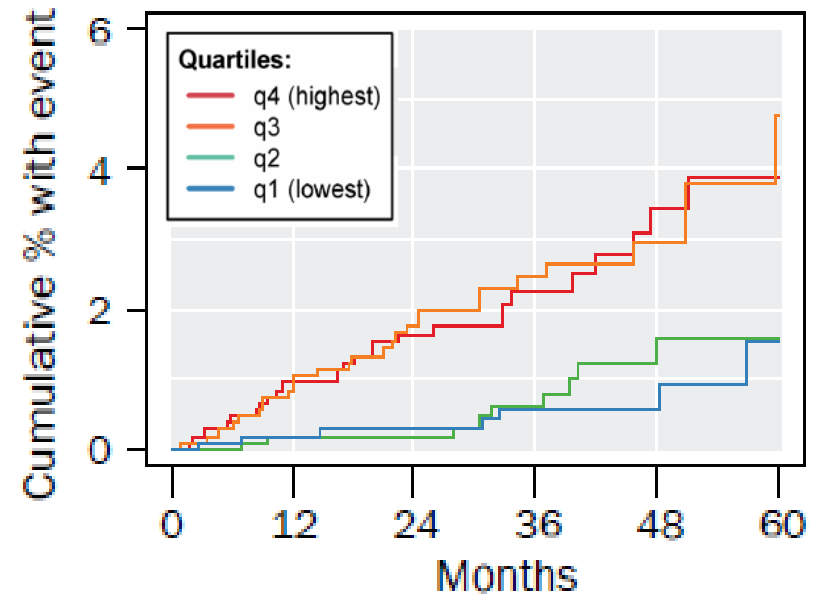
Even in those starting ART early...

SMART / ESPRIT / SILCAAT
(Median Current CD4: 500; Nadir: 181)

START
(CD4 >500)



HR: 1.64 per 2-fold increase



HR: 1.61 per 2-fold increase

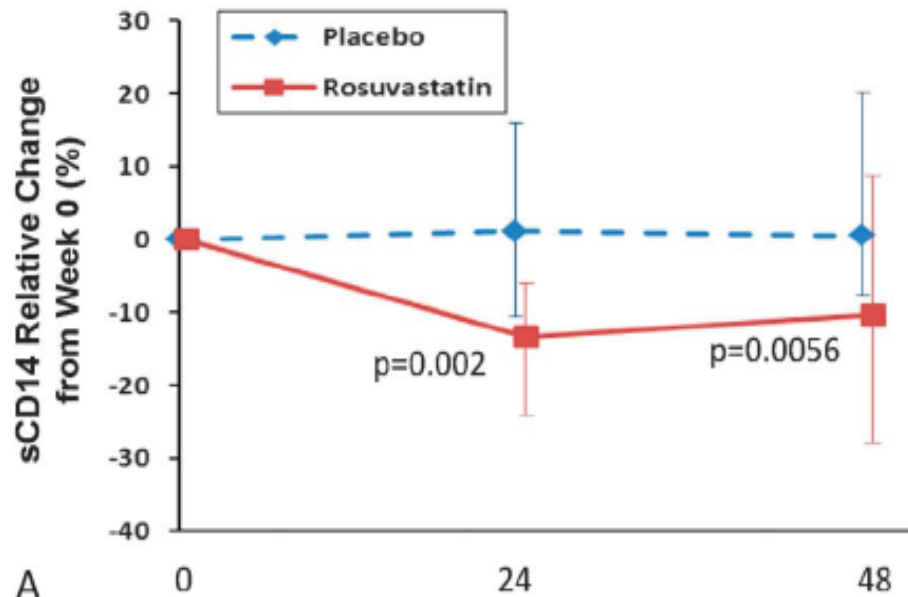
Strategy for Interventional Trials

- Low-hanging fruit
 - Commonly used meds with antiinflammatory properties
 - Test in pilot studies with immunologic endpoints
 - Advance scalable “winners” to clinical endpoint trials

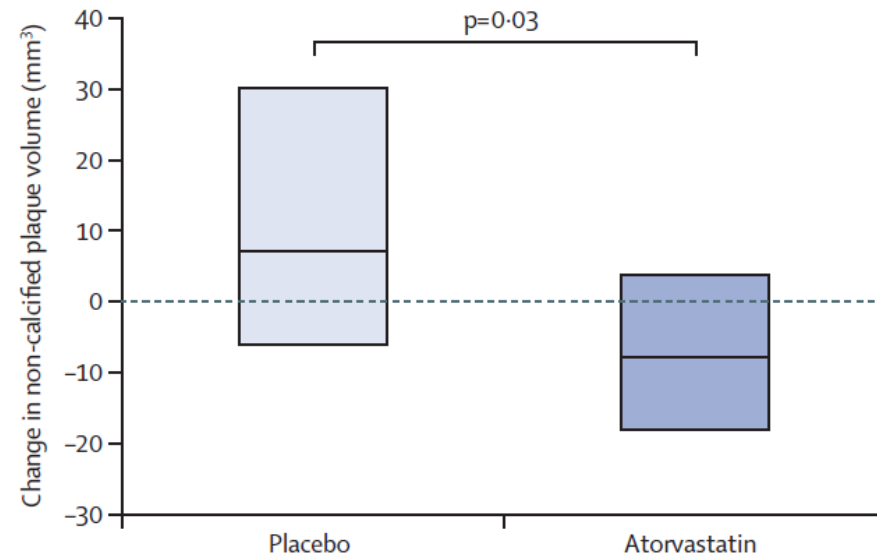


Statins Decrease Immune Activation and Aortic Plaque in Treated HIV Infection

sCD14 Declines with Rosuvastatin



Plaque Regression with Atorvastatin



Funderburg/McComsey, JAIDS, 2015

Lo/Grinspoon, Lancet HIV, 2015

(See also: Nakanjako, Trop Med Int Health, 2014)

Not all statin studies positive (A5275): target populations or dose?



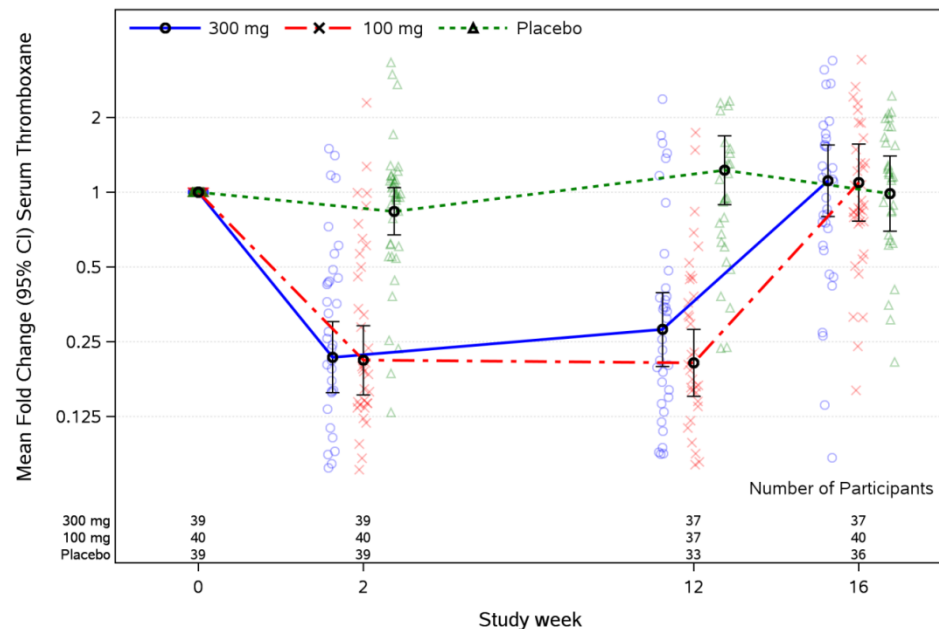
REPRIEVE

- Potential to change clinical guidelines
- Does decreasing immune activation reduce morbidity / mortality?
 - Cardiovascular endpoints
 - Noncardiovascular: infections, cancer, etc.
- Which biomarker reductions correlate with reduced disease risk?
 - Essential for defining true surrogate markers

Aspirin Fails to Reduce Immune Activation or Improve Vascular Function (A5331)

