

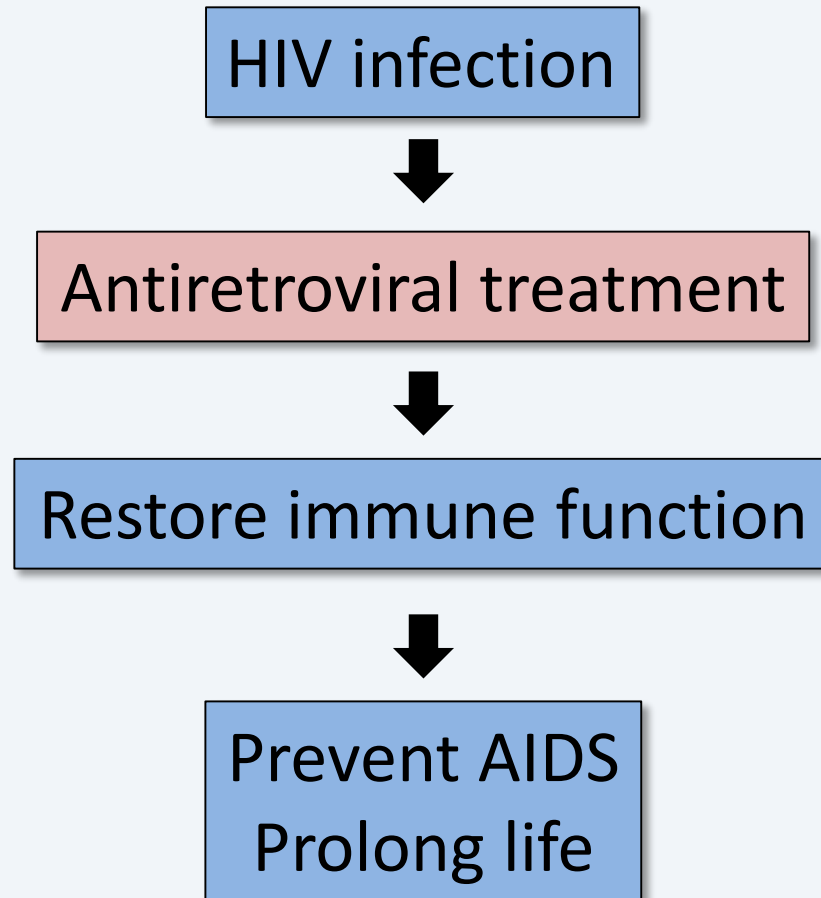
The Impact of HIV and its Treatment on Healthy Aging

Steven G. Deeks

Professor of Medicine

University of California, San Francisco

Most of the clinical focus over the past 25 years has been on inhibiting HIV replication and preventing AIDS



Although ART prevents AIDS and improves health, the risk for developing many morbidities remains higher than expected (~1.5 to 2.0 fold)

- **Cardiovascular disease** [1-3]
- **Cancer (notable exceptions include prostate and breast CA)** [4]
- **Bone fractures / osteoporosis** [5,6]
- **Liver disease** [7]
- **Kidney disease** [8]
- **Cognitive decline (controversial)** [9]
- **Frailty (rare but 80% more common)** [10]

1. Klein D, et al. *J Acquir Immune Defic Syndr*. 2002;30:471-477. 2; Hsue P, et al. *Circulation*. 2004;109:316-319. 3. Grinspoon SK, et al. *Circulation*. 2008;118:198-210. 4. Patel P, et al. *Ann Int Med*, 2008;148:728-736. 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. Desquilbet L, et al. *J Gerontol A Biol Sci Med Sci*. 2007;62:1279-1286; ... Also reviewed in Hunt, *Curr HIV/AIDS Reports*, (2012) 9:139–147.



ONLINE FIRST

HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW; Elliott Lowy, PhD; Kevin L. Kraemer, MD, MSc; Adeel A. Butt, MD, MS; Matthew Bidwell Goetz, MD; David Leaf, MD, MPH; Kris Ann Oursler, MD, ScM; David Rimland, MD; Maria Rodriguez Barradas, MD; Sheldon Brown, MD; Cynthia Gibert, MD; Kathy McGinnis, MS; Kristina Crothers, MD; Jason Sico, MD; Heidi Crane, MD, MPH; Alberta Warner, MD; Stephen Gottlieb, MD; John Gottdiener, MD; Russell P. Tracy, PhD; Matthew Budoff, MD; Courtney Watson, MPH; Kaku A. Armah, BA; Donna Doebler, DrPH, MS; Kendall Bryant, PhD; Amy C. Justice, MD, PhD

