

Inflammaging: Discover the Fountain of Youth

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Professor of Medicine

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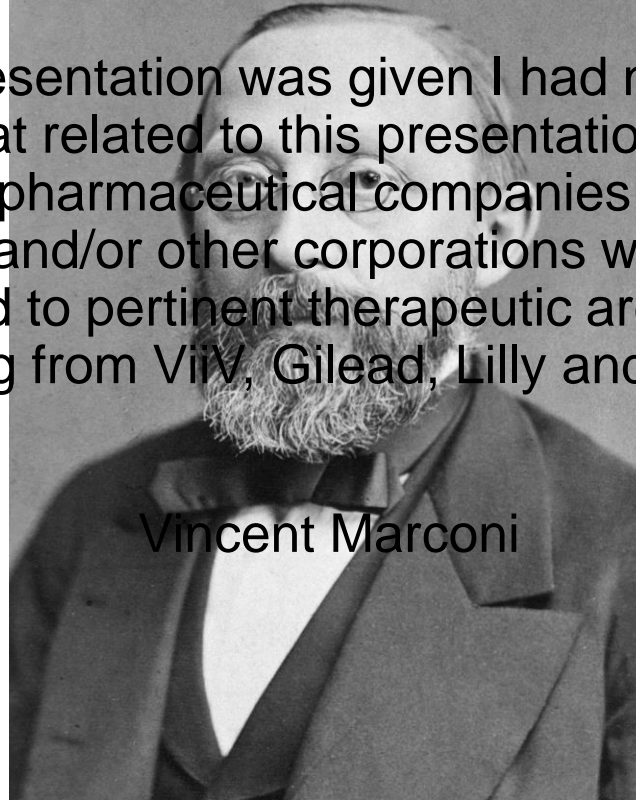
Rollins School of Public Health

Emory Vaccine Center



Disclosure

At the time this presentation was given I had no real or perceived vested interests that related to this presentation nor did I have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas. I have received funding from Viiv, Gilead, Lilly and Bayer.



Vincent Marconi

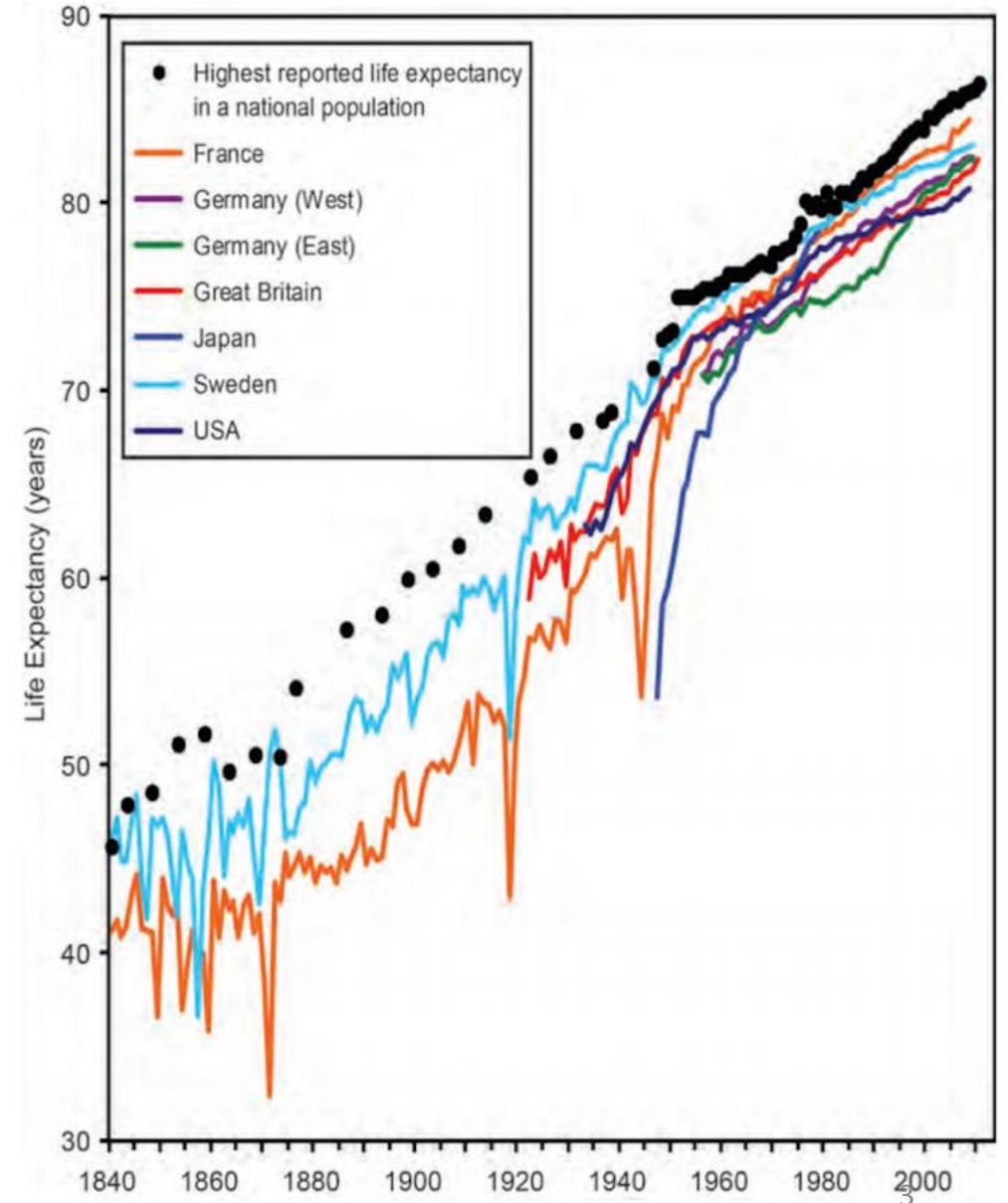
“If I could live my life over again, I would devote it to proving that germs seek their natural habitat – diseased tissue – rather than being the cause of diseased tissue. For example, mosquitoes seek stagnant water, but do not cause the pool to become stagnant” --- Rudolf Virchow 19th Century

Do we live longer today than in the past?

- Paleontological evidence shows same percentage of Neanderthals lived to various ages as modern humans
- Mortality in the past due to epidemics and wounds
- Life expectancy skewed by infant/childhood mortality (decreased due to vaccinations and clean water)



Female Life Expectancy in Developed Countries: 1840-2009

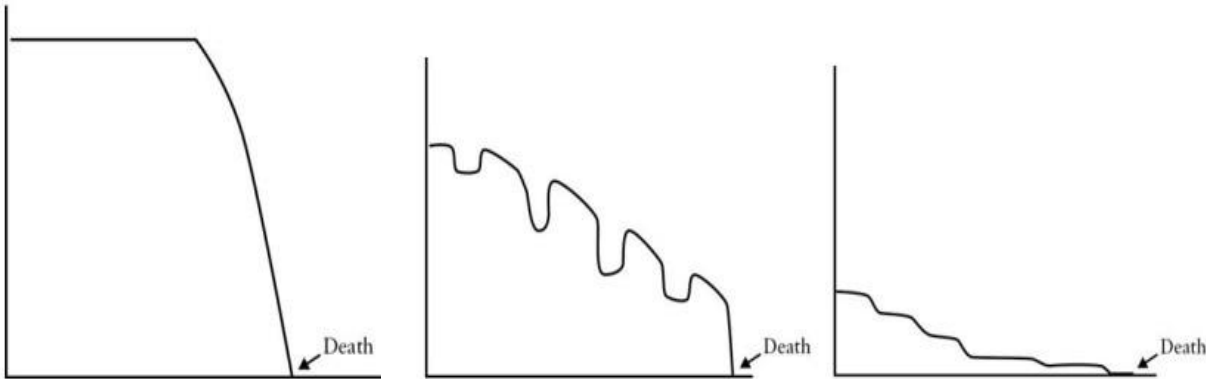


What would you rather?

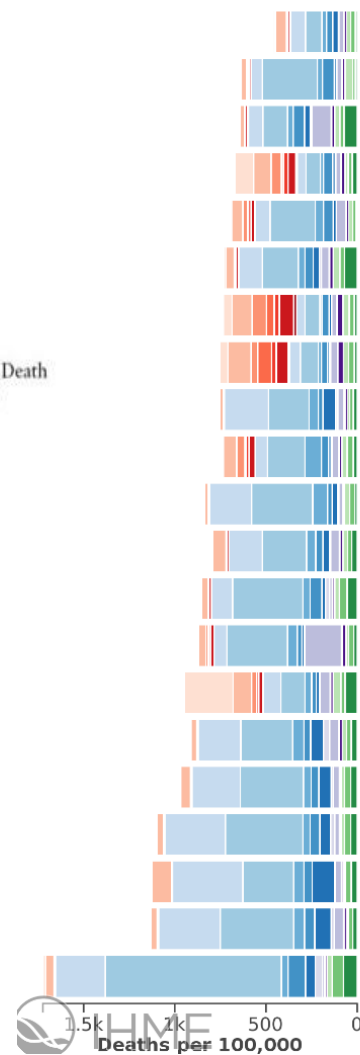
- A. Die in 20 years without pain or regrets
- B. Die in 30 years with immense pain and regrets in the last several years



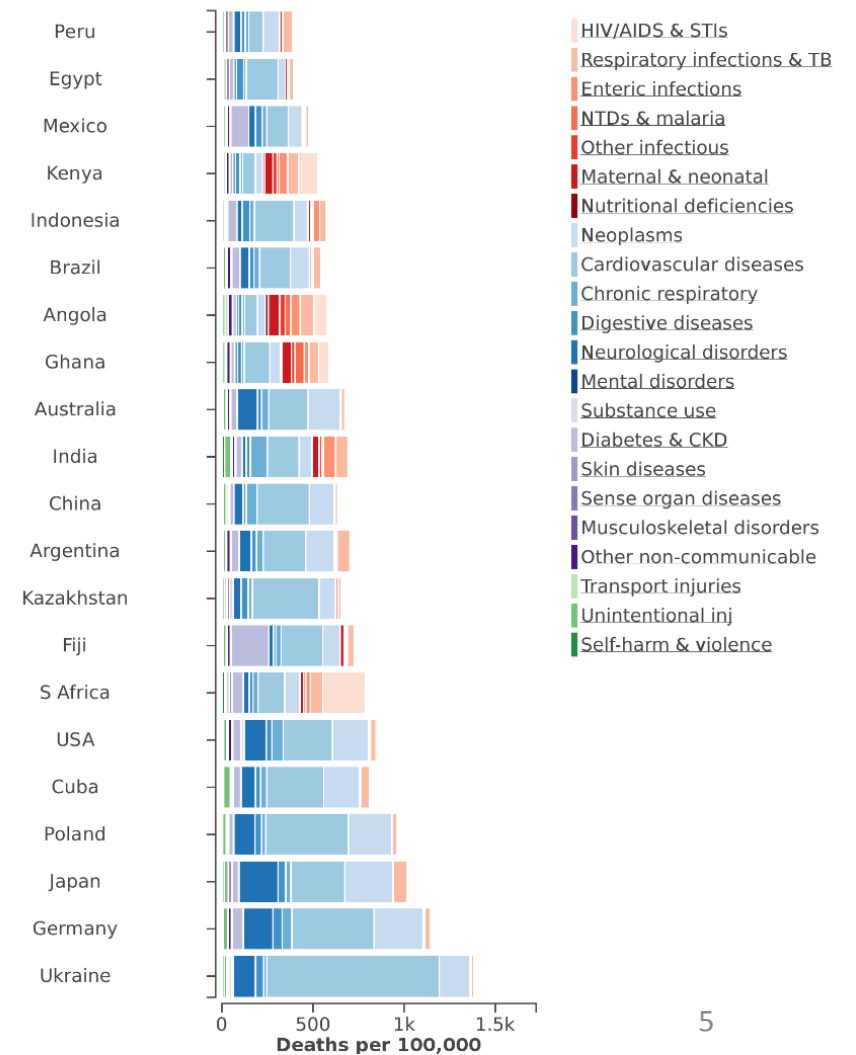
Lifespan versus Healthspan and Age-Related Diseases