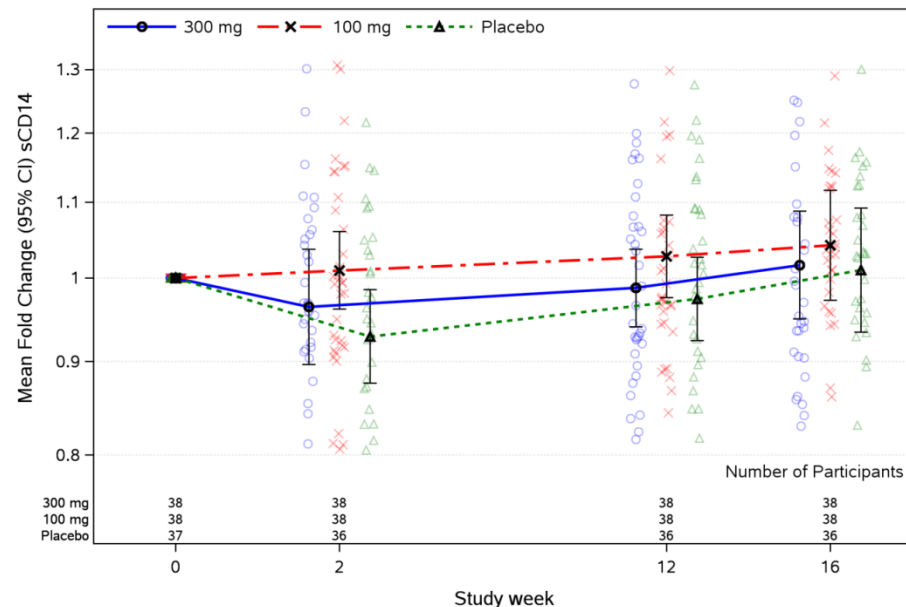
Serum thromboxane (cyclooxygenase inhibition)

Overall



sCD14

Overall



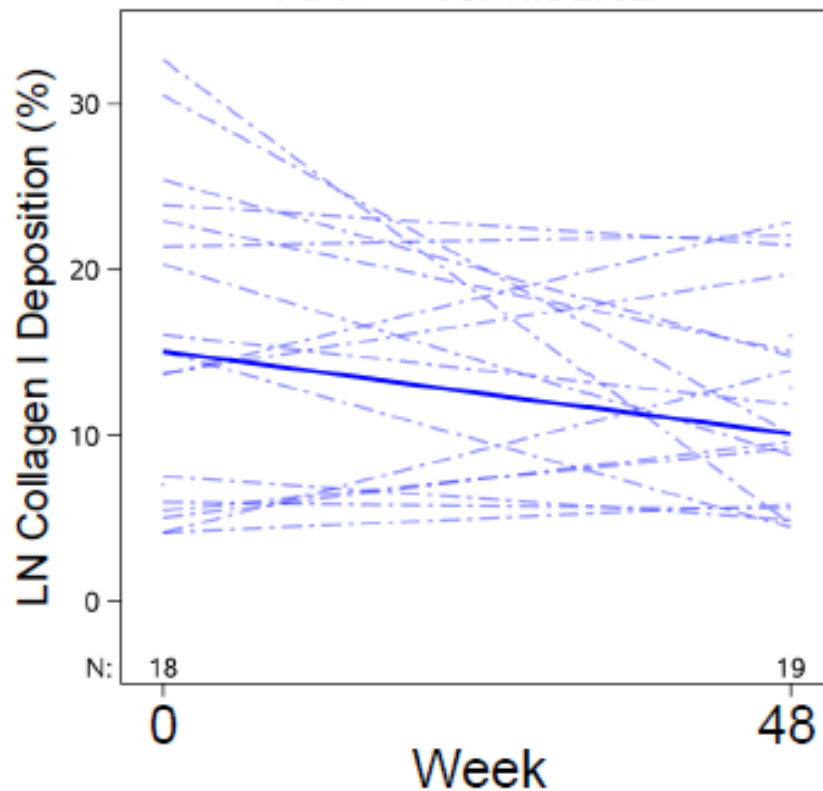
Placebo

100 mg ASA

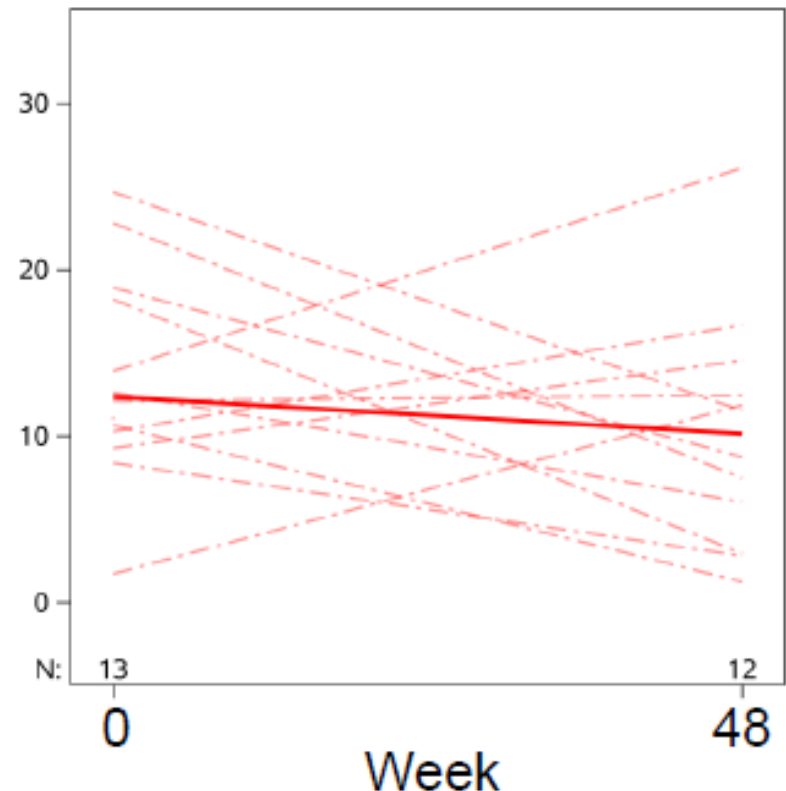
300 mg ASA

Telmisartan (Angiotensin Receptor Blocker) Fails to Improve Lymphoid Fibrosis in Treated HIV (A5317)