ORIGINAL RESEARCH

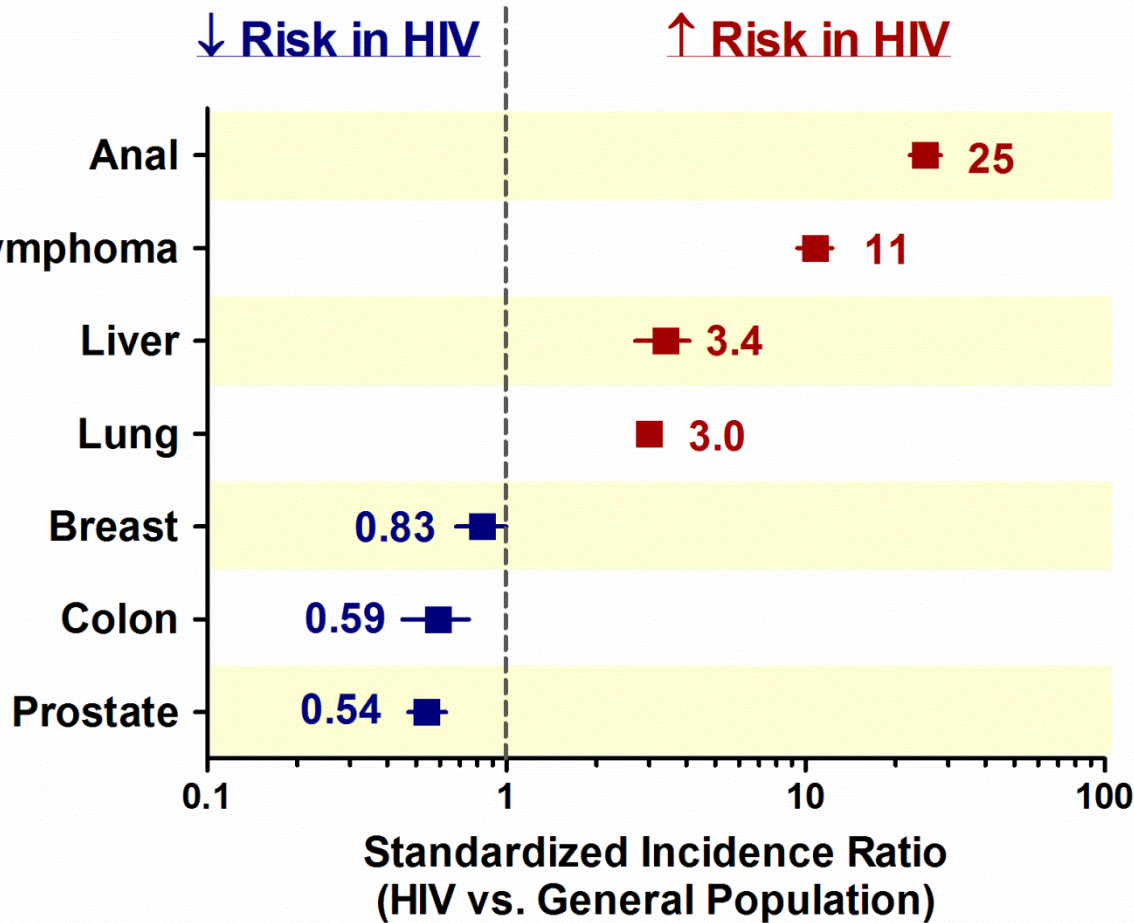
Annals of Internal Medicine

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

Impact of HIV on risk in some studies comparable to traditional risk factors including HTN, DM and hyperlipidemia

Risk of many - *but not all* - cancers is increased in patients with HIV/AIDS



Strikingly similar pattern of cancer risk in RA and psoriasis (Smitten, Arth Res 08)

Adjusted for age, gender, race, calendar year, and cancer registry.

Shiels, Annals Int Med, 2010 (see also: Silverberg, AIDS, 2009)

There is even a concern in the popular press that HIV “accelerates” aging

The New York Times
ON THE WEB



**59 year old man less
“robust” than father**

Gross G. AIDS Patients Face Downside of Living Longer. *NY Times*. Jan 6, 2008

NEW YORK



**HIV associated with multiple
morbidity of aging**

France D. Another Kind of AIDS Crisis. *New York*. Nov 1, 2009

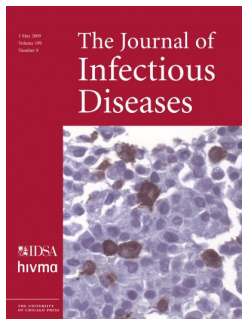
Integrative nature of geriatric syndromes (“aging”)

- **General medicine:** focus on specific diseases (CVD, cancer) with linear pathways
- **Geriatric medicine:** focus on functional status
 - Loss of redundancy (or physiologic reserve) that arises as a consequence of multiple deficits that accumulate (often exponentially) with age
 - Frailty, incontinence, immobility, falls
- **Biology:** mitochondrial toxicity, chronic inflammation, telomerase/telomere dysfunction, cell senescence, stem cell dysfunction, excess nutrients (insulin resistance)
- **HIV:** Kidney/hepatic dysfunction, neuropathy, sarcopenia, metabolic syndrome, obesity, mitochondrial DNA damage



A Frailty-Related Phenotype Before HAART Initiation as an Independent Risk Factor for AIDS or Death After HAART Among HIV-Infected Men

Loïc Desquilbet,^{1,2} Lisa P. Jacobson,² Linda P. Fried,³ John P. Phair,^{4,5} Beth D. Jamieson,⁶ Marcy Holloway,⁷ and Joseph B. Margolick⁸



Association of Functional Impairment with Inflammation and Immune Activation in HIV Type 1-Infected Adults Receiving Effective Antiretroviral Therapy

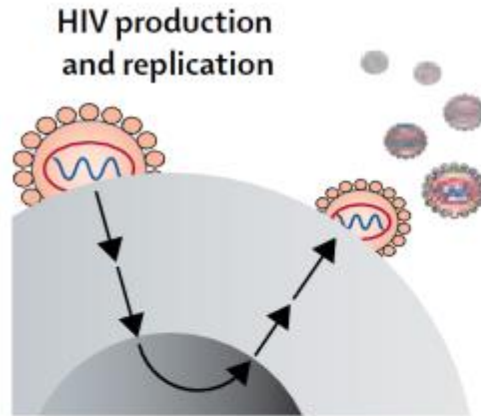
Kristine M. Erlandson,^{1,2} Amanda A. Allshouse,³ Catherine M. Jankowski,² Eric J. Lee,¹ Kevin M. Rufner,⁴ Brent E. Palmer,⁵ Cara C. Wilson,¹ Samantha MaWhinney,³ Wendy M. Kohrt,² and Thomas B. Campbell¹

**Frailty-like syndrome occurs earlier in HIV disease
(predicted by CD4 nadir, duration of infection)**

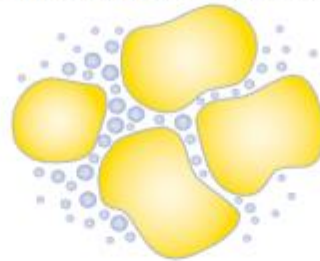
**Prevalence among those receiving modern
treatment regimens unknown**

Role of chronic inflammation in health

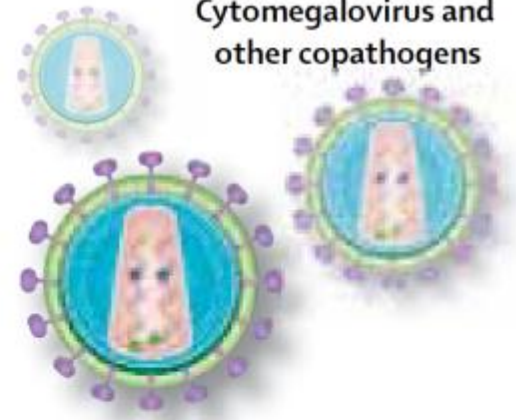
Multiple factors cause persistent inflammation during ART



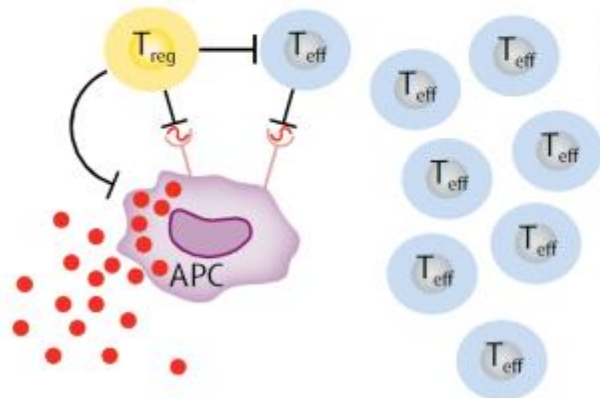
ART toxicity, lipodystrophy, and traditional risk factors