Males, All ages, 2017

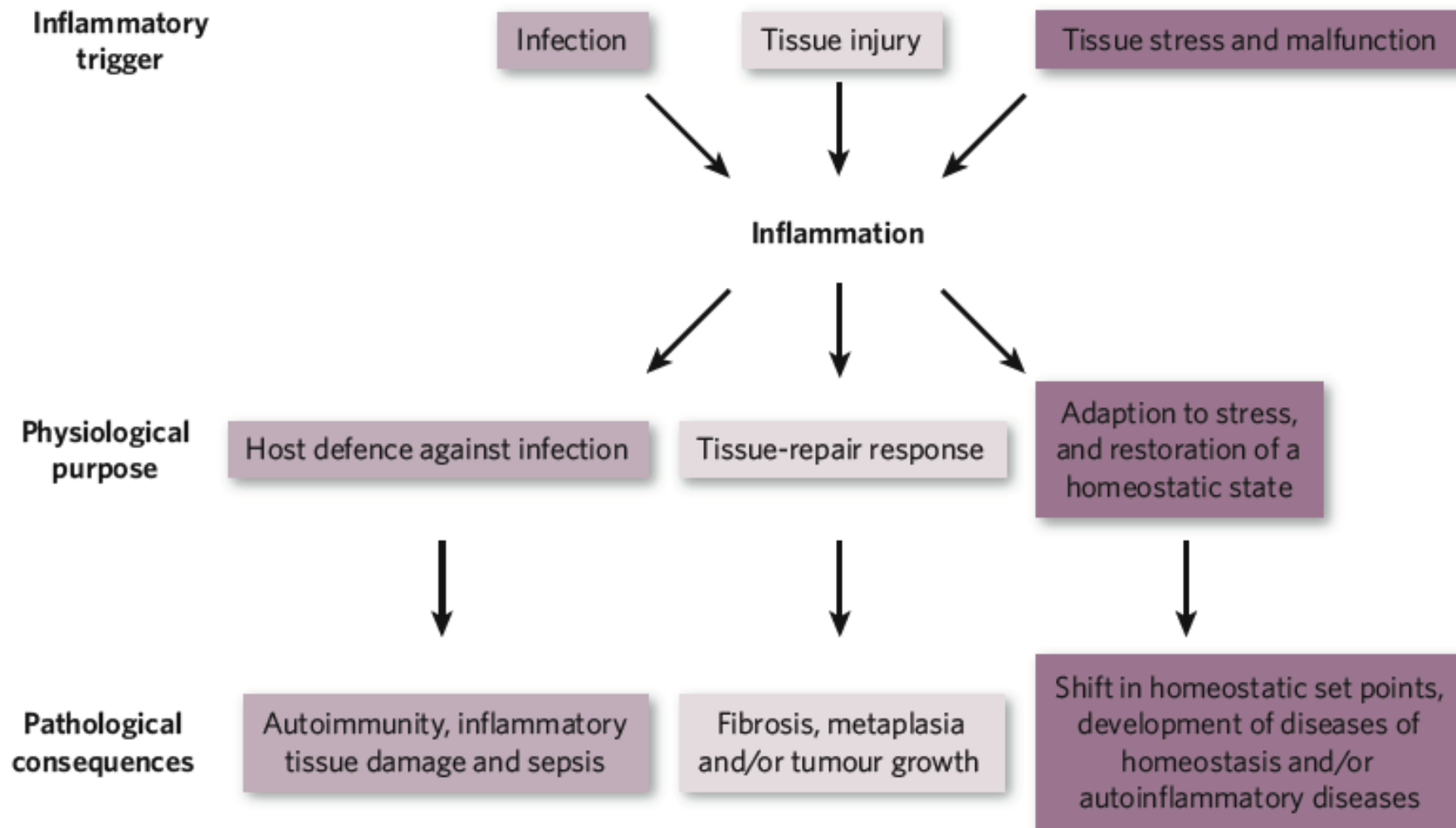


Females, All ages, 2017

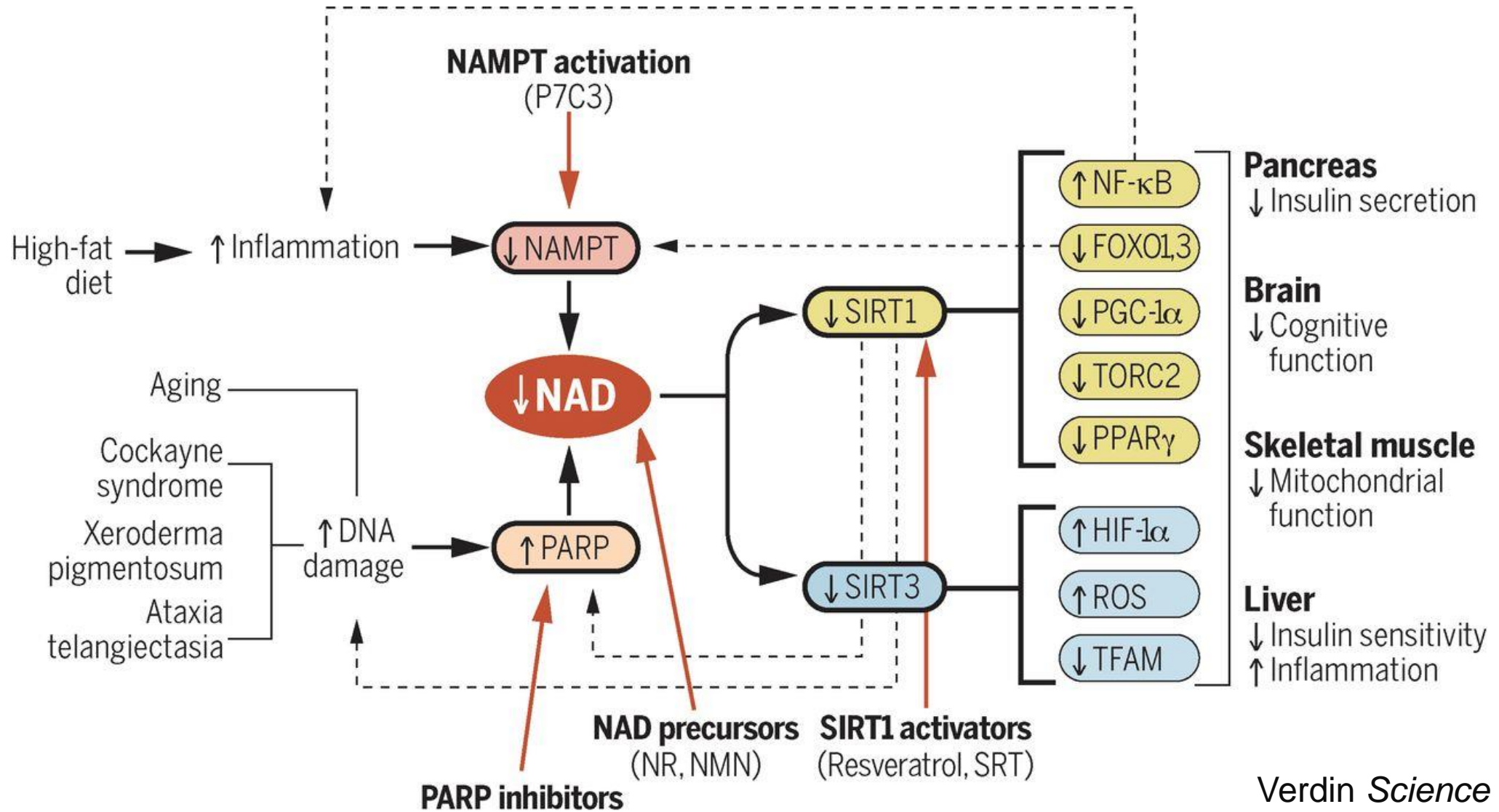


- HIV/AIDS & STIs
- Respiratory infections & TB
- Enteric infections
- NTDs & malaria
- Other infectious
- Maternal & neonatal
- Nutritional deficiencies
- Neoplasms
- Cardiovascular diseases
- Chronic respiratory
- Digestive diseases
- Neurological disorders
- Mental disorders
- Substance use
- Diabetes & CKD
- Skin diseases
- Sense organ diseases
- Musculoskeletal disorders
- Other non-communicable
- Transport injuries
- Unintentional inj
- Self-harm & violence

The Good and the Bad of Inflammation

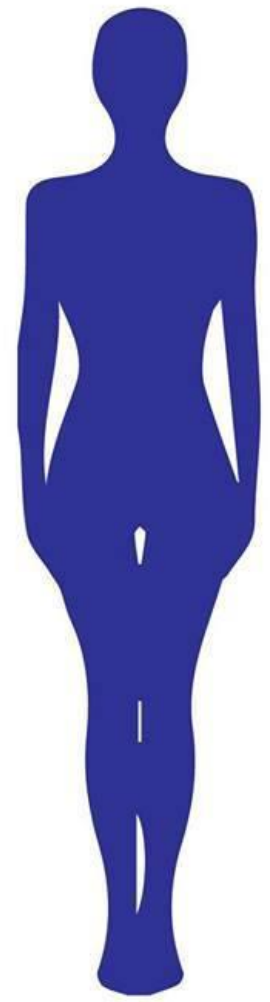


The Role of Inflammation in Age-related Diseases



HOW INFLAMMATION AFFECTS THE BODY

"Inflammation is at the root of practically all known chronic health conditions"



BRAIN

Pro-inflammatory cytokines cause autoimmune reactions in the brain, which can lead to depression, autism, poor memory, Alzheimer's disease and MS.



SKIN

Chronic inflammation compromises the liver & kidneys, resulting in rashes, dermatitis, eczema, acne, psoriasis, wrinkles & fine lines.



CARDIOVASCULAR

Inflammation in the heart & arterial & venous walls contributes to heart disease, strokes, high blood sugar (diabetes) and anemia.



KIDNEYS

Inflammatory cytokines restrict blood flow to the kidneys. Complications like edema, hypertension, nephritis & kidney failure can result.



BONES

Inflammation interferes with the body's natural ability to repair bone mass, increasing the number of fractures & leading to conditions like osteoporosis.



LIVER

Build-up of inflammation leads to an enlarged liver or fatty liver disease. Increased toxic load build-up in the body.



THYROID

Autoimmunity as a result of inflammation can reduce total thyroid receptor count & disrupts thyroid hormone function.



LUNGS

Inflammation induces autoimmune reactions against the linings of airways. Can result in allergies or asthma.