Telmisartan + ART



ART Alone



**Analysis of other systemic markers ongoing*

Utay, CROI 2017, Abstract 251

“Probe” Studies of Immune-based Therapeutics

Immune Activation As a Tree

Leaves

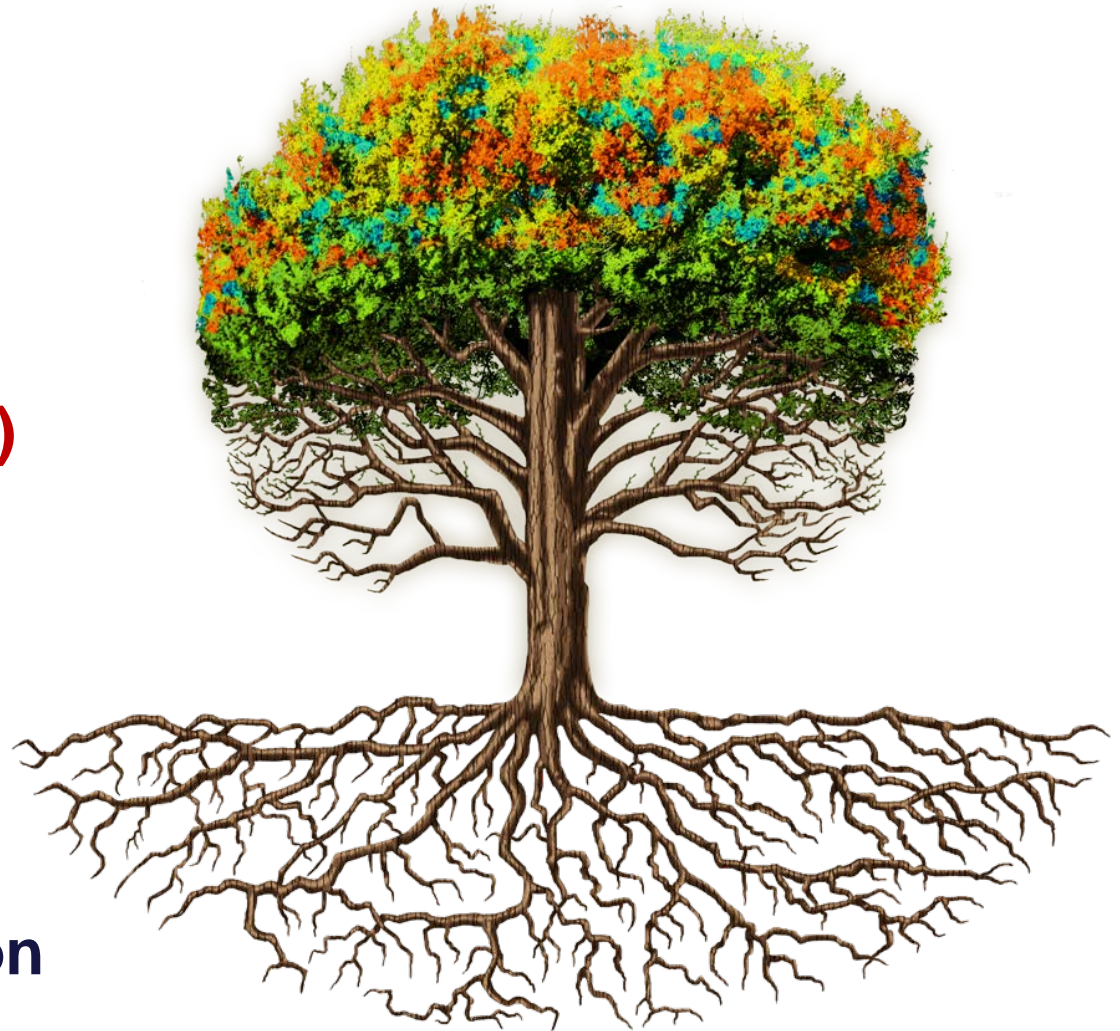
End-organ diseases

Branches

IL-6 (Inflammation)
D-dimer (Coagulation)
Lymphoid Fibrosis

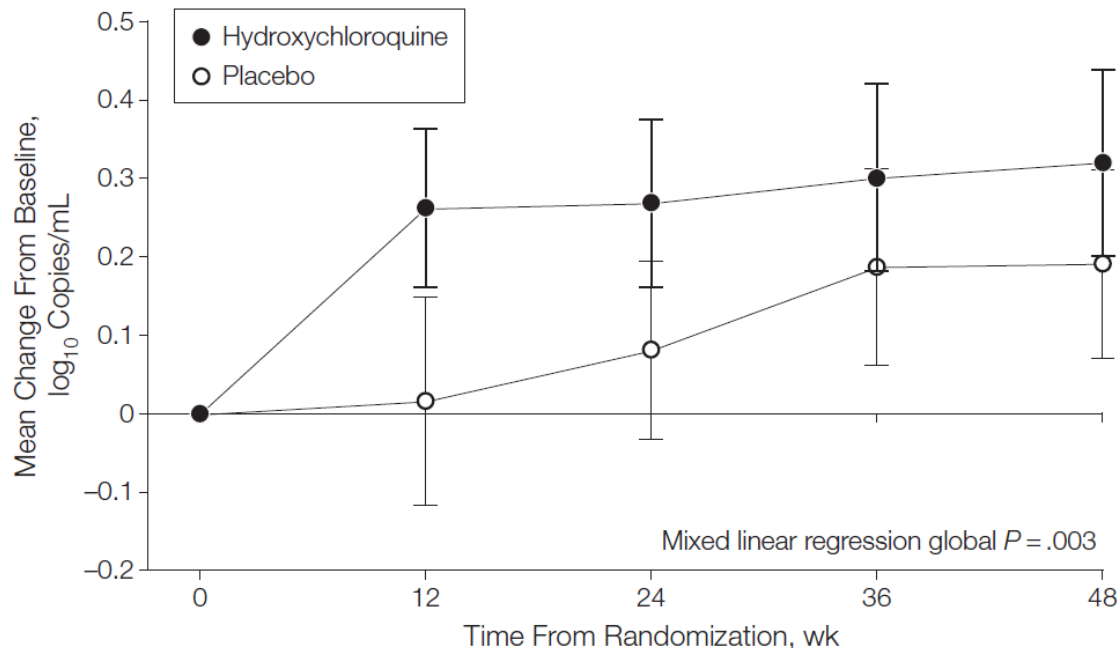
Roots

HIV reservoirs
CMV
Microbial translocation



Targeting Roots and Branches: The Whack-a-Mole Problem

Hydroxychloroquine \uparrow VL in untreated HIV



Paton, JAMA, 2012 (see also Jacobson ARHR, 2016)

Can we find the tree trunk?

Branches

IL-6

D-dimer

Lymphoid Fibrosis

Trunk

Jak/Stat: Ruxolitinib (A5336)

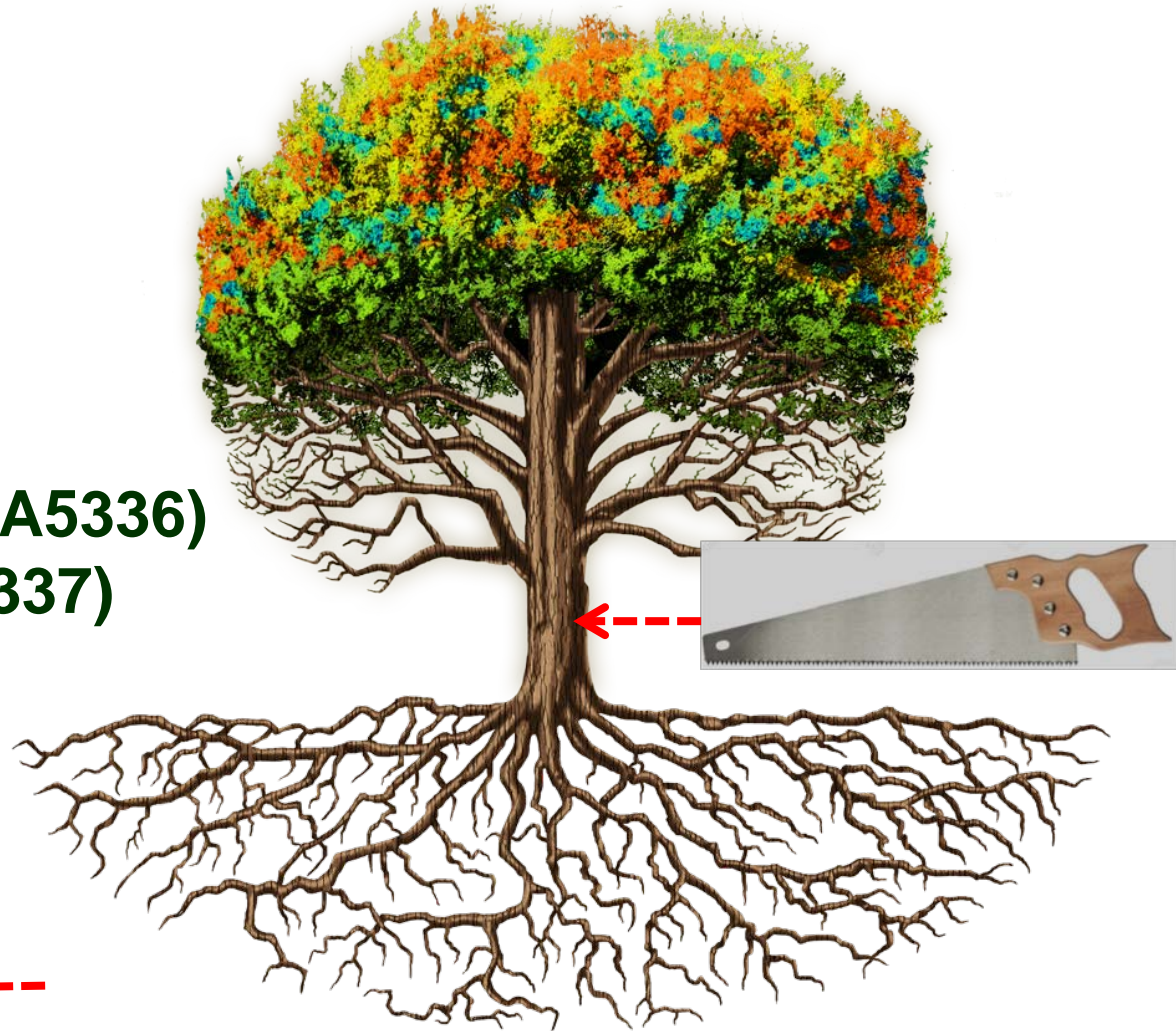
mTOR: Sirolimus (A5337)