Cytomegalovirus and other copathogens



Loss of regulatory cells



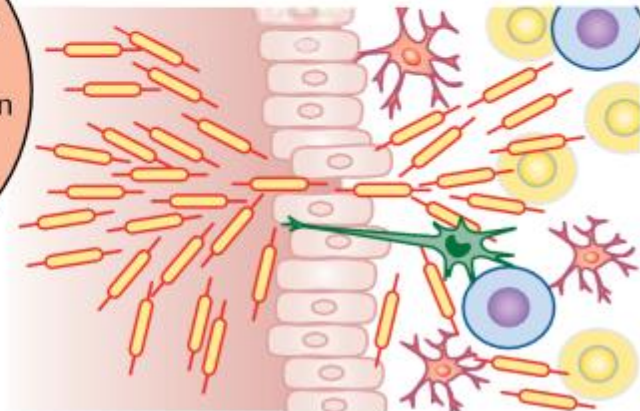
Inflammation

↑ Monocyte activation
↑ T-cell activation
↑ Endothelium adhesion
Dyslipidaemia
Hypercoagulation

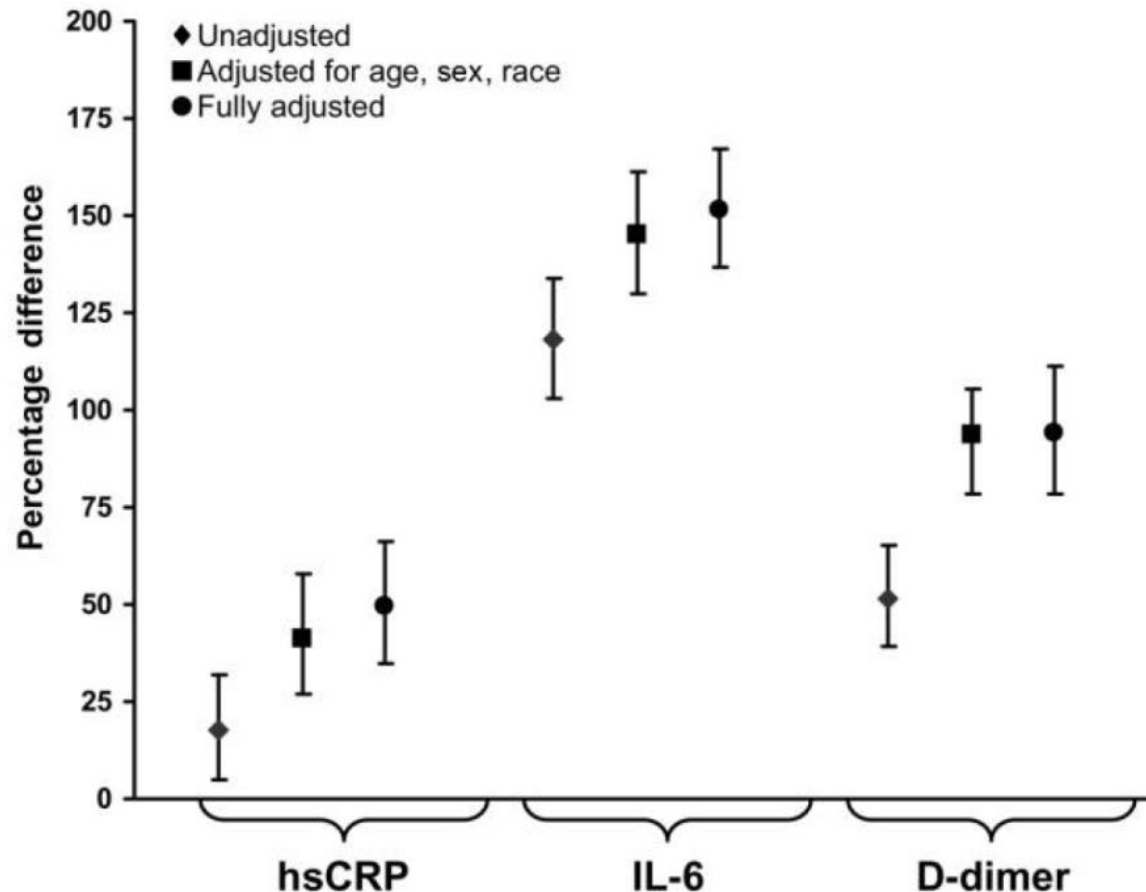
Comorbidities

(cardiovascular disease, cancer, kidney disease,
liver disease, osteopenia/osteoporosis, neurocognitive disease)