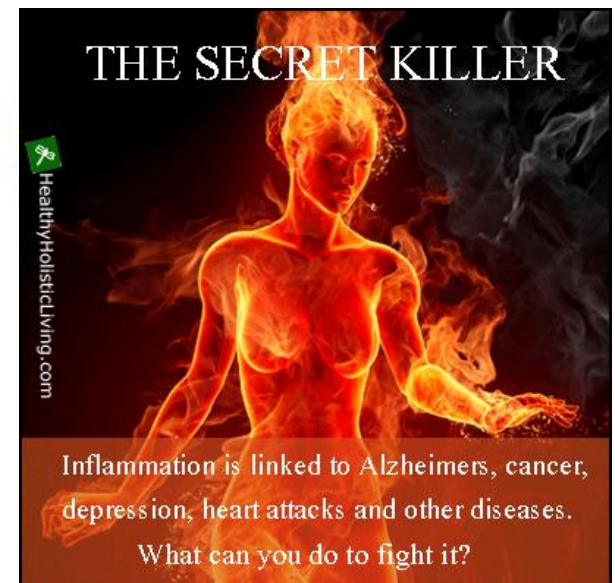
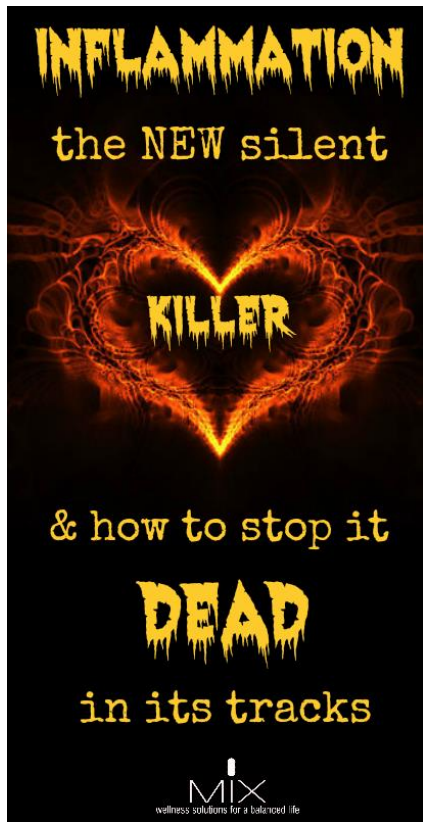
GI TRACT

Chronic inflammation damages our intestinal lining and can result in issues like GERD, Chron's disease and Celiac disease.

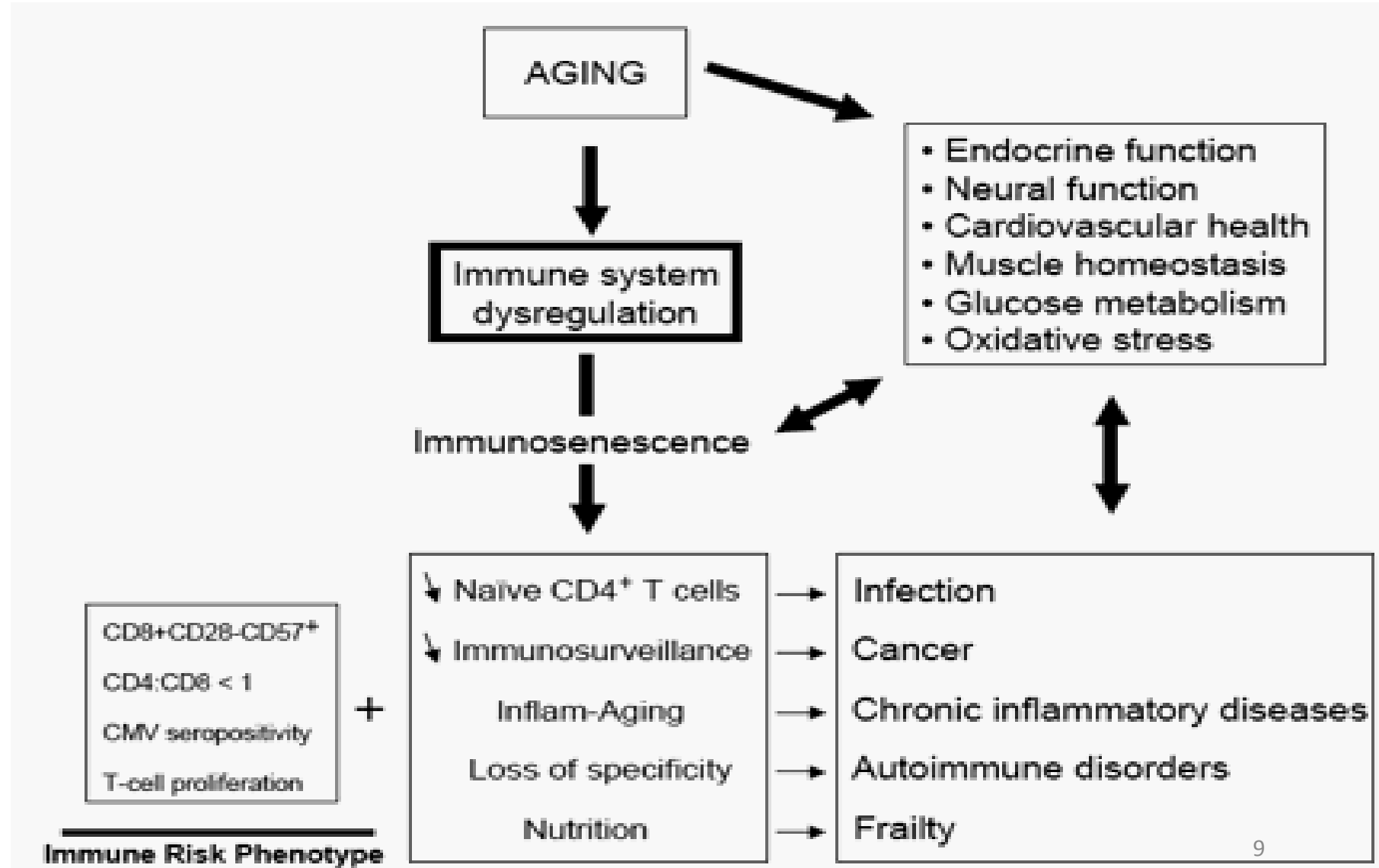


MUSCLE

Inflammatory cytokines can cause muscle pain & weakness. Can manifest as carpal tunnel syndrome, or polymyalgia rheumatica, to name a few.

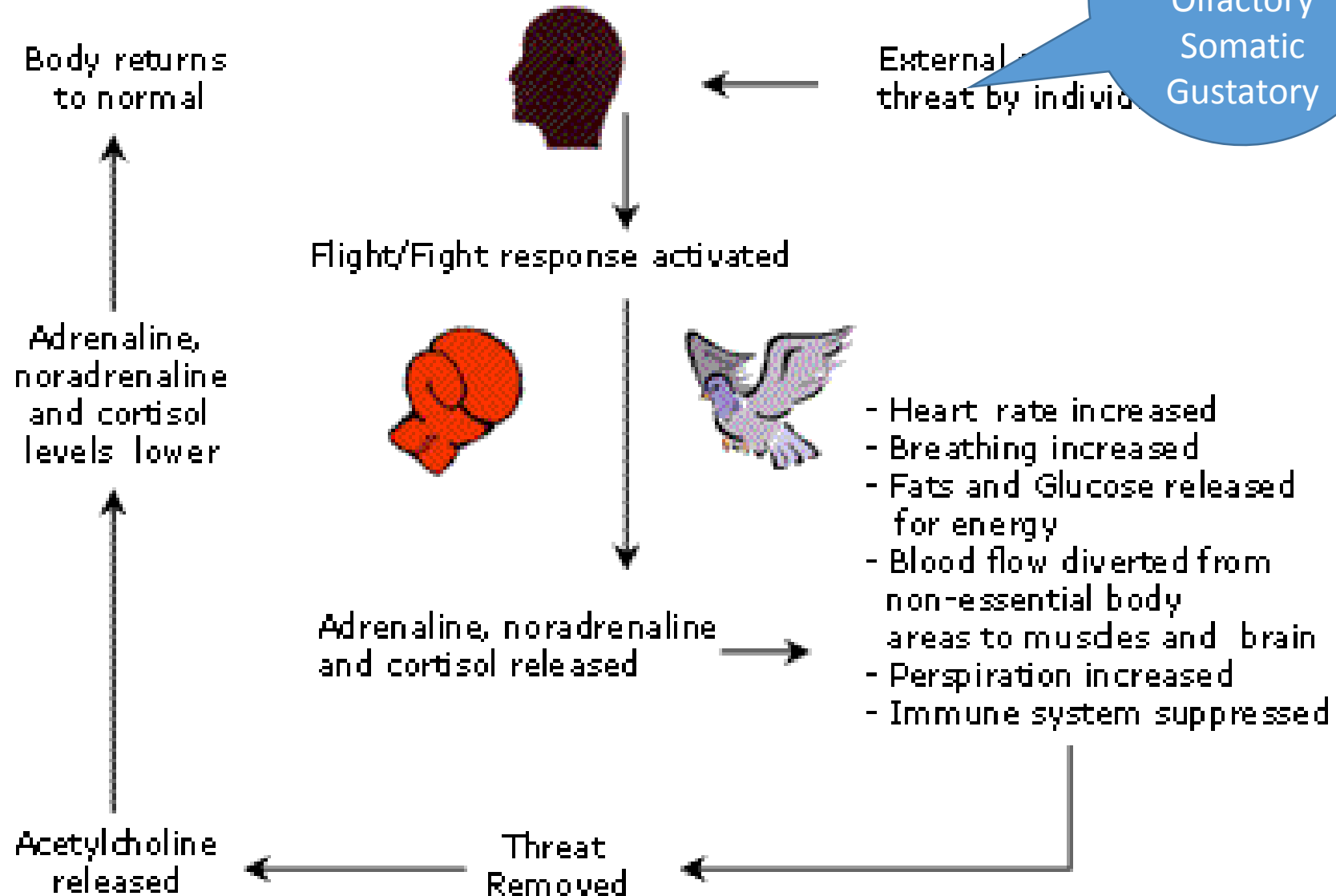


Inflammation is only part of the story

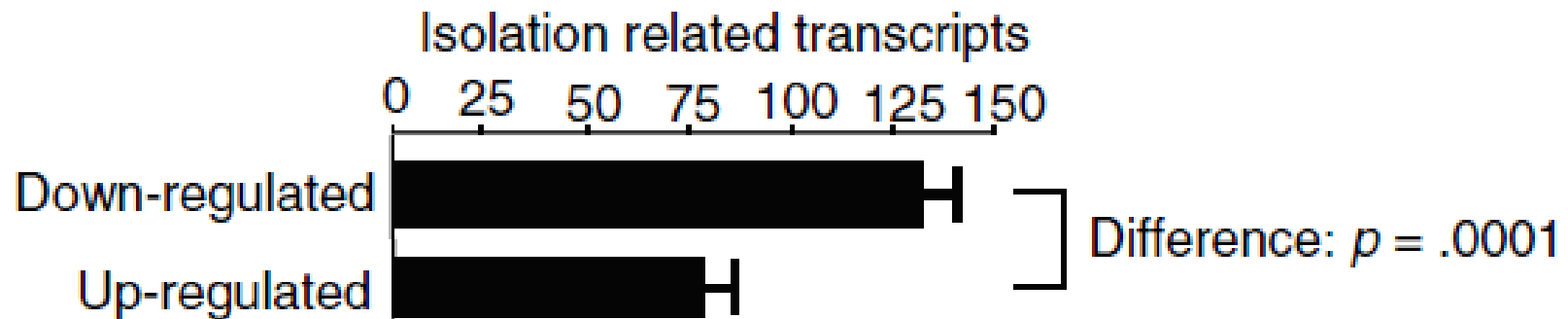
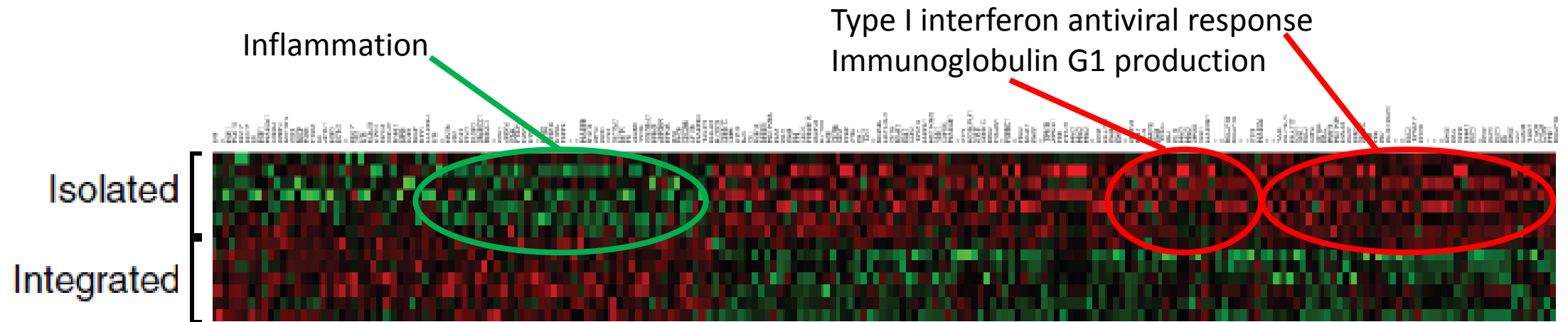