Roots

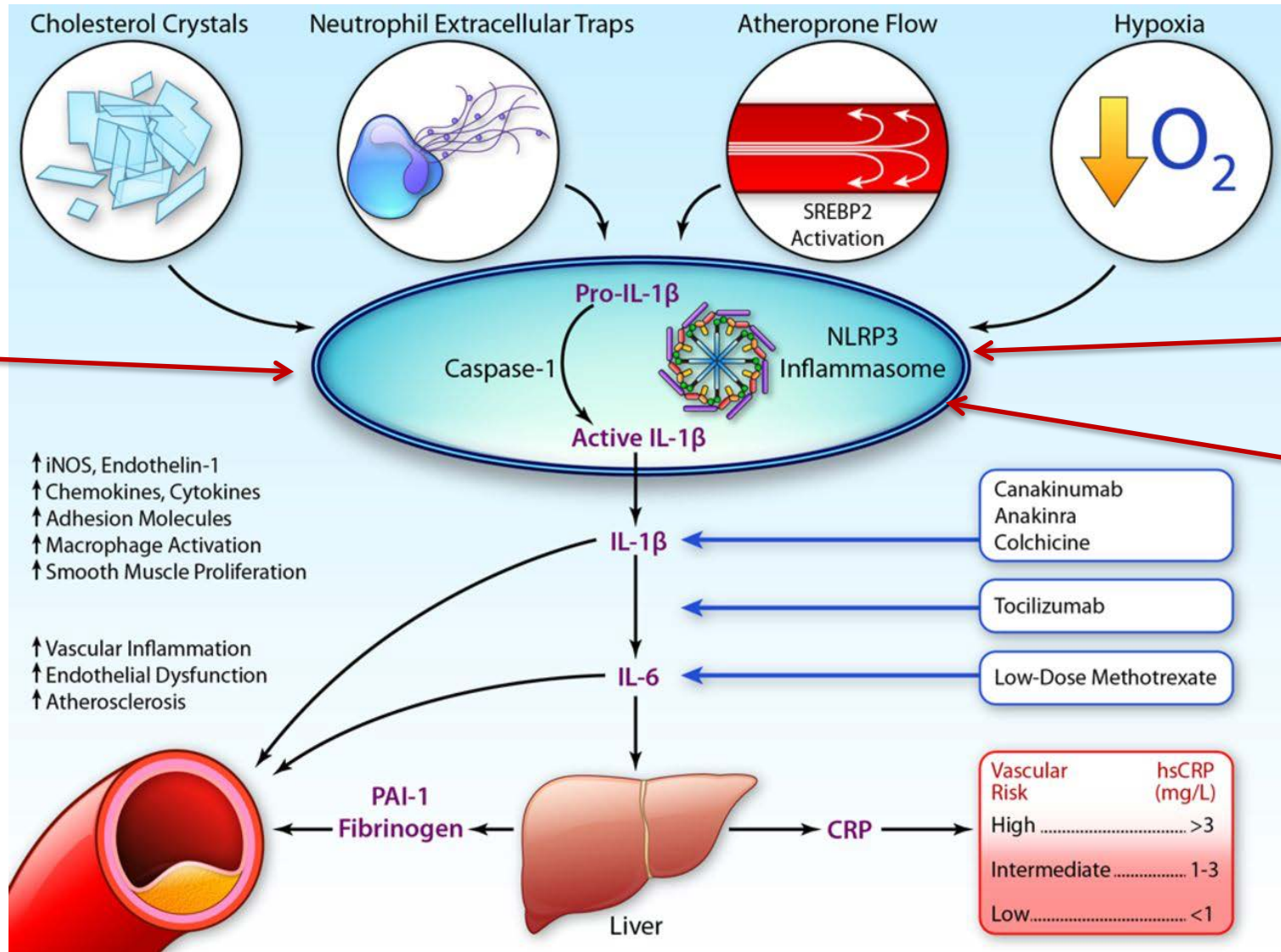
HIV reservoirs

CMV (A5351s) ←-----

Microbial translocation



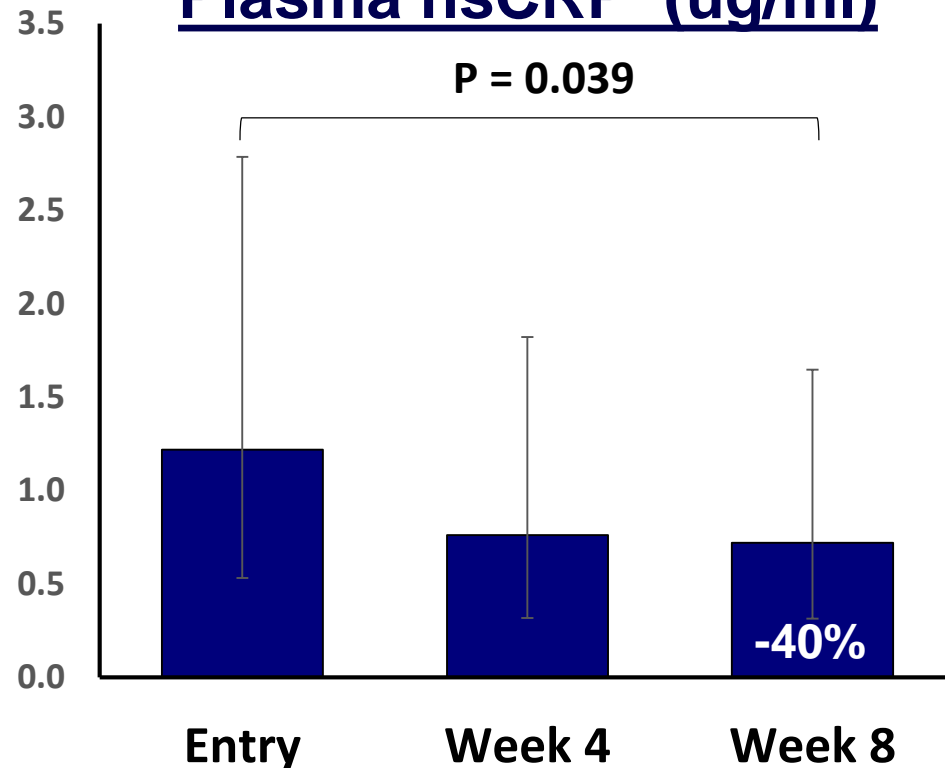
Targeting the Tree Trunk: IL-1 β



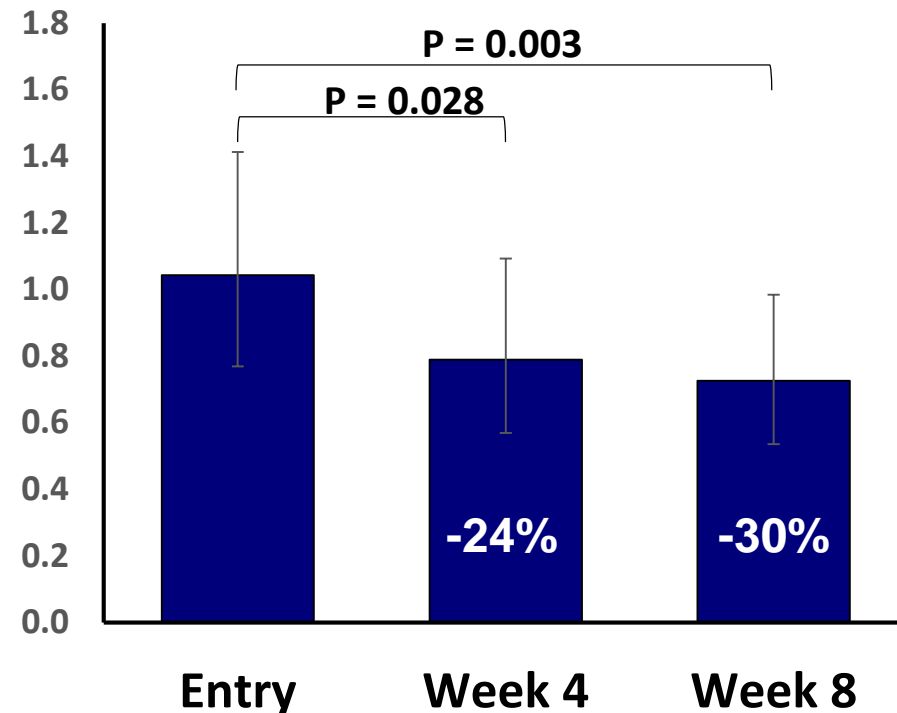
IL-1b Inhibition with Canakinumab* Appears to Reduce Inflammation in Treated HIV

(N = 10, Uncontrolled Pilot Study)

Plasma hsCRP (ug/ml)



Plasma IL-6 (pg/ml)



*Single subcutaneous dose of 150mg

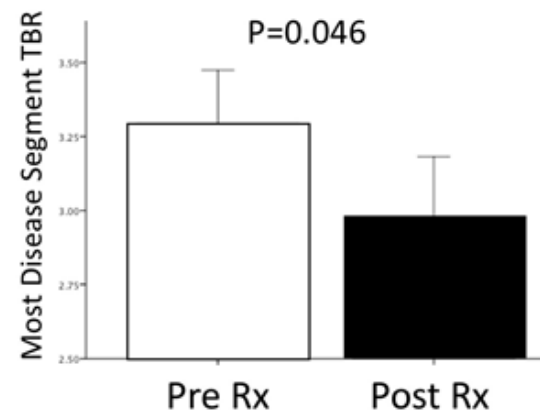
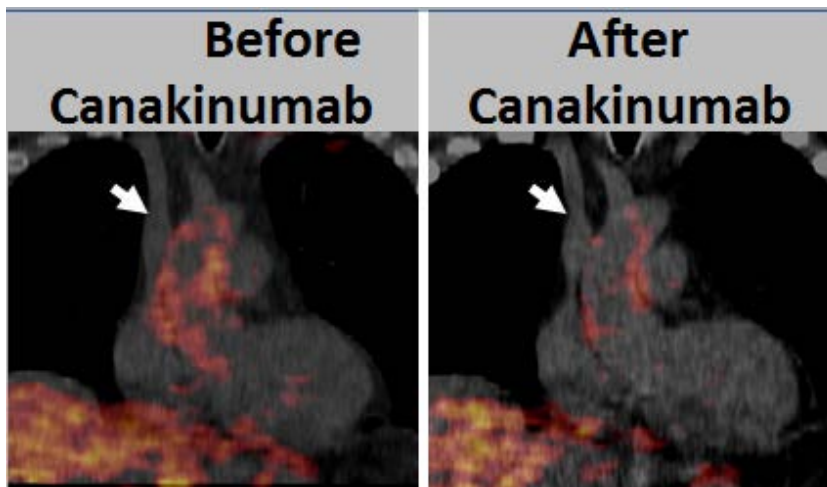
A 30% ↓ in IL-6 associated with a 25% ↓ odds of Non-AIDS event (Tenorio, JID 2014)