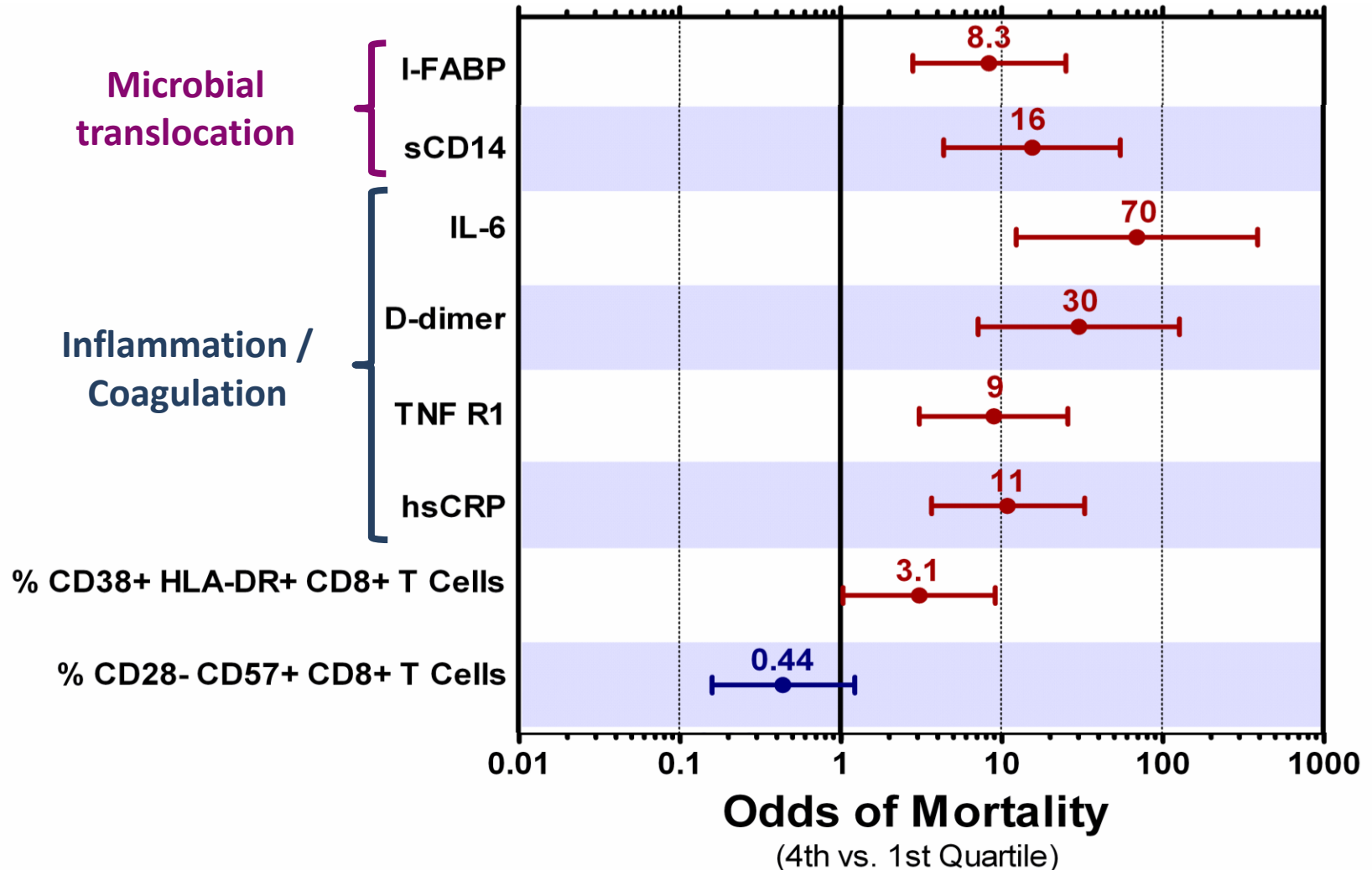
Microbial translocation



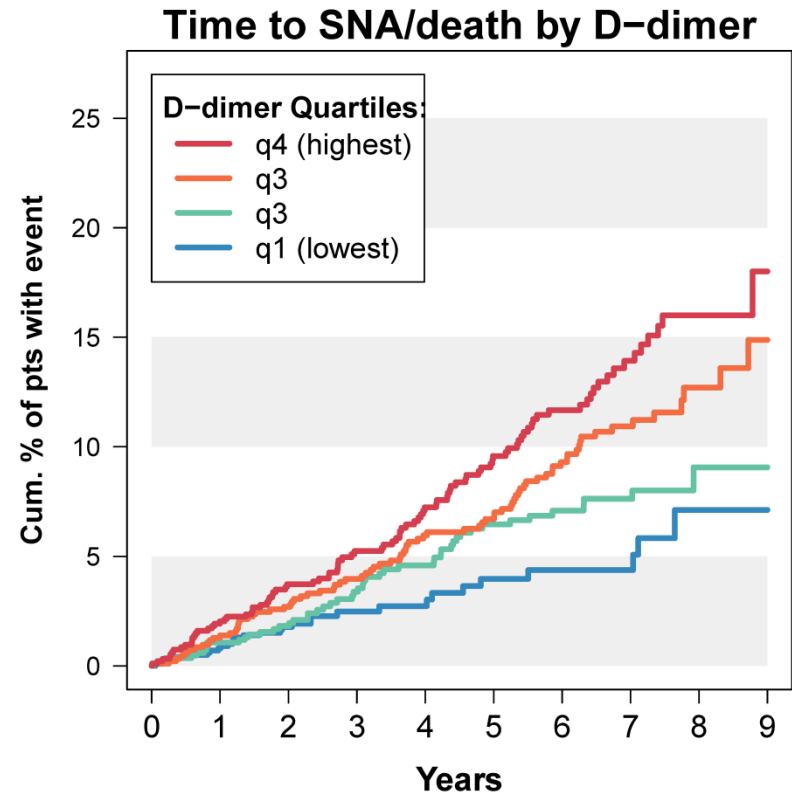
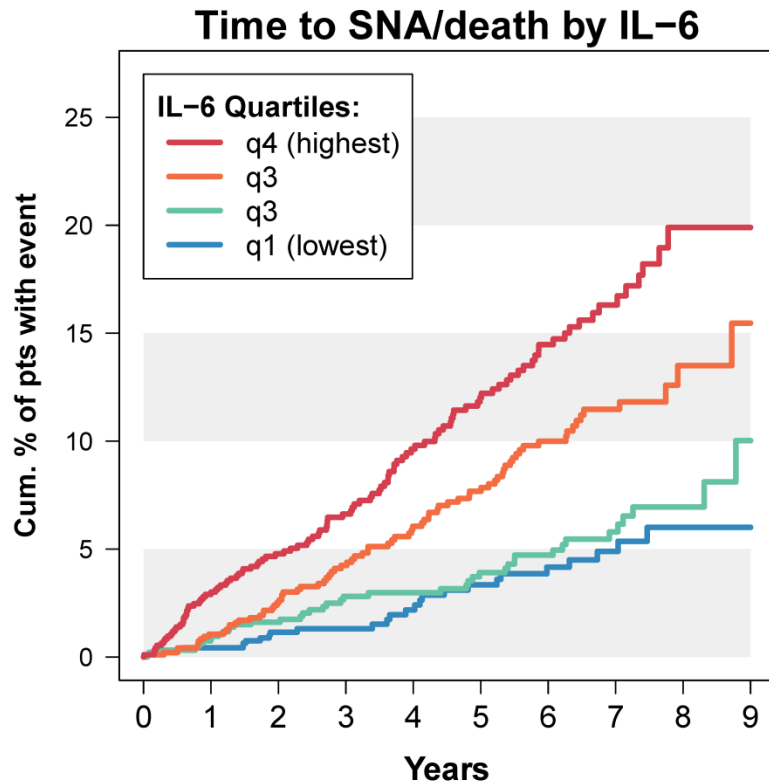
After adjusting for traditional risk factors, inflammatory biomarkers remain elevated during long-term ART, and strongly predictive of disease progression