Normal Stress Response

Visual
Auditory
Olfactory
Somatic
Gustatory

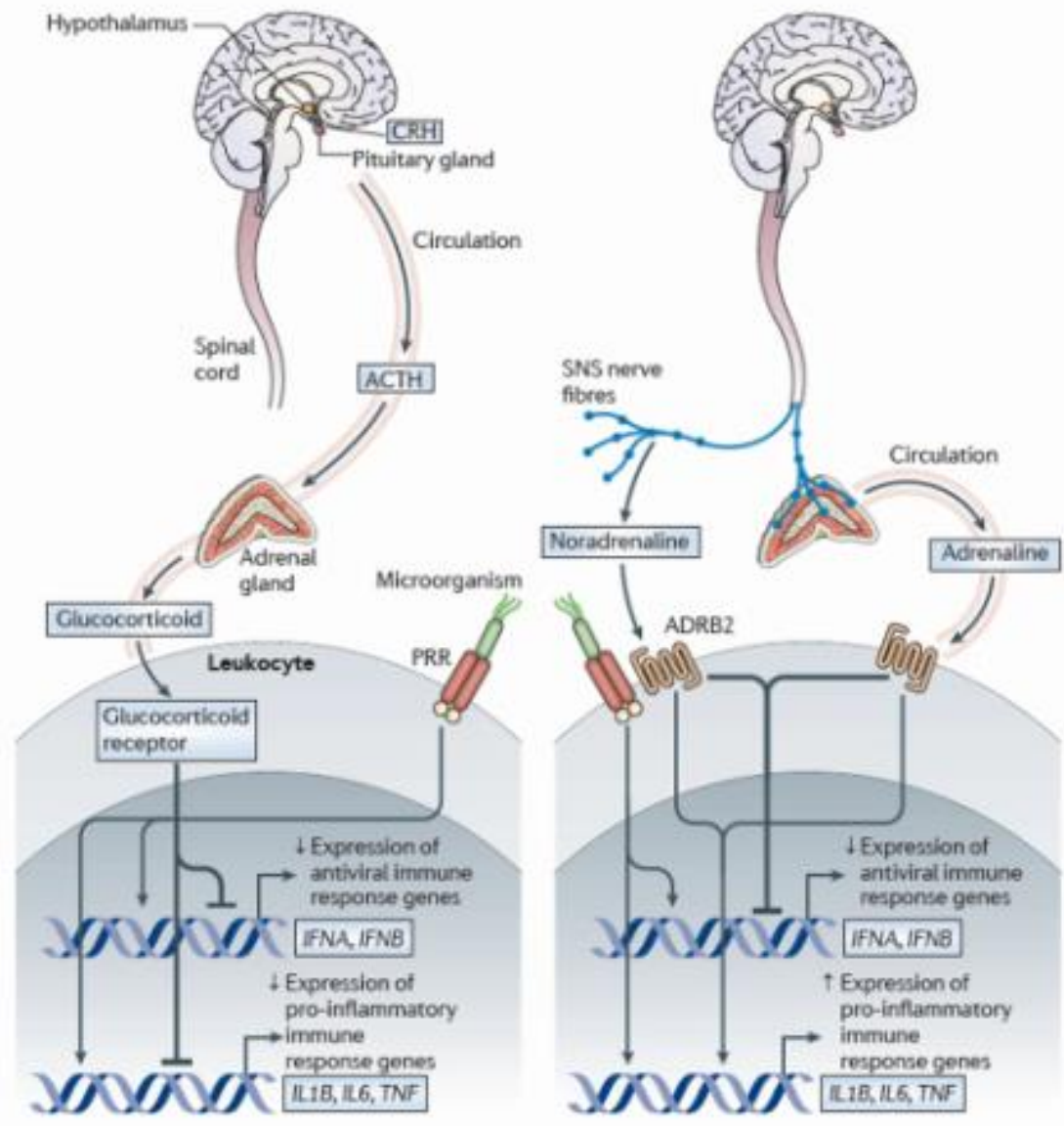
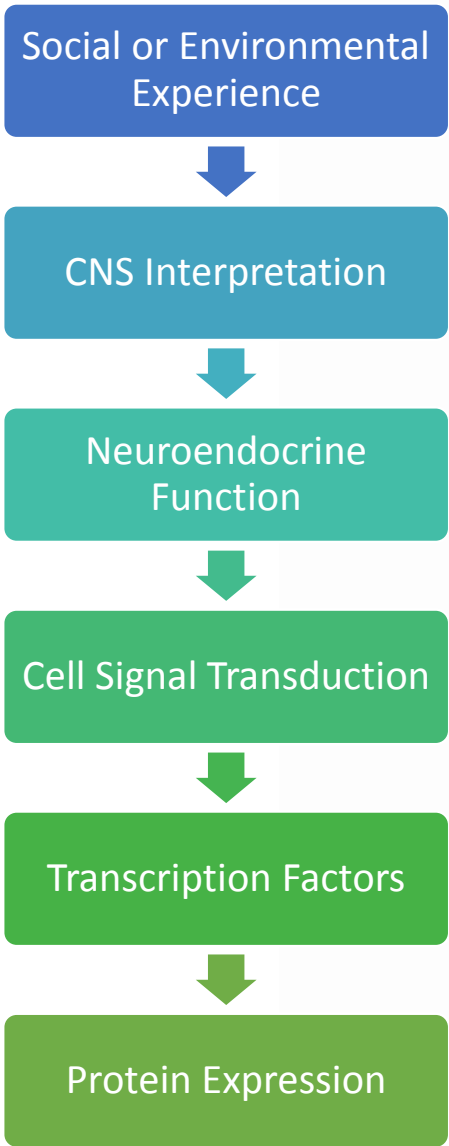


The Stress Response Influences Immunity and Inflammation



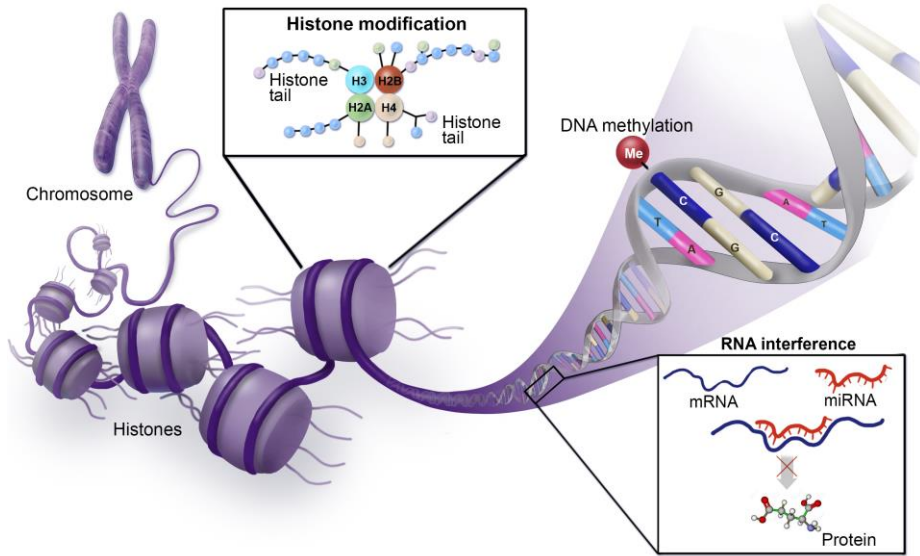
Extreme Acute Stress

Chronic Stress



Irwin & Cole. Nature Reviews Immunology 2011

Epigenetic Modification Can Be Durable



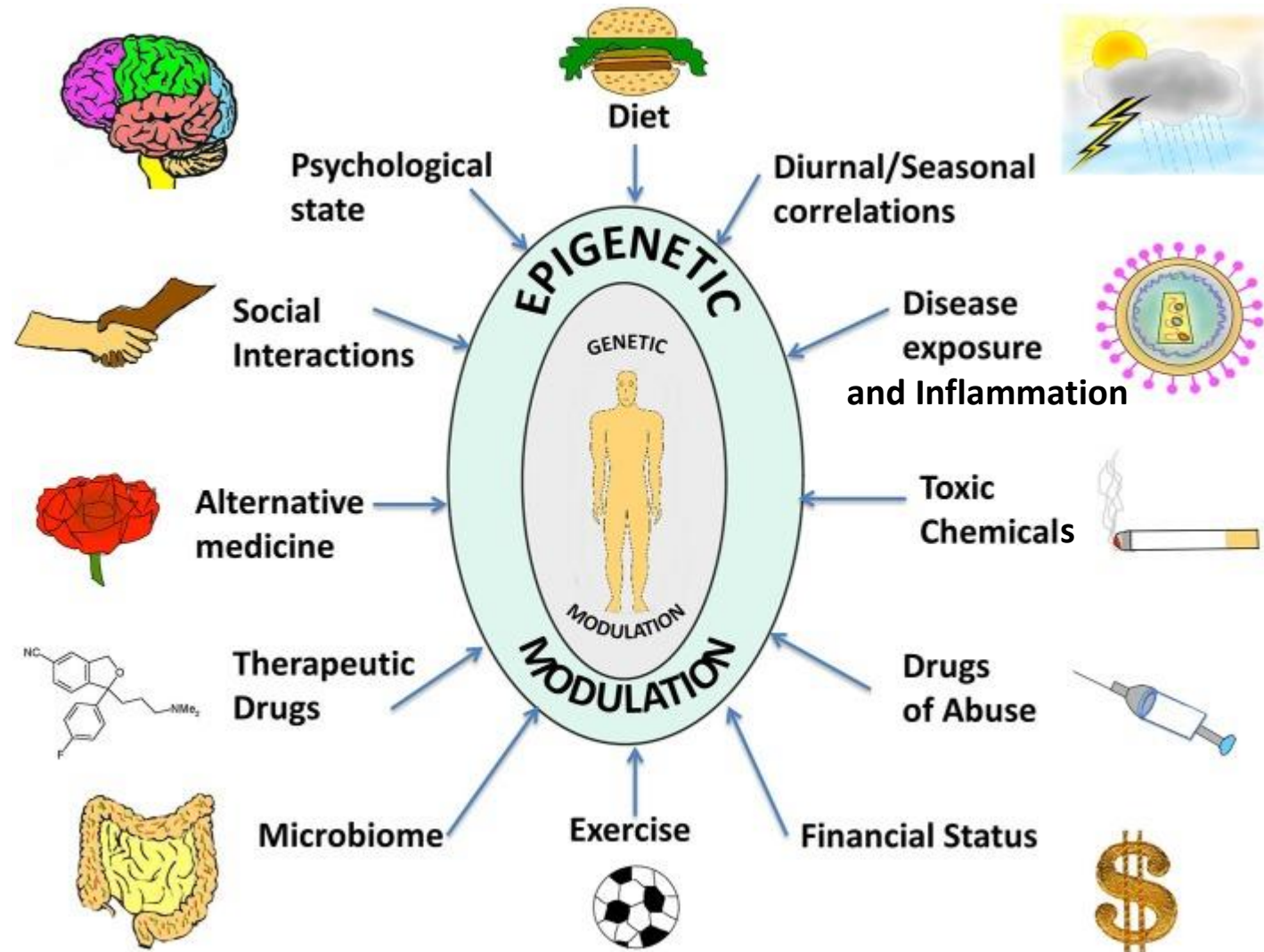
Epigenetics 10:10, 893-902; October 2015; © 2015 Taylor & Francis Group, LLC