Hsue, CROI 2017, Abstract 126

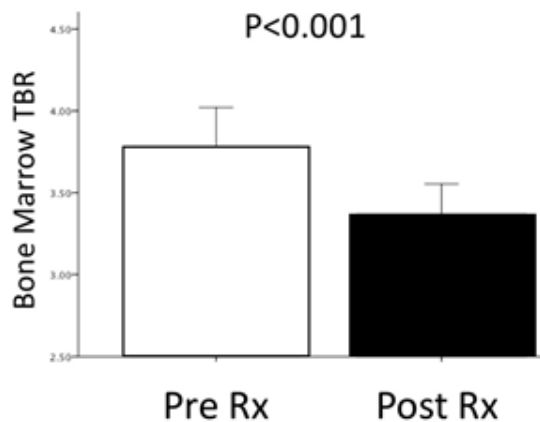
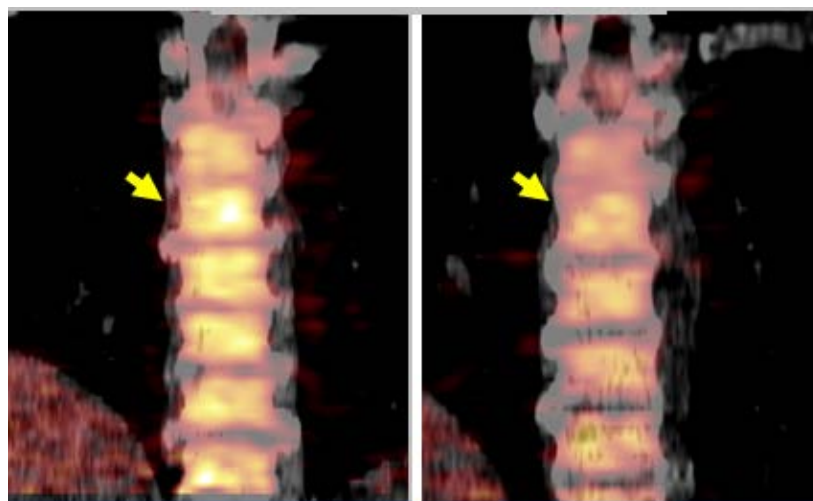
IL-1b Inhibition Also Appears to Decrease Aortic Inflammation (by FDG/PET)

(N = 10, Uncontrolled Pilot Study)

Aortic Inflammation



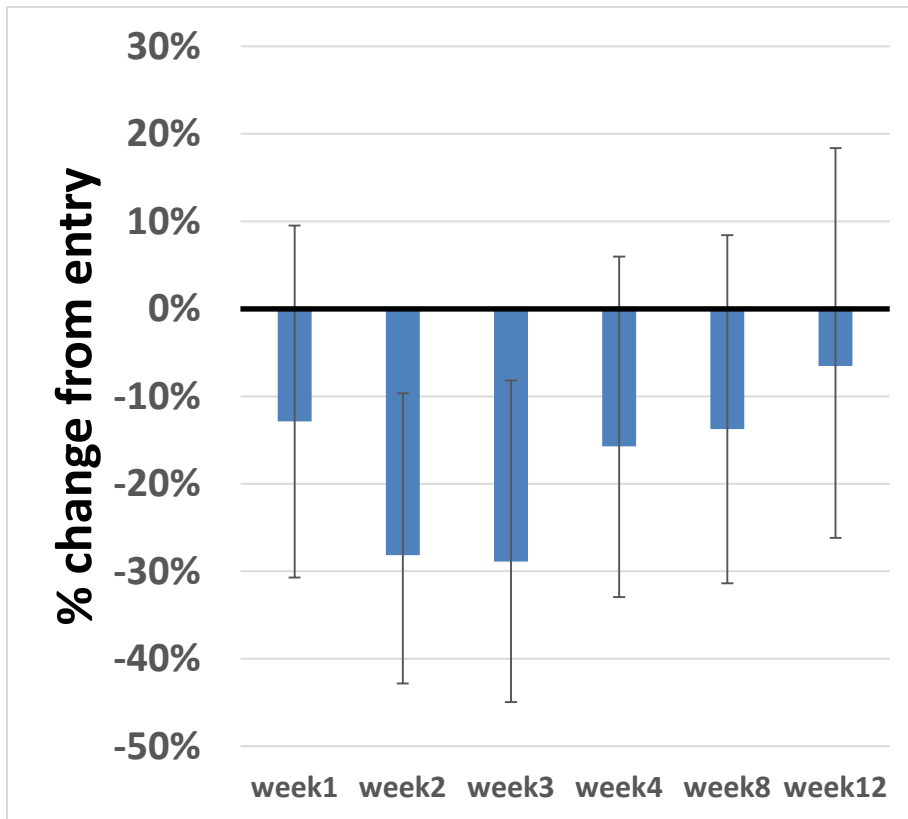
Bone Marrow Activity



IL-1b Inhibition Transiently ↓ Neutrophil Cts

Long-term Safety Needs to Be Established

% Change in Neutrophil Count



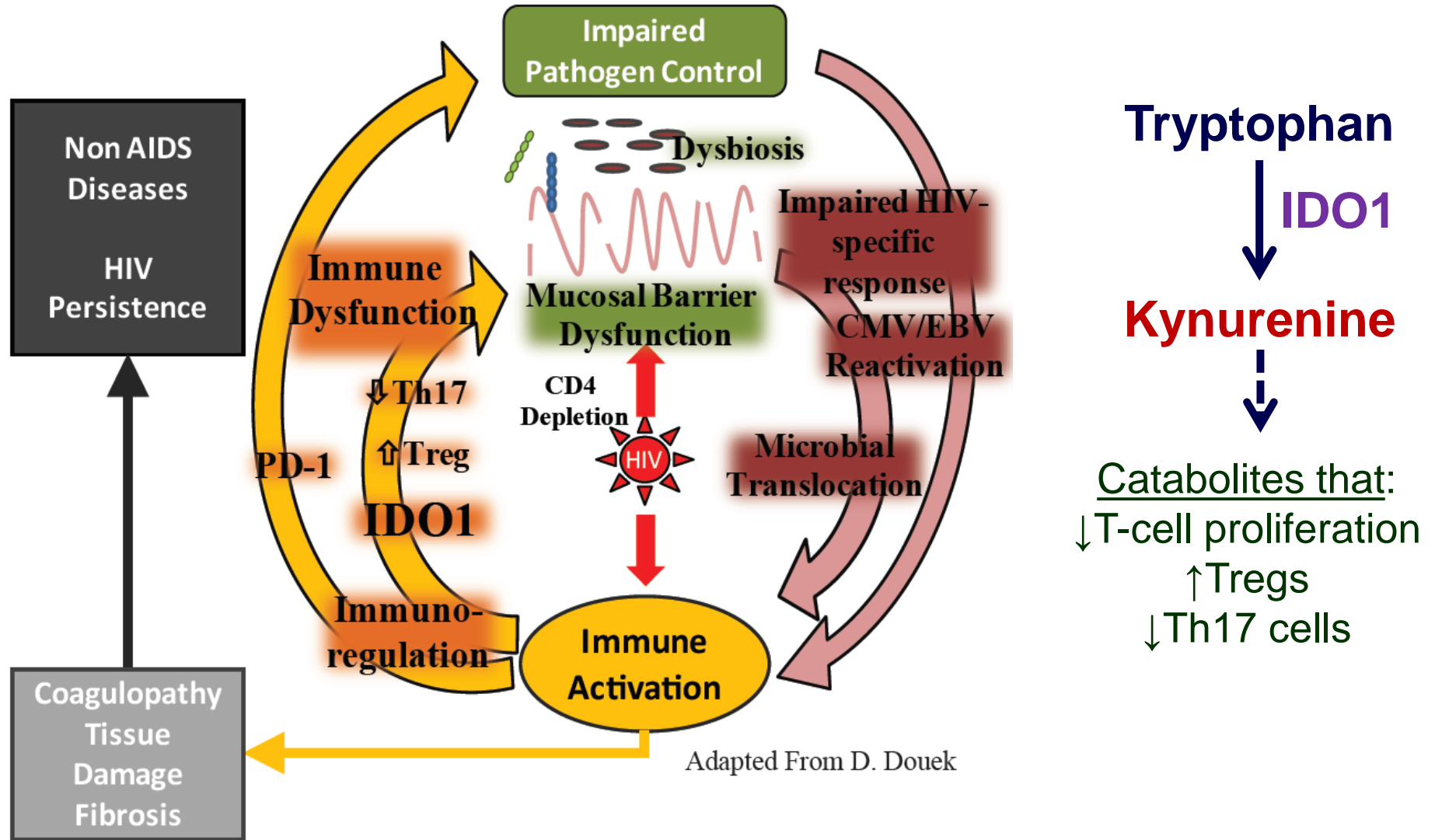
Safety Labs

- Transient declines in neutrophils
- ↓ monocyte IL-1b and IL-6 response to LPS stimulation
- No significant change in CD4 count (median 758 to 714 at wk8)
- No sig change in CD4/CD8 ratio
- No loss of HIV VL suppression