Microbial Translocation Predicts Mortality during ART-mediated Viral Suppression



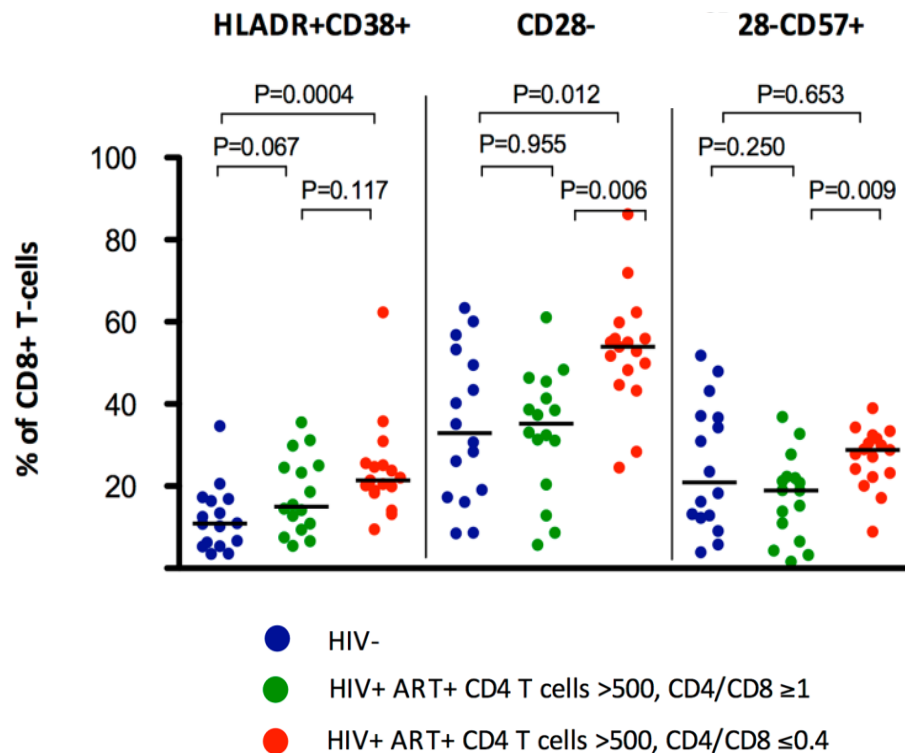
After adjusting for traditional risk factors, inflammatory biomarkers remain elevated during long-term ART, and strongly predictive of disease progression



**Can harmful
inflammation and/or
immune dysfunction be
monitored in the clinic?**

HIV-Infected Individuals with Low CD4/CD8 Ratio despite Effective Antiretroviral Therapy Exhibit Altered T Cell Subsets, Heightened CD8+ T Cell Activation, and Increased Risk of Non-AIDS Morbidity and Mortality

Sergio Serrano-Villar^{1*}, Talia Sainz², Sulggi A. Lee³, Peter W. Hunt³, Elizabeth Sinclair³, Barbara L. Shacklett⁴, April L. Ferre⁴, Timothy L. Hayes⁴, Ma Somsouk³, Priscilla Y. Hsue³, Mark L. Van Natta⁵, Curtis L. Meinert⁵, Michael M. Lederman⁶, Hiroyu Hatano³, Vivek Jain³, Yong Huang⁷, Frederick M. Hecht³, Jeffrey N. Martin⁸, Joseph M. McCune³, Santiago Moreno¹, Steven G. Deeks³

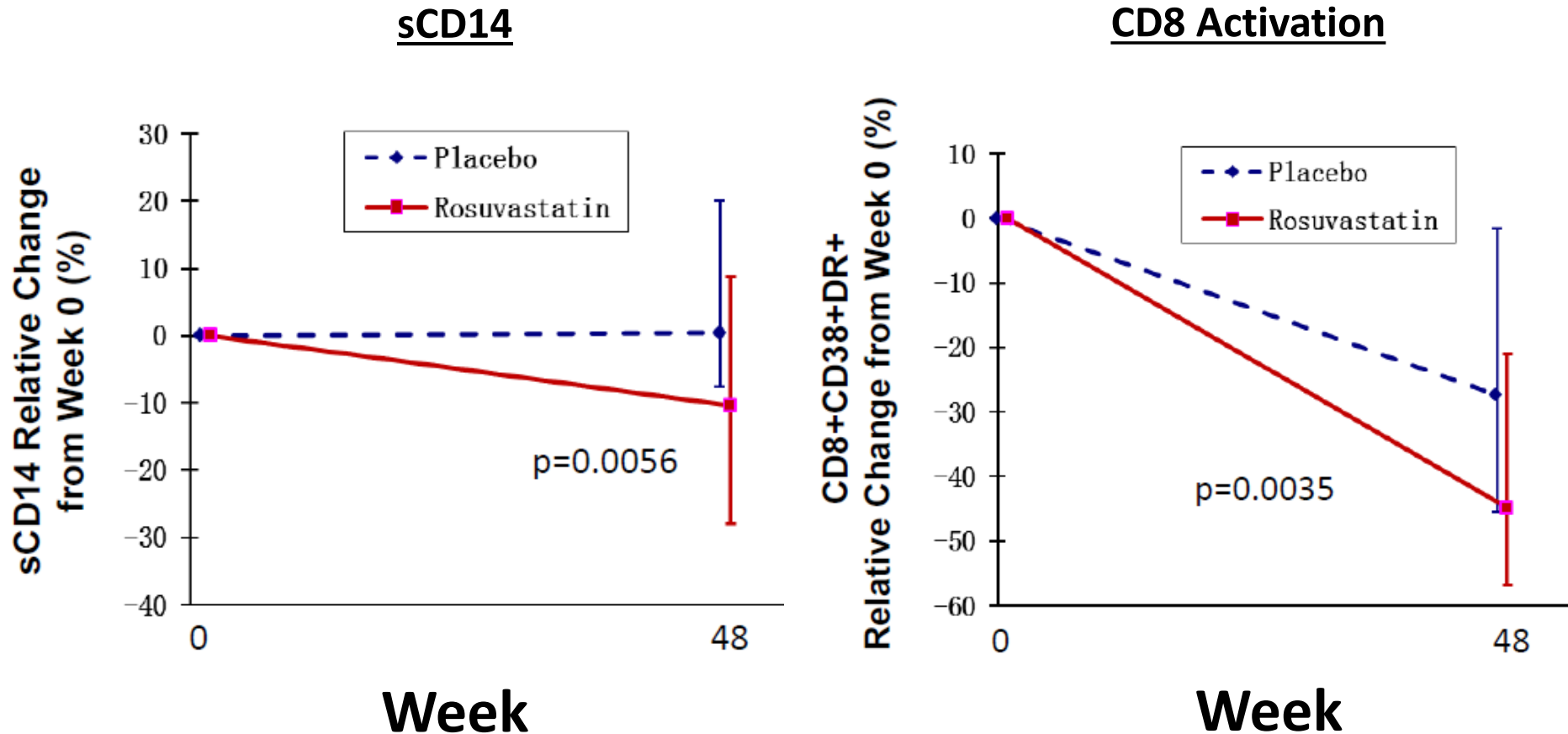


Among individuals with a high CD4+ T cell count (> 500 cells/mm³), a low ratio is associated with markers of immune dysfunction (n=67)

**It may be easier to prevent
age-associated
complications than reverse
them**

Rosuvastatin Decreases Both Monocyte and T Cell Activation during Suppressive ART

SATURN Trial (n=147)



Several rigorous high-profile studies aimed at reducing microbial translocation failed