Maternal psychosocial stress during pregnancy alters the epigenetic signature of the glucocorticoid receptor gene promoter in their offspring: a meta-analysis

H Palma-Gudiel¹, A Córdova-Palomera^{1,2}, E Eixarch^{3,4}, M Deuschle⁵, and L Fañanás^{1,2,*}

¹Anthropology Unit; Department of Animal Biology, Faculty of Biology; and Instituto de Biomedicina (IBUB); Universidad de Barcelona (UB); Barcelona, Spain; ²Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); Madrid, Spain; ³Fetal i+D Fetal Medicine Research Center; BCNatal - Barcelona Center for Maternal-Fetal and Neonatal Medicine; Hospital Clinic and Hospital Sant Joan de Deu; IDIBAPS; University of Barcelona; Barcelona, Spain; ⁴Centre for Biomedical Research on Rare Diseases (CIBER-ER); Madrid, Spain; ⁵Central Institute of Mental Health; Faculty of Medicine Mannheim; University of Heidelberg; Heidelberg, Germany

Change in birth outcomes among infants born to Latina mothers after a major immigration raid (Novak *IJE* 2017)

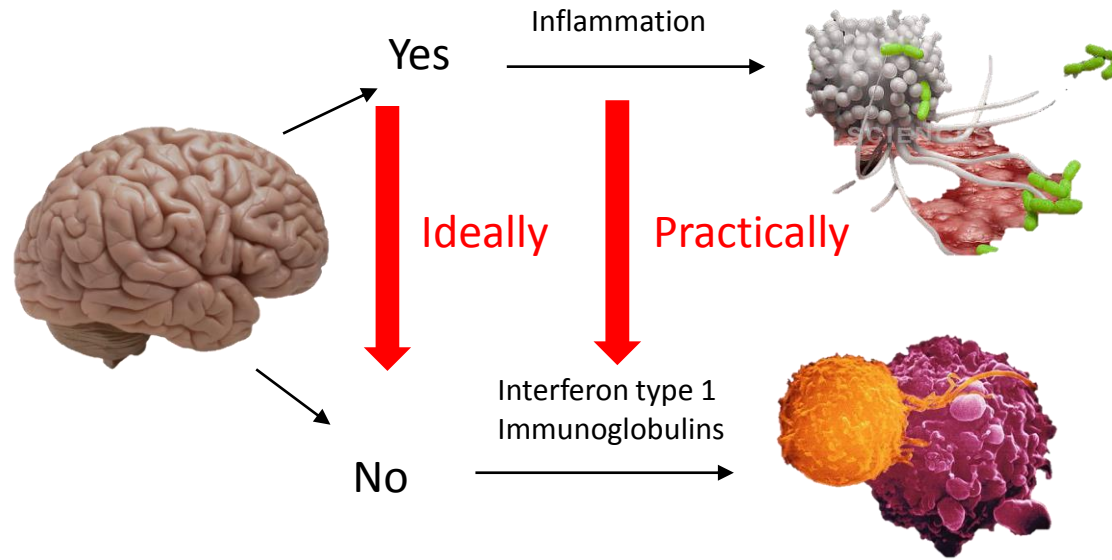


Ancient Humans



Perceived Threat?

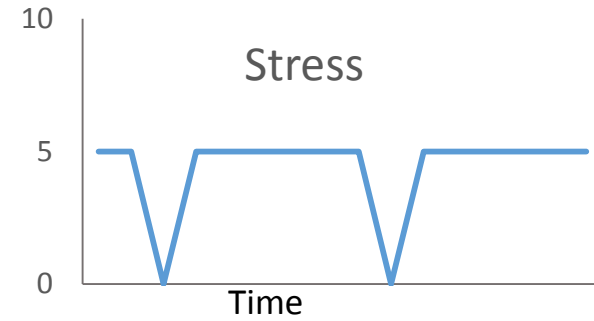
End-organ disease
Susceptible to infections
Autoimmune disorders