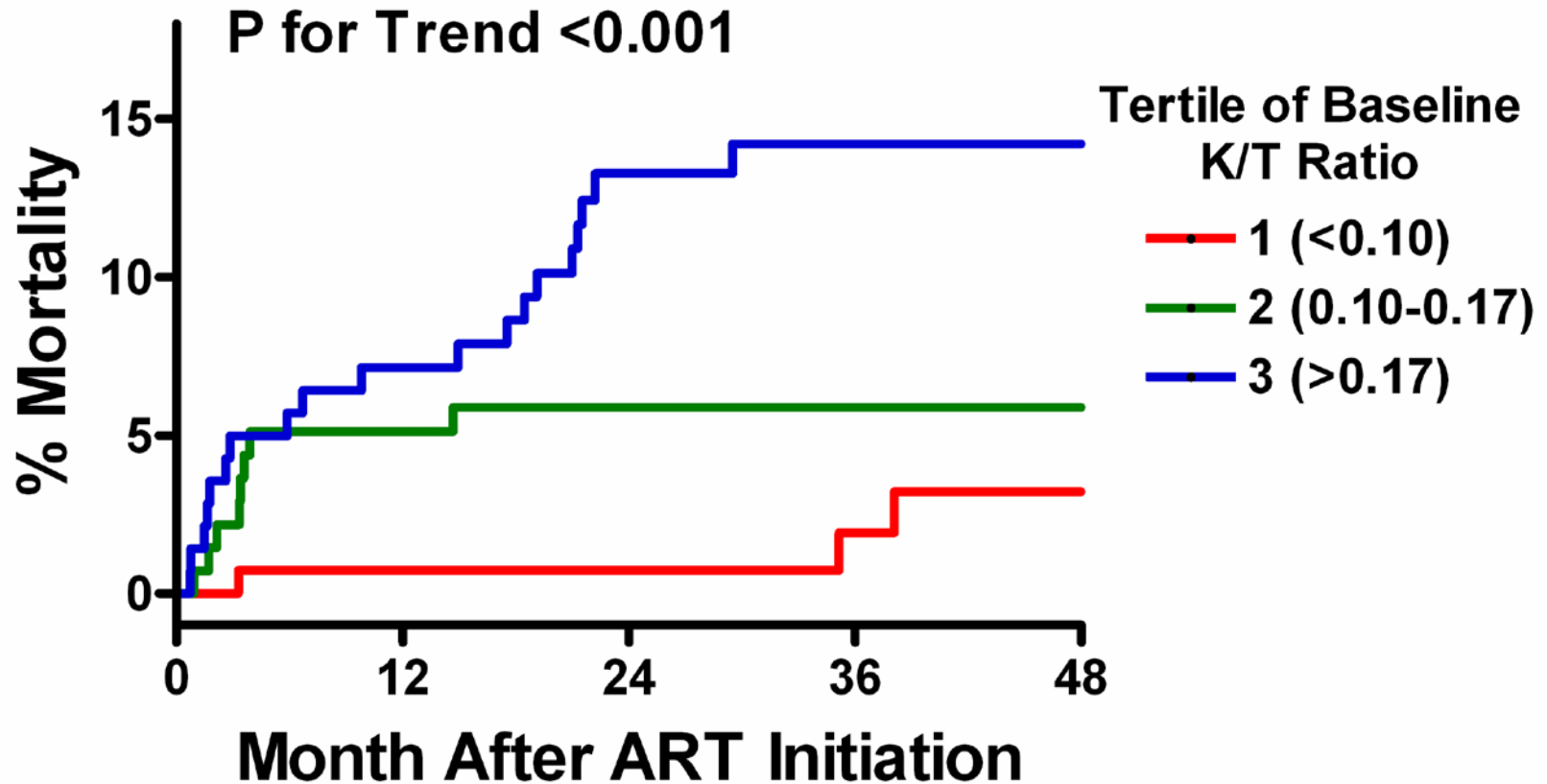
Clinical Safety

- One case of zoster, typical course

Indoleamine 2,3-dioxygenase-1 (IDO1) As a Therapeutic Target in Treated HIV Infection



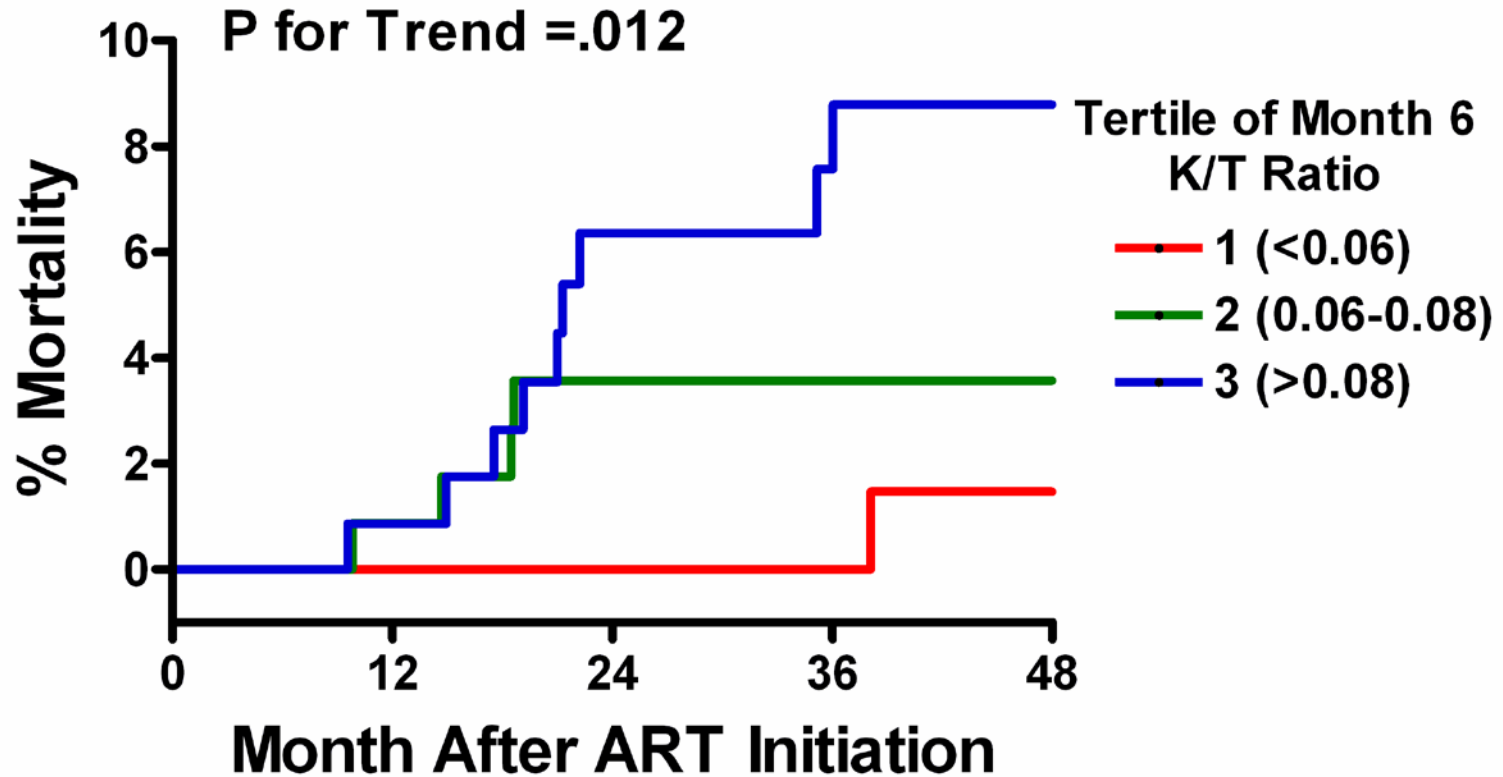
Higher IDO1 Activity (K/T ratio) Predicts ↑ Mortality during ART in HIV+ Ugandans



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).