- Sevelamer: blocks LPS absorption
 - Single arm study (n=40) of chronic untreated HIV disease
- Mesalimine: local anti-inflammatory in GALT
 - RCT cross-over study (n=30)
- Rifaximin: non-absorbed antibiotic, decreases LPS and hepatic encephalopathy in cirrhosis
 - RCT (immunologic non-responders)

No effect on LPS, sCD14 or measures of inflammation

Destruction to mucosa barriers may be irreversible

Concerns regarding microbial translocation (not dysbiosis) have led to number of pilot studies of probiotics/prebiotics, with most reporting a modest but inconsistent immune benefit

ORIGINAL ARTICLE

Probiotic Yogurt Consumption is Associated With an Increase of CD4 Count Among People Living With HIV/AIDS

Stephanie L. Irvine, BSc,* Ruben Hummelen, MSc,†‡ Sharareh Hekmat, PhD,* Caspar W. N. Looman, MSc,† J. Dik F. Habbema, PhD,† and Gregor Reid, PhD, MBA†§

ORIGINAL ARTICLE

Yogurt Containing Probiotic *Lactobacillus rhamnosus* GR-1 and *L. reuteri* RC-14 Helps Resolve Moderate Diarrhea and Increases CD4 Count in HIV/AIDS Patients

Kingsley C. Anukam, PhD,*†‡ Emmaal O. Osazuwa, PhD,* Humphrey B. Osadolor, MD,§ Andrew W. Bruce, MD,‡ and Gregor Reid, PhD, MBA†§

Open

Specific prebiotics modulate gut microbiota and immune activation in HAART-naïve HIV-infected adults: results of the “COPA” pilot randomized trial

A Gori¹, G Rizzardini², B van't Land^{3,4}, KB Amor⁵, J van Schaik³, C Torti⁵, T Quirino⁶, C Tincati², A Bandera¹, J Knol¹, K Benhassan-Chahour⁶, D Trabattton⁶, D Bray⁴, A Vrieseema³, G Welling¹⁰, J Garssen^{1,4} and M Clerici¹¹

Oral serum-derived bovine immunoglobulin improves duodenal immune reconstitution and absorption function in patients with HIV enteropathy

David M. Asmuth^{a,b}, Zhong-Min Ma^{c,d}, Anthony Albanese^b, Netanya G. Sandler^e, Sridevi Devaraj^f, Thomas H. Knight^a, Neil M. Flynn^a, Tammy Yotter^a, Juan-Carlos Garcia^a, Emily Tsuchida^g, Tsung-Teh Wu^h, Daniel C. Douek^e and Christopher J. Miller^{b,c}

Micronutrient supplemented probiotic yogurt for HIV-infected adults taking HAART in London, Canada

Jaimie Caitlin Hemsworth*, Sharareh Hekmat, Gregor Reid

RESEARCH Open Access

Synbiotic therapy decreases microbial translocation and inflammation and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial

Luz A González-Hernández¹, Luis F Jáve-Suarez¹, Mary Fafutis-Morris², Karina E Montes-Salcedo¹, Luis G Valle-Gutierrez², Ariel E Campos-Loza¹, Luis Fermin Enciso-Gómez¹ and Jaime F Andrade-Villanueva^{1*}

Intensification of Antiretroviral Therapy With Raltegravir or Addition of Hyperimmune Bovine Colostrum in HIV-Infected Patients With Suboptimal CD4⁺ T-Cell Response: A Randomized Controlled Trial

Helen Byakwaga,¹ Mark Kelly,² Damian F. J. Purcell,¹ Martyn A. French,¹ Janaki Amin,¹ Sharon R. Lewin,^{5,6,7} Hila Haskeberg,¹ Anthony D. Kelleher,^{1,8} Roger Garcia,⁷ Mark A. Boyd,¹ David A. Cooper,^{1,8} and Sean Emery,¹ for the CORAL Study Group

MAJOR ARTICLE HIV/AIDS

The Immunomodulatory Nutritional Intervention NR100157 Reduced CD4⁺ T-Cell Decline and Immune Activation: A 1-Year Multicenter Randomized Controlled Double-Blind Trial in HIV-Infected Persons Not Receiving Antiretroviral Therapy (The BITE Study)

P. Cahm,¹ K. Ruxrungtham,^{2,3} B. Gazzard,¹ R.S. Diaz,⁴ A. Gori,⁵ D.P. Kotler,⁶ A. Vrieseema,⁷ N. A. Georgiou,¹ J. Garssen,^{1,8} M. Clerici,⁹ and J. M. A. Lange,¹⁰ for the BITE (Blinded Nutritional Study for Immunity and Tolerance Evaluation) Study Team*

Research article Open Access

Randomized pilot trial of a synbiotic dietary supplement in chronic HIV-1 infection