Goal →

Less end-organ disease
Resistant to infections
Increased longevity

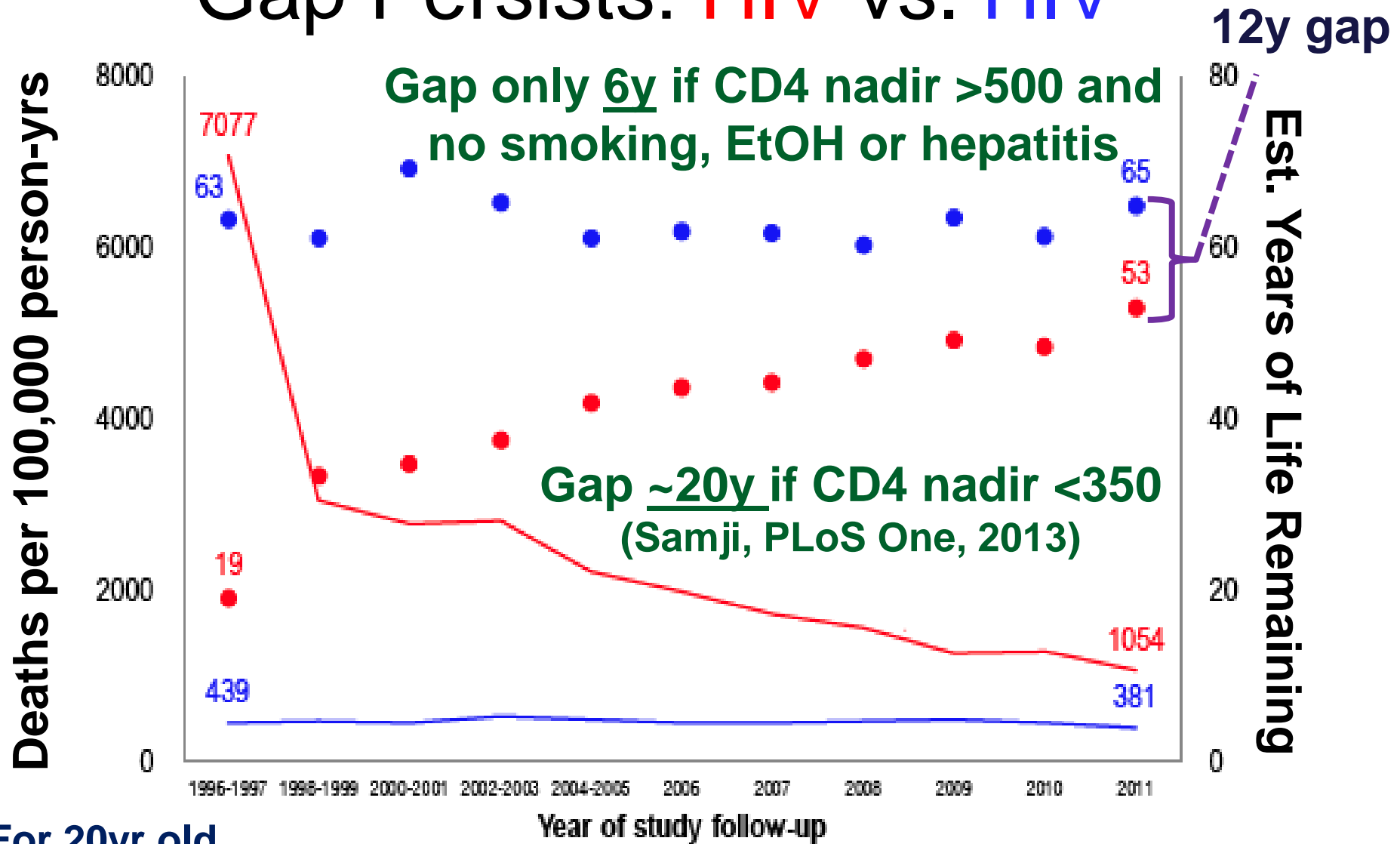
Modern Humans



HIV as a Model for Aging



Improved Life Expectancy*, but Gap Persists: HIV vs. HIV-

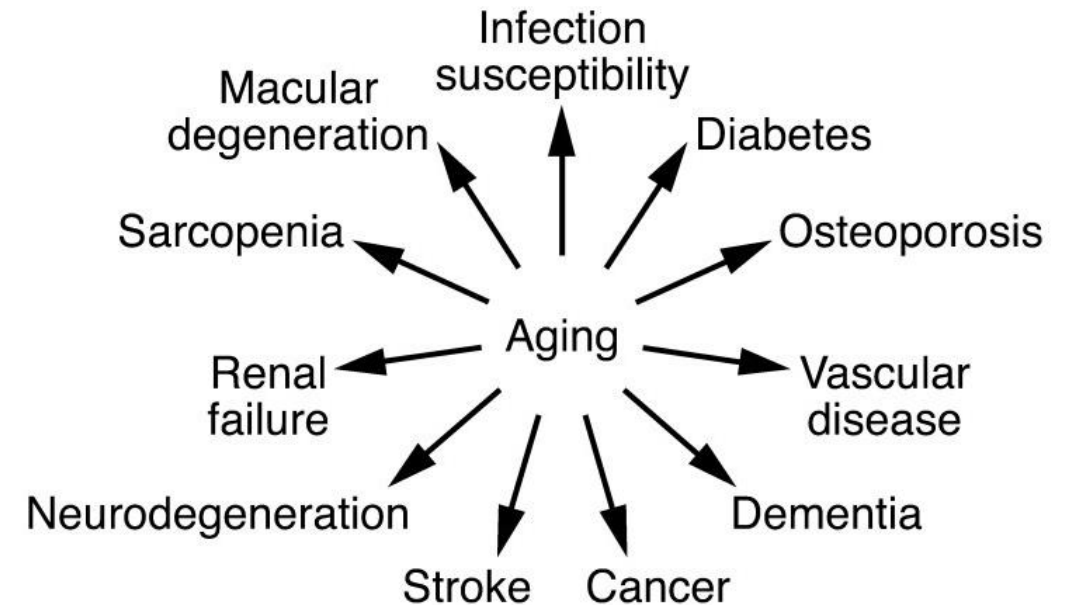


*For 20yr old

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

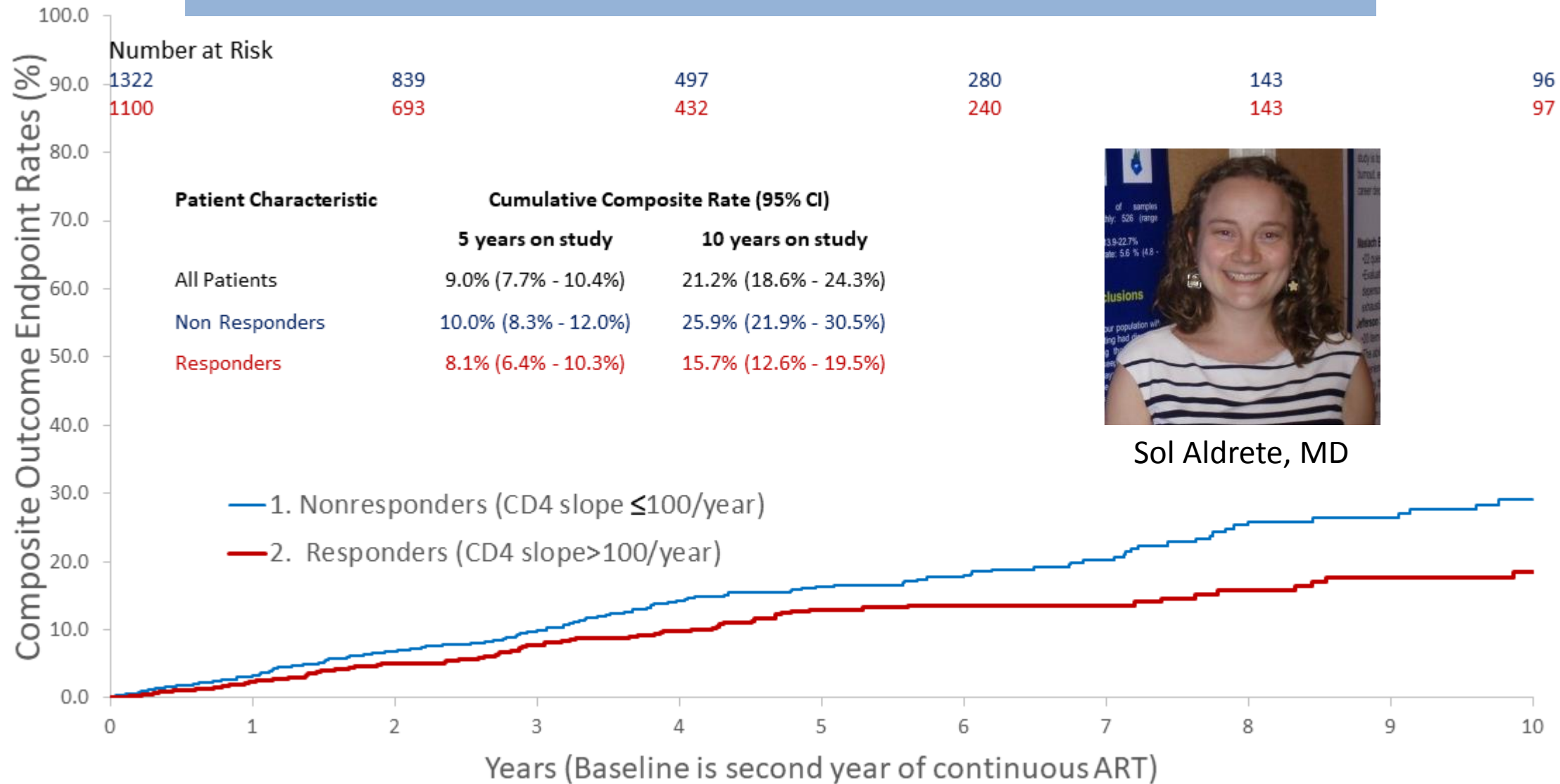
Many age-associated comorbidities are **increased** in treated HIV

- 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]
- Frailty [11]



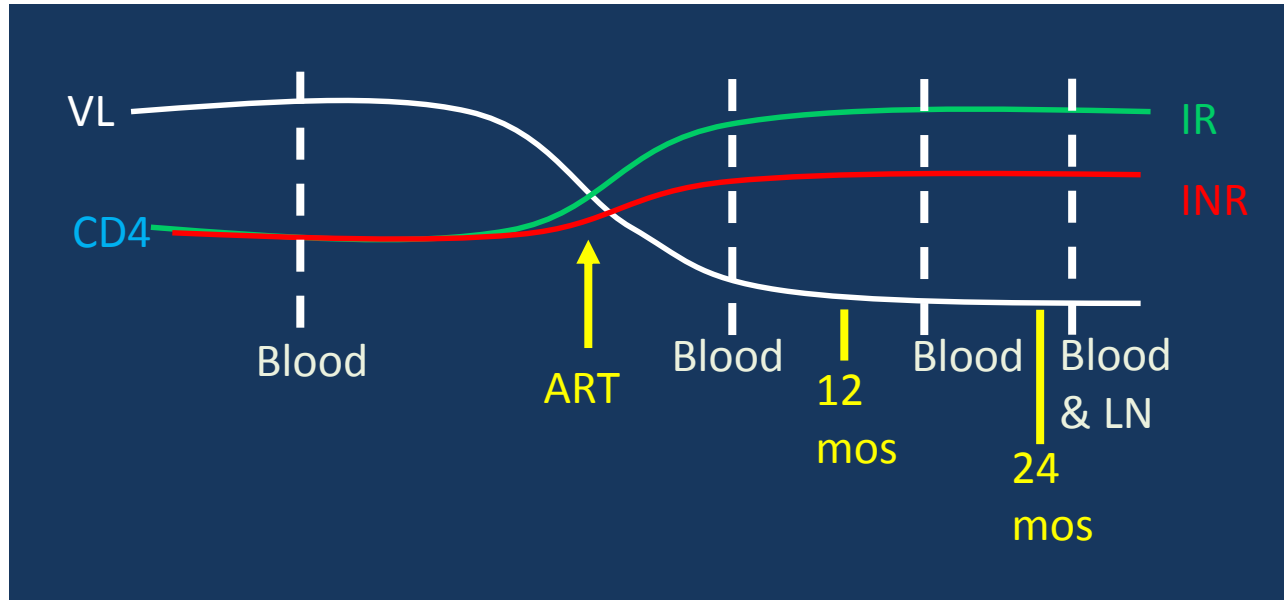
1. Freiberg, M., et al. JAMA Int Med. 2013;173(8):614-22. 2; Tseng, Z, et al. JACC. 2012;59(21):1891-6. 3. Grinspoon SK, et al. Circulation. 2008;118:198-210. 4. Silverberg, M., et al. AIDS, 2009;23(17):2337-45. 5. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504. 6. Arnsten JH, et al. AIDS. 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

CD4 Recovery Predicts End-Organ Disease



Sol Aldrete, MD

Central Memory T Cell Study



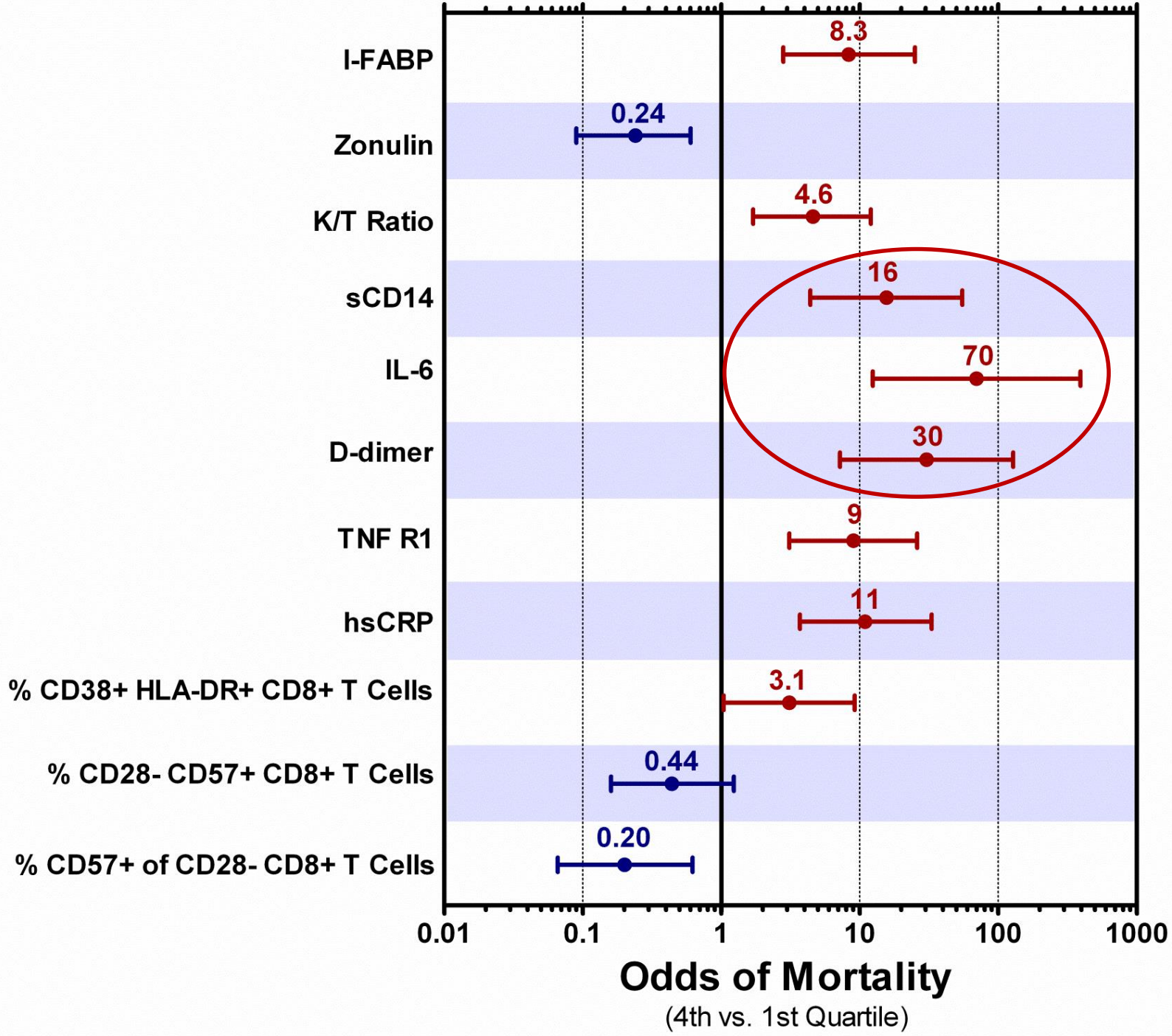
Mirko Paiardini, PhD

- IR and INR at the following time points
 - One Pre-ART
 - 2-3 Post-ART

Inflammation **Predicts** Disease and Mortality in Treated HIV Infection

- **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)
- **Mortality** (Kuller, PLoS Med, 2008; Tien, JAIDS, 2010; Tenorio, JID 2014; Hunt, JID 2014)