Higher KT Ratio Continues to Predict Mortality during Suppressive ART

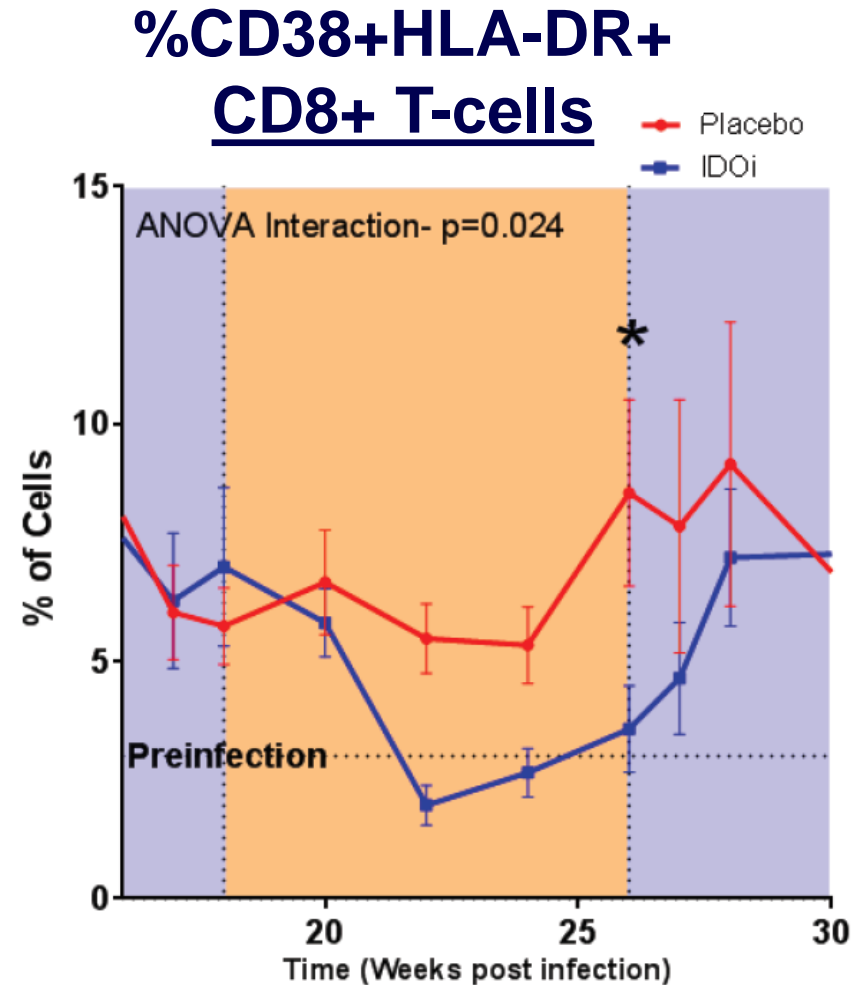
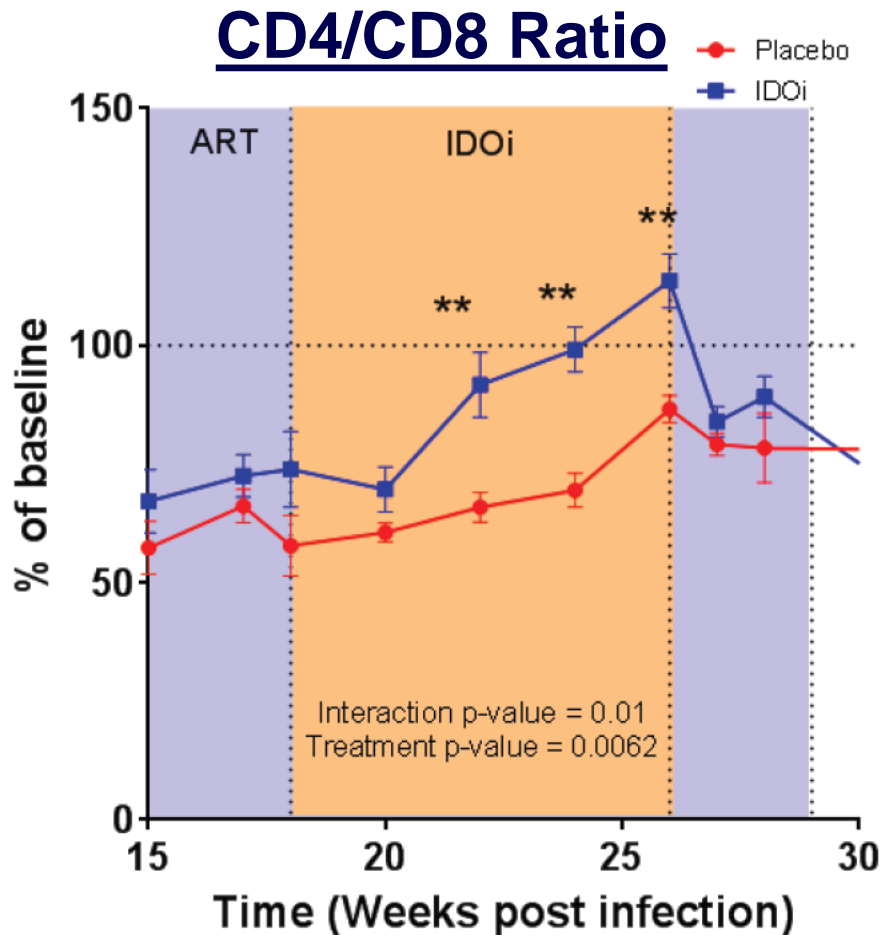
(VL <400 at Month 6 of ART)



Also associated with increased atherosclerosis in WIHS (Qi et al, CROI 2017, #636LB)

Independent of: IL-6, D-dimer, sCD14, sCD163, T-cell activation (Lee et al, JID, 2017)

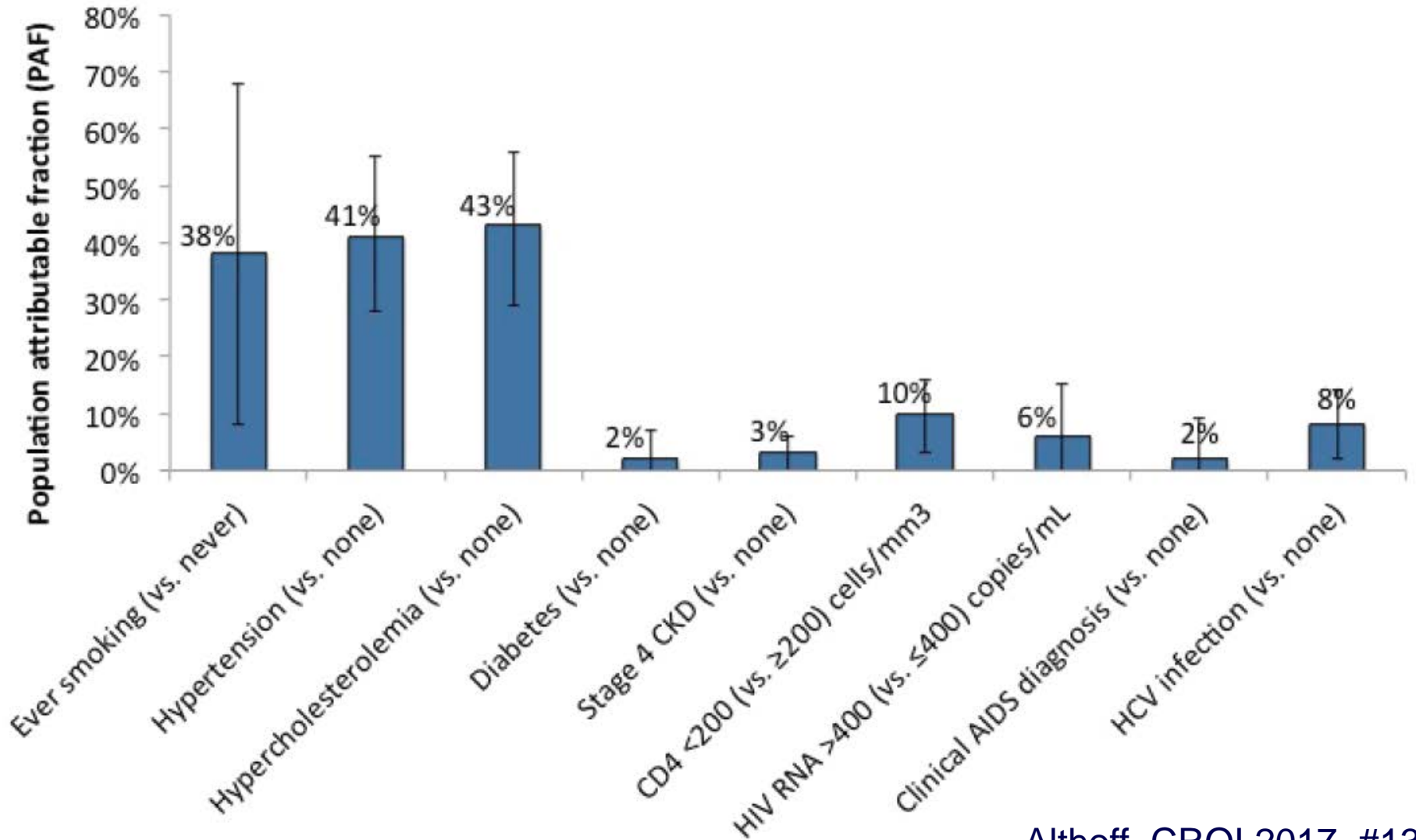
IDO Blockade \uparrow CD4/CD8 Ratio and \downarrow T-Cell Activation in Treated SIV+ Macaques (INCB024360)