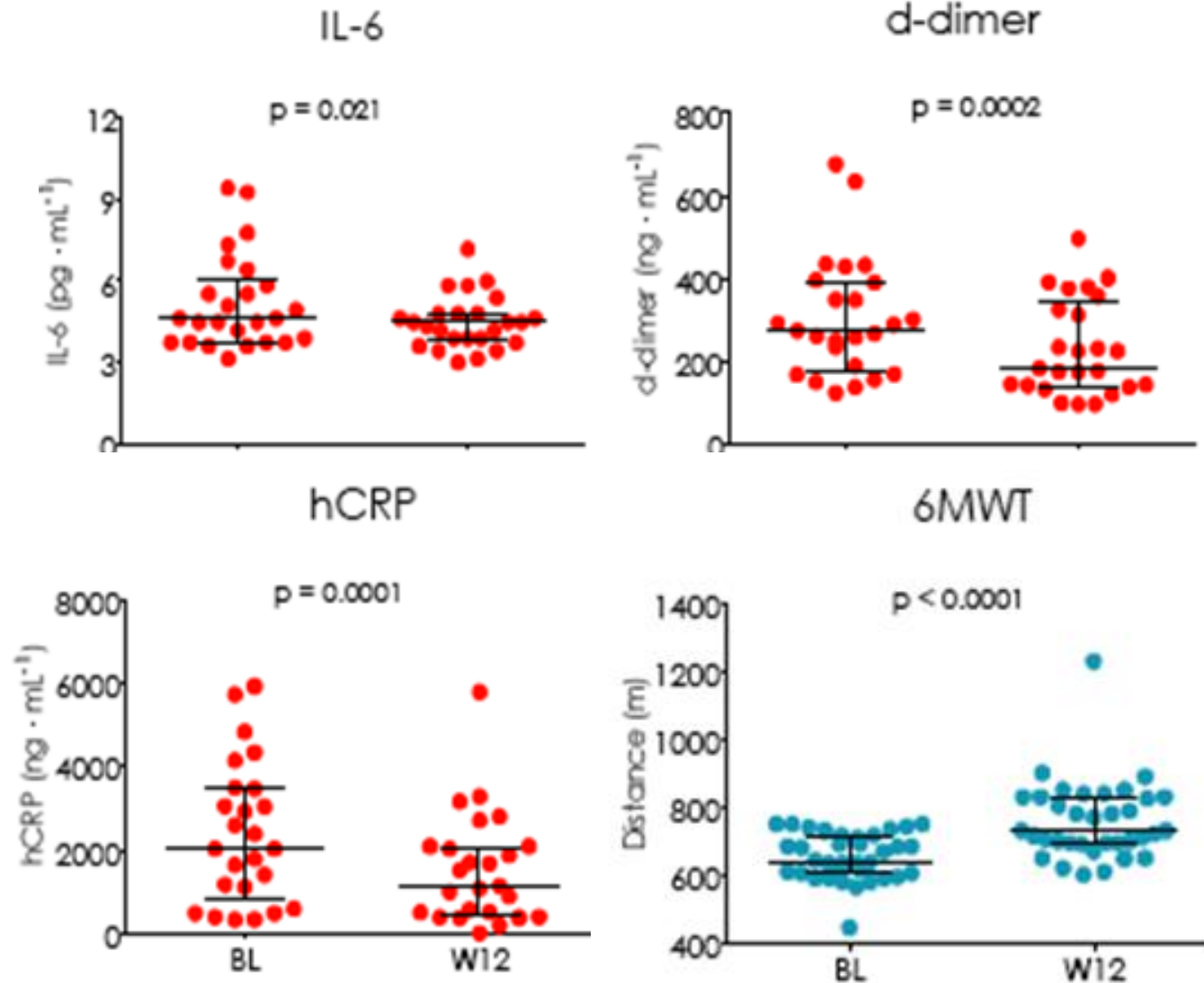
Marco Schunter¹, Hiutung Chu¹, Timothy L Hayes¹, Delandy McConnell¹, Sean S Crawford¹, Paul A Luciw², Stig Bengmark³, David M Asmuth⁴, Jennifer Brown⁴, Charles L Bevins¹, Barbara L Shacklett^{1,5} and J William Critchfield^{1,*}

Gut Microbes 2:2, 80-85; March/April 2011; © 2011 Landes Bioscience

Effect of 25 weeks probiotic supplementation on immune function of HIV patients

Ruben Hummelen,^{1,*} John Chagalucha,² Nicodemus L. Butamanya,³ Tara E. Koyama,⁴ Adrian Cook,⁴ J. Dik F. Habbema⁵ and Gregor Reid¹

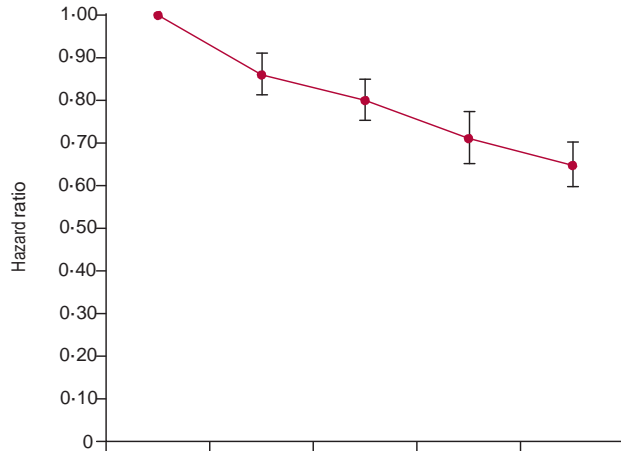
Moderate exercise (brisk walking/strength training 3 times/week decreases inflammation during ART (n=49)



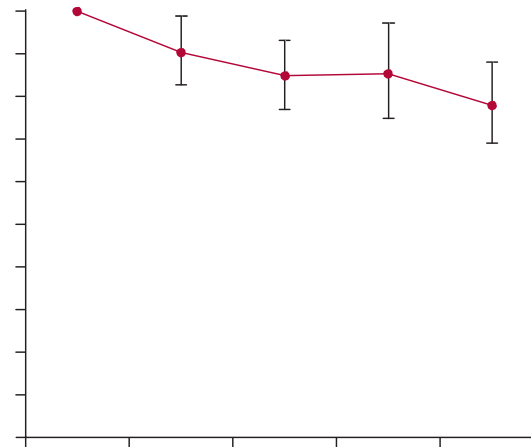
Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi Pang Wen*, Jackson Pui Man Wai*, Min Kuang Tsai, Yi Chen Yang, Ting Yuan David Cheng, Meng-Chih Lee, Hui Ting Chan, Chwen Keng Tsao, Shan Pou Tsai, Xifeng Wu

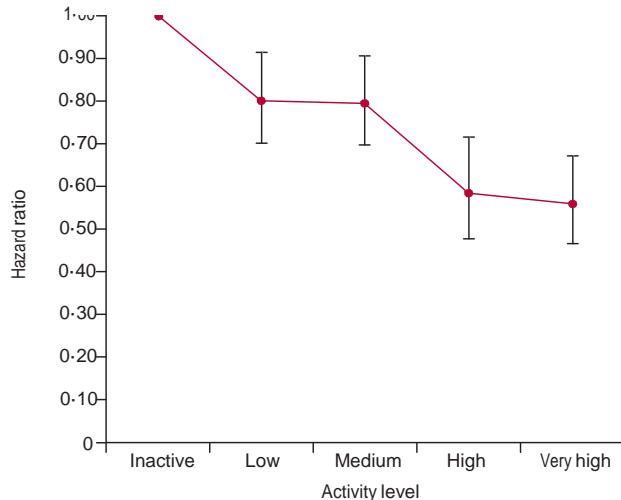
All cause mortality



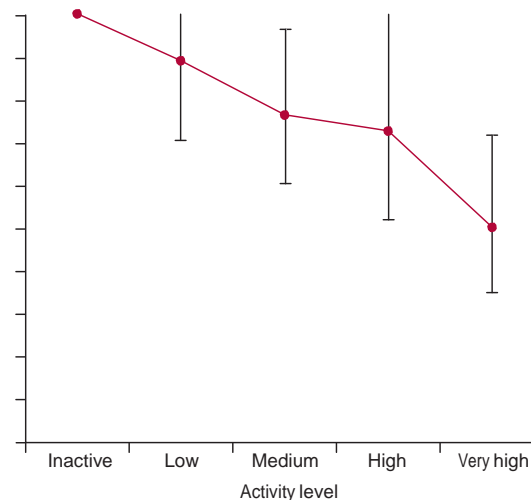
Cancer



Cardiovascular



Diabetes mellitus



Over a mean duration of 8 years, higher intensity activity predicted reduced morbidity/mortality (N=416,175)