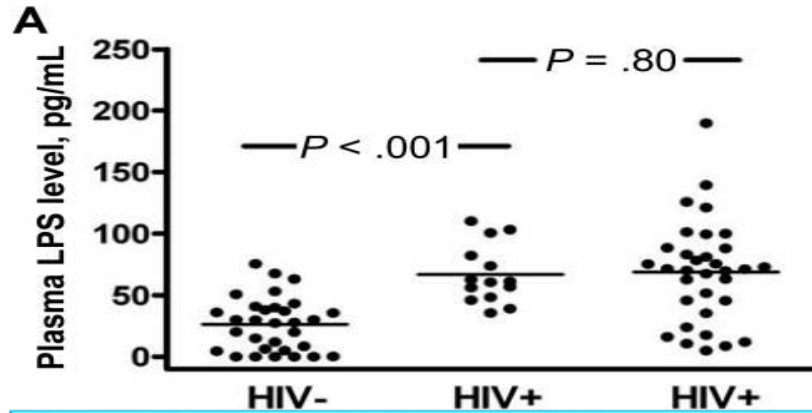




Hunt *JID* 2014
 Tenorio *JID* 2014
 French *AIDS* 2015

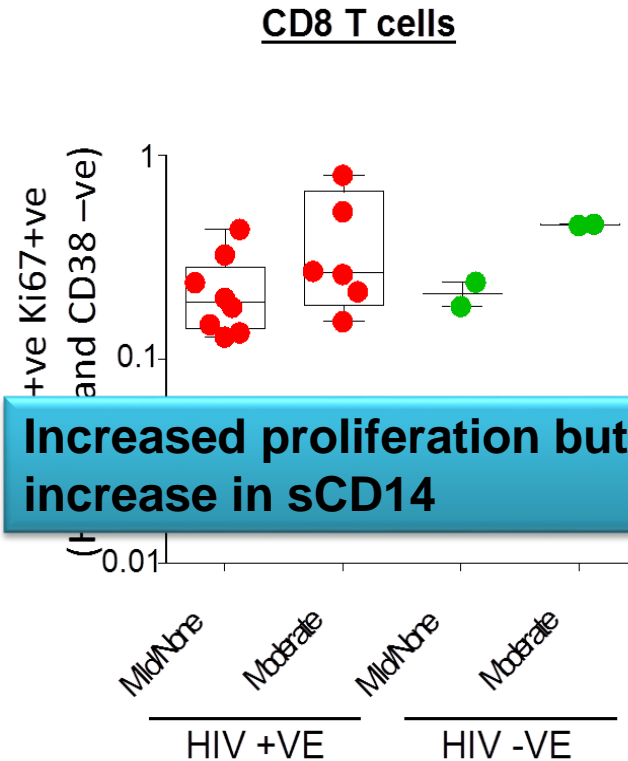
Microbial Translocation

Gastrointestinal



Plasma LPS correlates with HIV infection and CD8 TCA but not VL

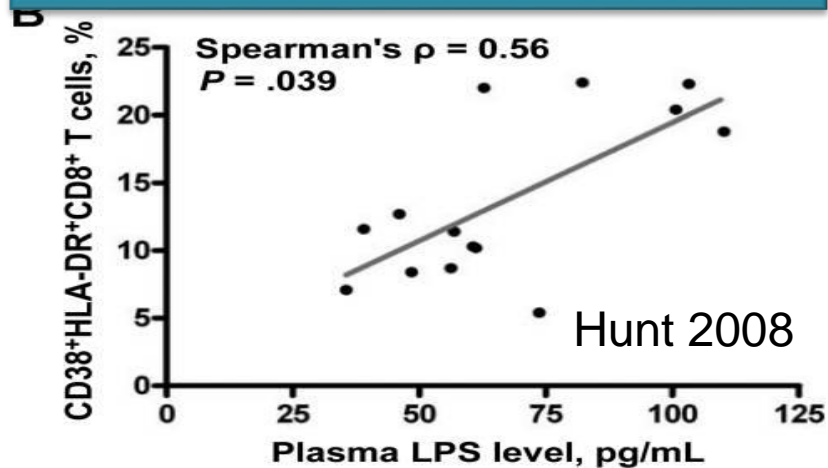
Periodontal/Oral



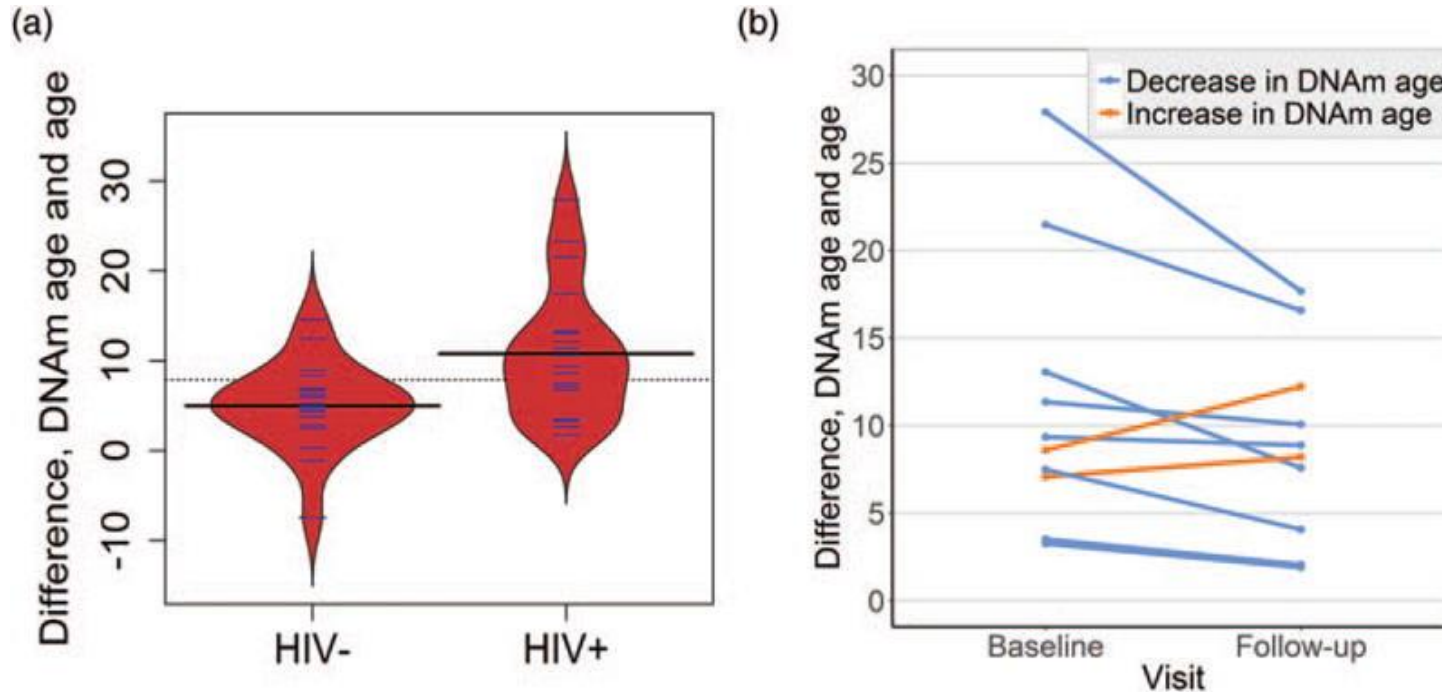
Increased proliferation but no increase in sCD14