**Lifestyle Interventions
Are Important!**

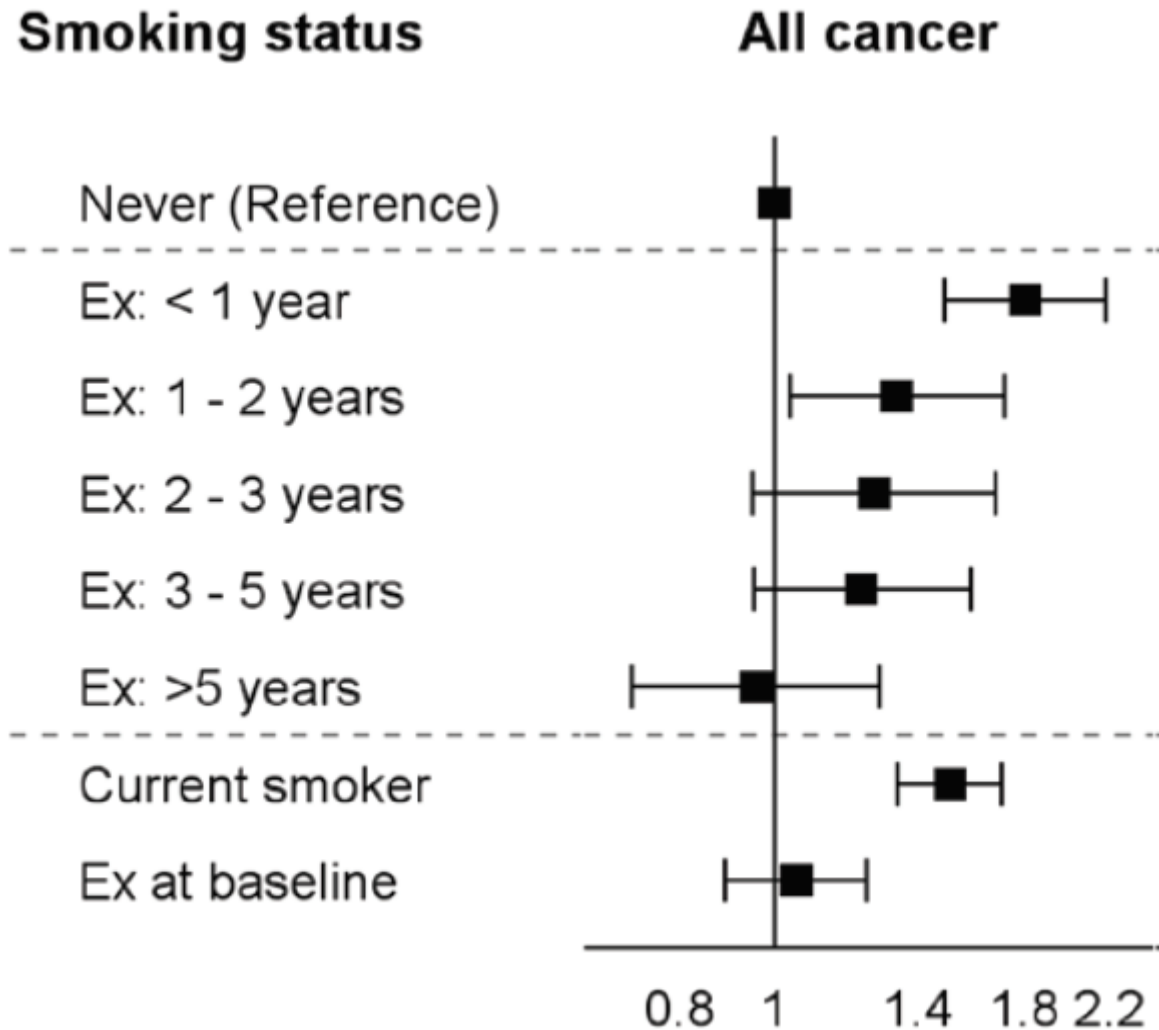
Traditional Risk Factors More Important for MI Risk Than HIV-related Factors

NA-ACCORD



Quitting Smoking Decreases Cancer Risk in Treated HIV Infection

D:A:D Study



Moderate Exercise Appears to Decrease Inflammation in Treated HIV Infection

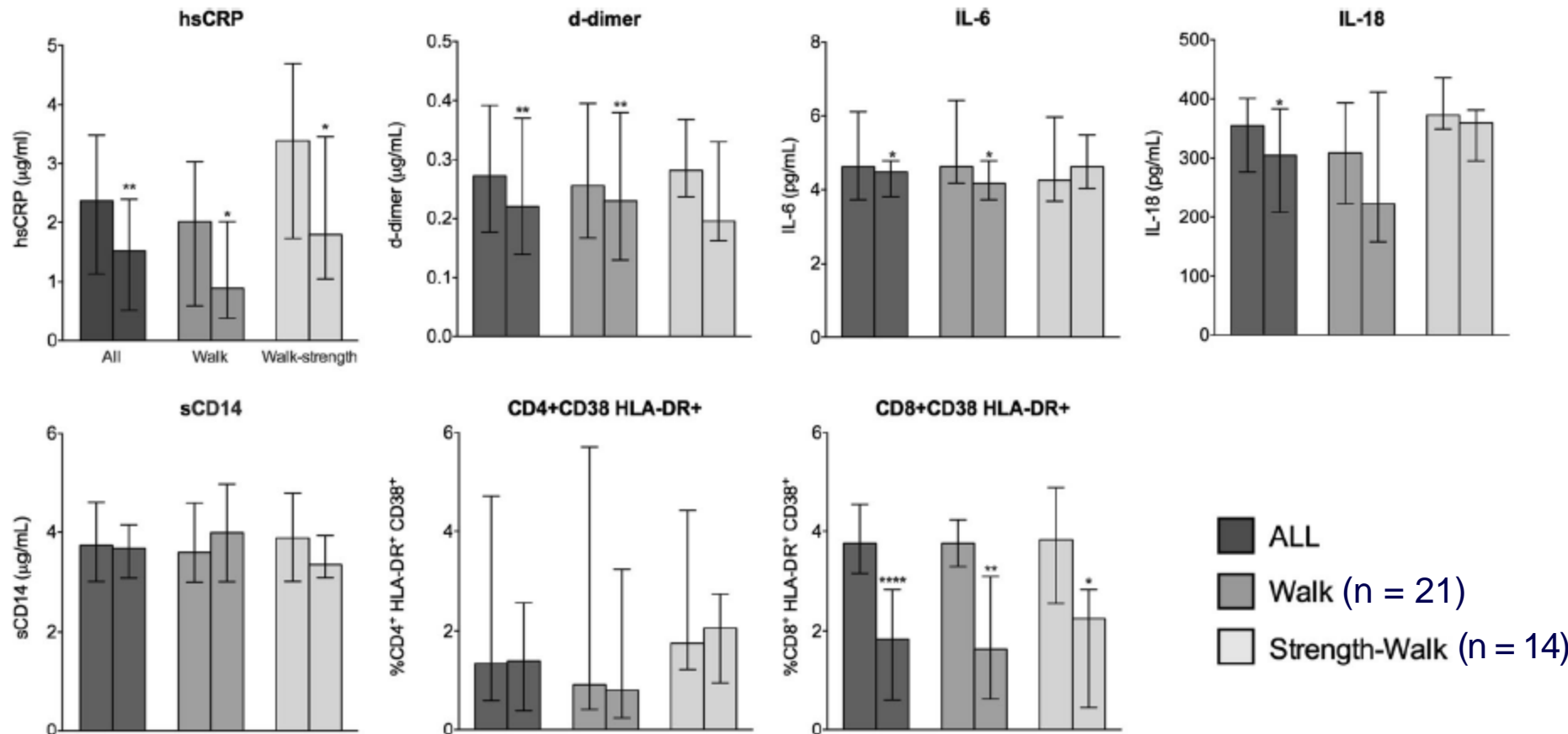


Fig. 2 Soluble and cell inflammatory markers at baseline (BL) and week-12 (W12)

- 3x per week brisk walking for 60 minutes
- +/- 30 min strength training

Summary

- Despite optimal ART, HIV shortens life expectancy and ↑ age-associated morbidities.
- Immune activation / inflammation persist despite ART and may predict these morbidities, even in those starting ART early.
- Statins show early promise and are now advanced to a clinical outcomes trial
- Probe studies may get us closer to the “tree trunk” and more potent / targeted interventions.
 - Inhibition of IL-1b or IDO1?
- Lifestyle interventions (diet, exercise, smoking cessation) are important!

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