Every additional 15 minutes of daily exercise reduced all-cause mortality by 4% (95% CI 2.5–7.0)

The NEW ENGLAND JOURNAL of MEDICINE

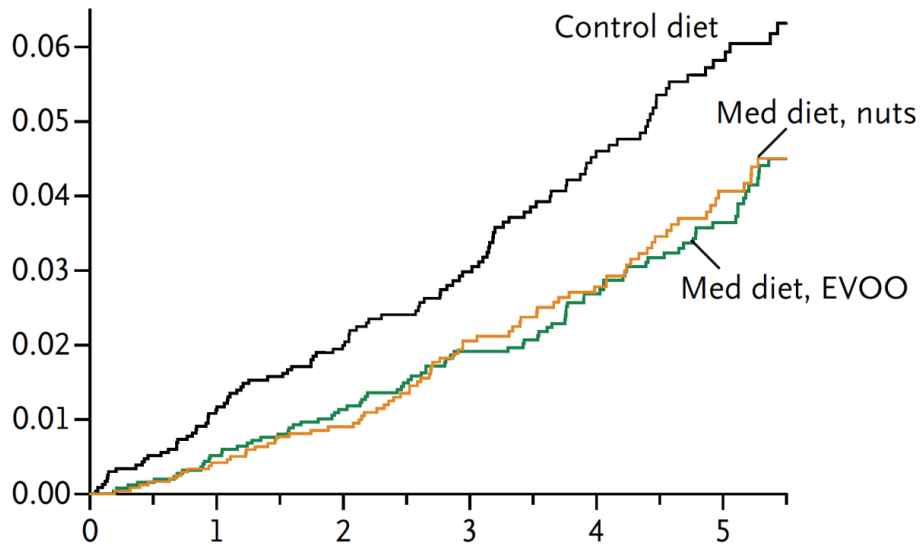
ESTABLISHED IN 1812

APRIL 4, 2013

VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D.,
Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D.,
Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D.,
José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D.,
Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D.,
José Alfredo Martínez, D.Pharm., M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D.,
for the PREDIMED Study Investigators*



**Healthy aging
requires aggressive
risk factor
management,
exercise and diet**

Early ART is associated with less inflammation during ART

Will this result in benefit?

ART-naïve with CD4+ count > 500 cells/mm³

Early ART Group

Initiate ART immediately

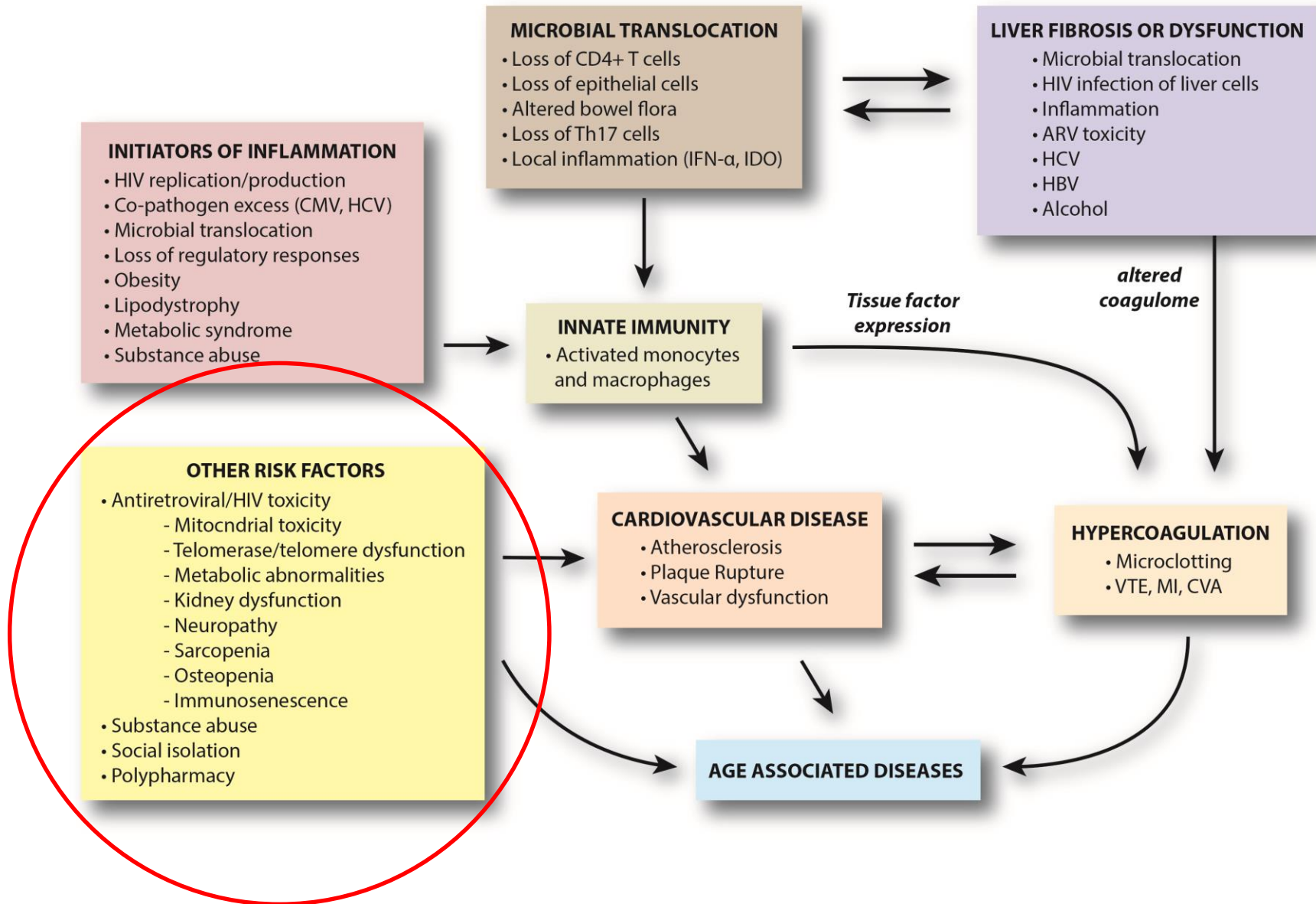
N=2,300

Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm³

N=2,300

Many HIV-associated factors could affect healthy aging



Conclusions

- HIV may or may not “accelerate” aging, depending on how one defines aging
- HIV infection and its treatment affects biology of aging (inflammation, cellular senescence, telomerase/telomeres, mitochondria disease)
- HIV infection and its treatment causes multi-morbidity (neuropathy, sarcopenia, vascular disease, metabolic syndrome, osteopenia)
- HIV disease associated with many known socioeconomic risk factors for aging (isolation, poverty)
- Healthy aging requires interventions early in life