Noguera-Julian *Medicine* 2017

CD8 TCA

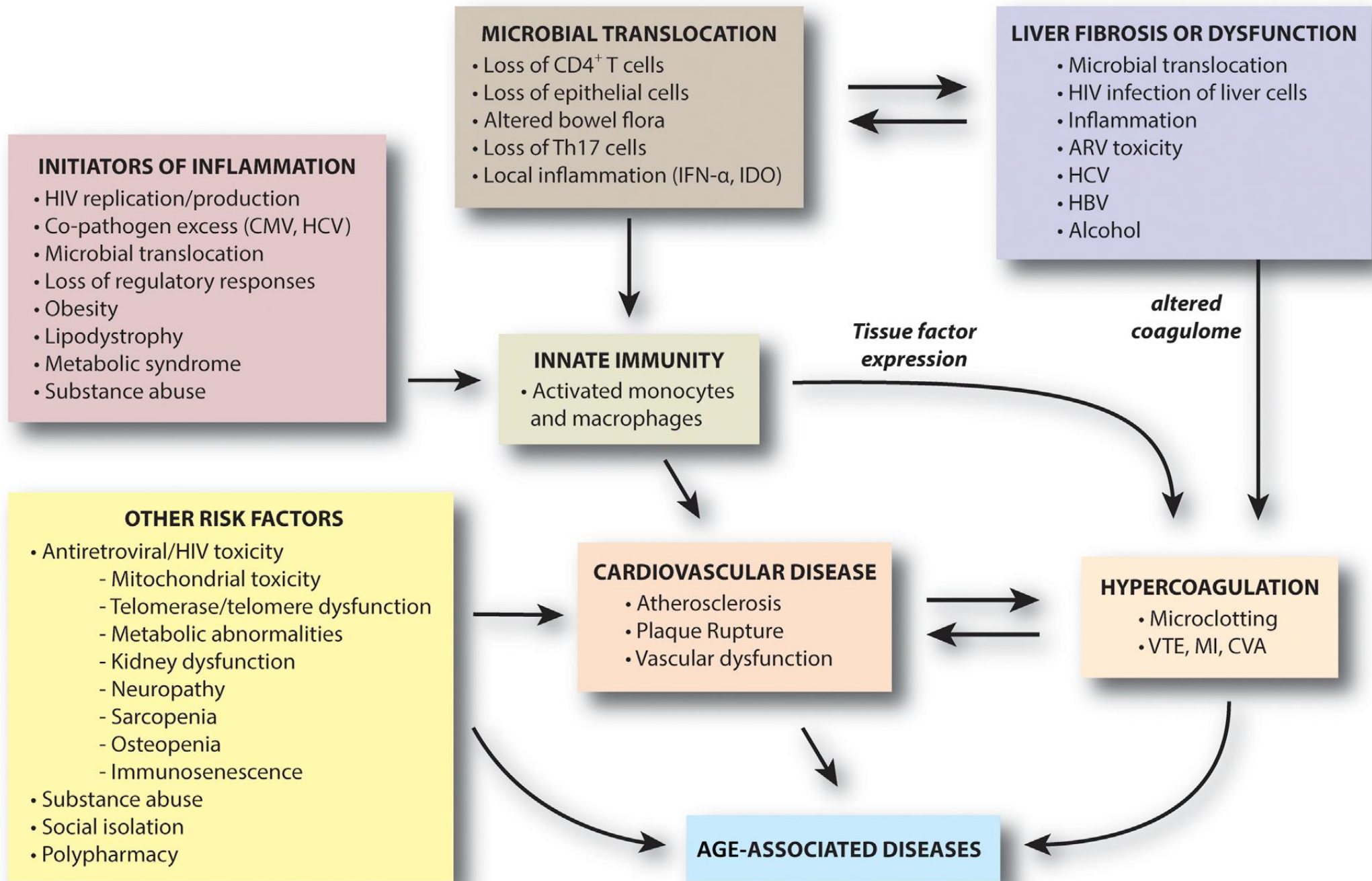


HIV+ DNA Methylation Clock older and associated with Inflammatory Genes



Yan Sun, PhD

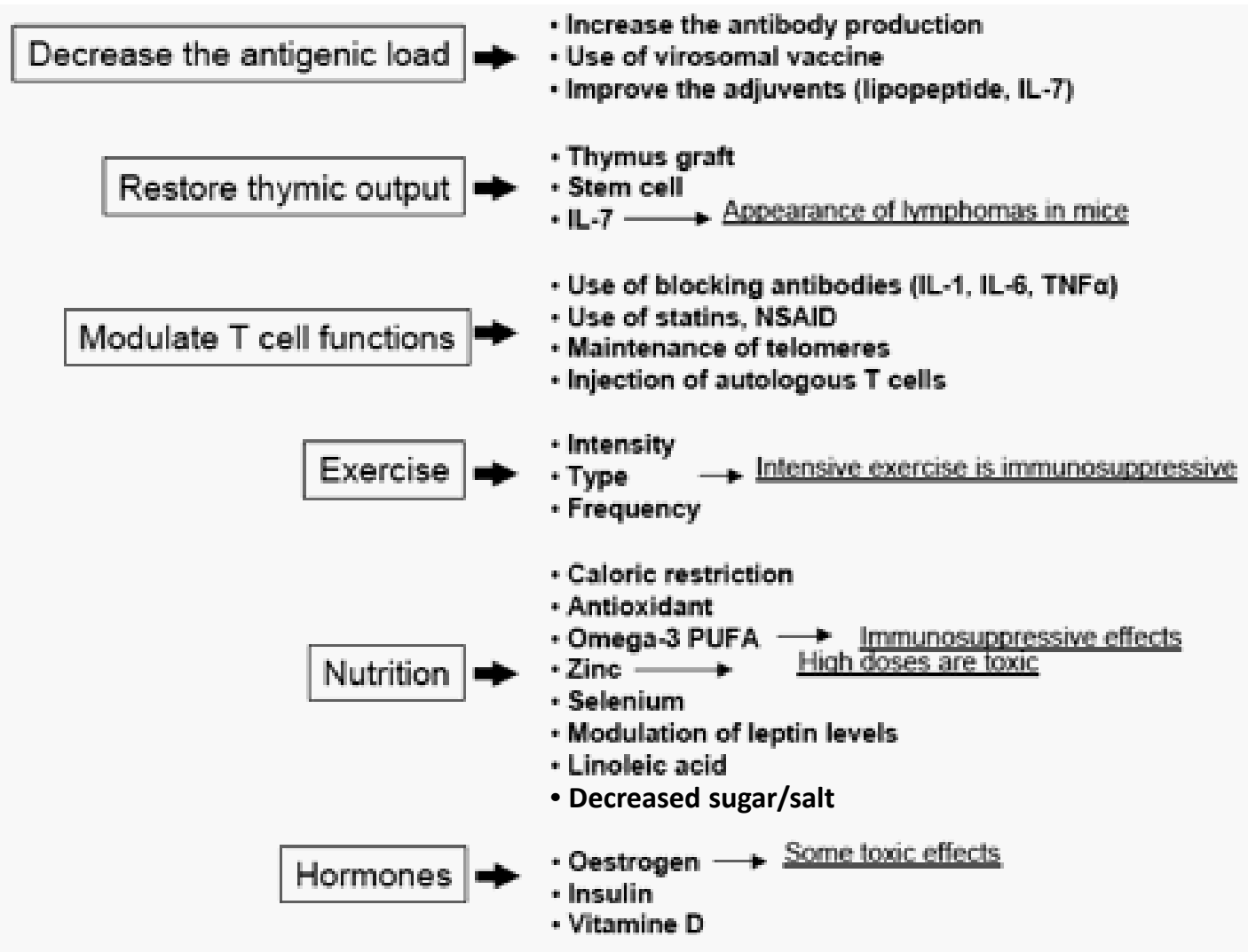
- DNAm age “biological aging” for HIV+ 11.2 years greater than matched HIV- (pre-ART)
- Most HIV+ approached HIV- levels after 9 years of ART; 2 increased in DNAm age
- Methylated sites were associated with inflammatory genes
- VPS37B significant: vesicular trafficking protein involved in HIV budding and transport



Interventions



Aging Interventions



Current Inflammation Strategies

Target	Drug or Intervention
residual or cryptic HIV replication	treatment intensification, optimized antiretroviral drug tissue penetration, novel antiretroviral drugs
excess copathogen burden	valacyclovir (HSV), valganciclovir (CMV), HCV cure
microbial translocation	sevelamer, rifaximin, mesalamine, isotretinoin, prebiotics, probiotics, colostrum
poor T cell function	interleukin-7, growth hormone, anti-PD1 antibodies
lymphoid and tissue fibrosis	perfenidone, ACE inhibitors, angiotensin II receptor blockers
chronic inflammation	HMG CoA reductase inhibitors ("statins"), chloroquine, hydroxychloroquine, celecoxib (COX-2 inhibitors), aspirin, methotrexate, lenalidomide, leflunomide, ruxolitinib (JAK inhibitors), sirolimus (mTOR inhibitors), IDO inhibitors, anti-interferon-alpha antibodies, anti-IL-6 antibodies, anti-IL-1-beta antibodies
hypercoagulation	aspirin, apixaban, dabigatran
cellular aging	sirtuin activators, sirolimus
metabolic syndrome, obesity	metformin, exercise, diet, vitamin D

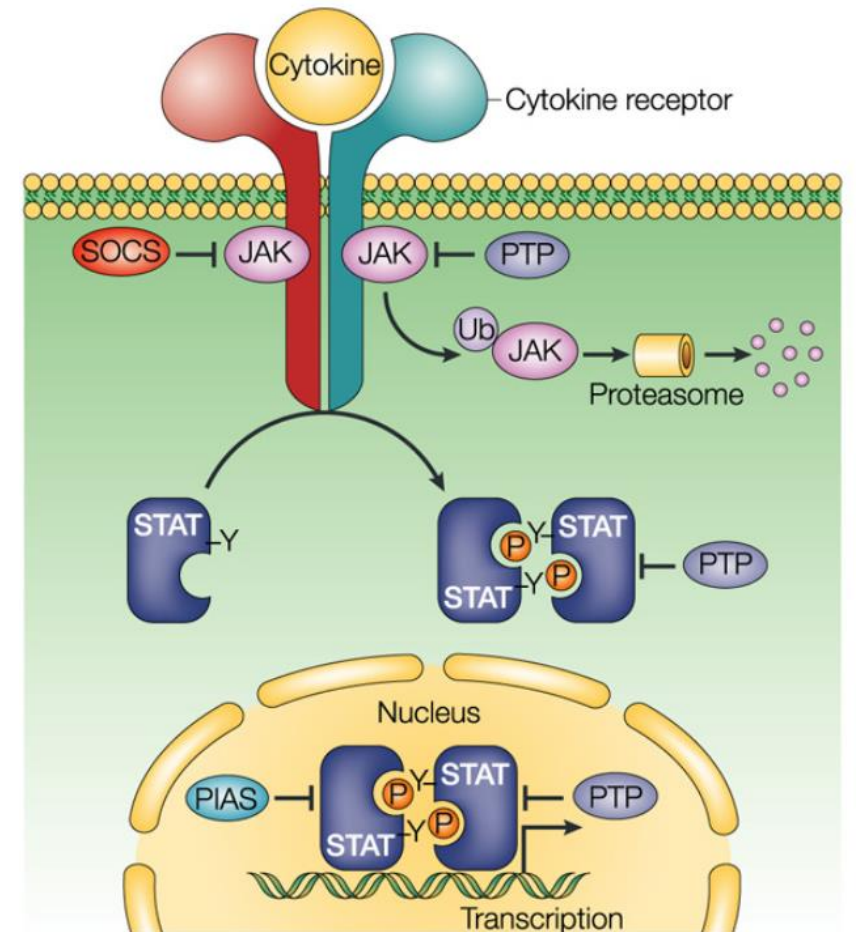
IL-21

Drugs aimed at reversing inflammation or its immediate consequences in antiretroviral-treated HIV infection are listed. Those drugs in more advanced stages of development (phase I/II) are listed first, followed by those that are still in development.

Deeks *Immunity* 2013
 Paiardini *PLoS Path* 2013
 Micci *JCI* 2015
 Funderburg *JAIDS* 2015
 Marconi *ACTG* 5336
 Henrich *ACTG* 5337

JAK-STAT signaling key mechanism for HIV disease

- Increased TNF- α , IL-1 α/β , IL-6, IL-7, IL-15 which promote:
 - Activation of latently infected and bystander uninfected cells
 - Homeostatic proliferation and cell survival
 - Recruitment of uninfected cells to sites with infected cells
 - Trafficking activated infected monocytes via BBB
 - Associated with increased end-organ disease
- STAT binding sites HIV-1 LTR



ACTG A5336 - Background and Rationale

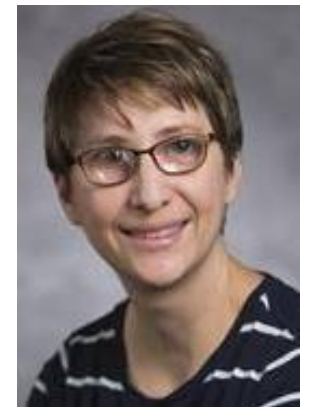
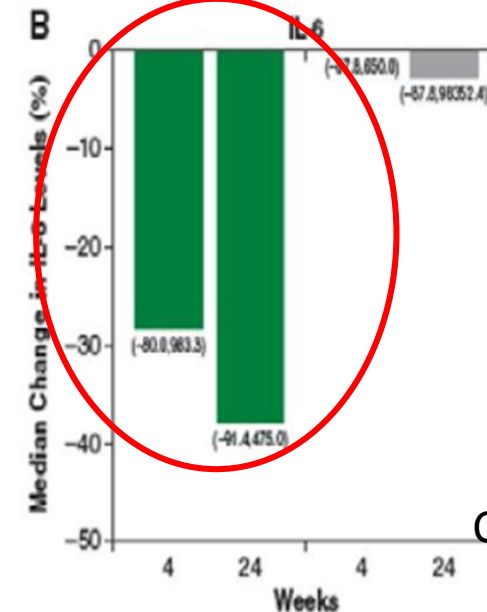
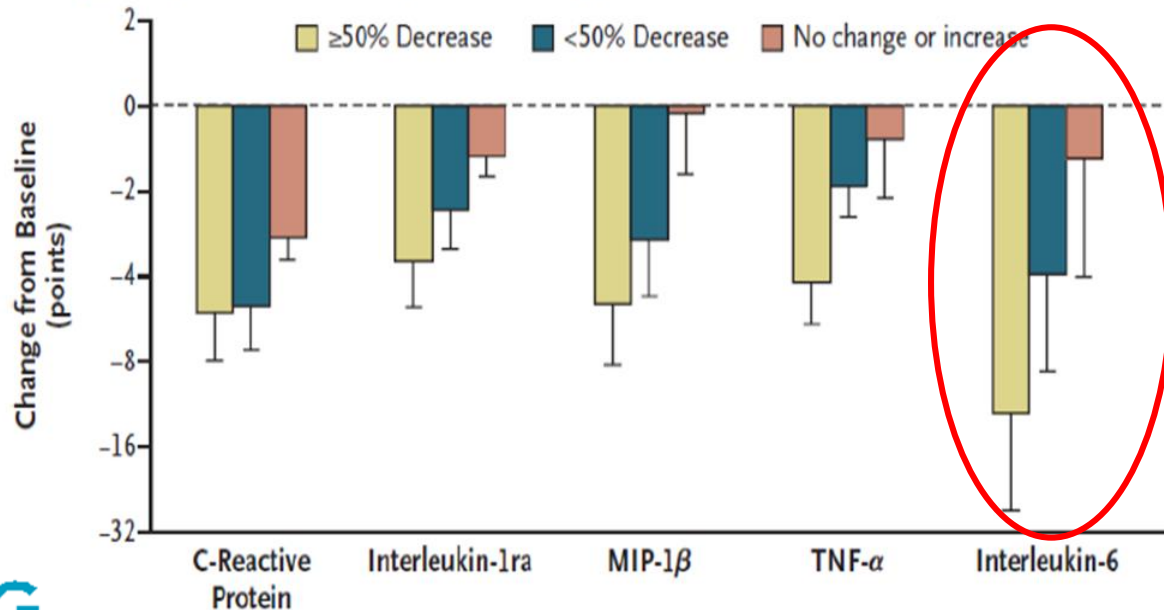
Ruxolitinib-Janus Kinase (JAK) 1 and 2 inhibitor

- FDA approved for myelofibrosis and PCV (5-25 mg BID)
- 43 clinical trials for MF, psoriasis, PCV, and rheumatoid arthritis*
- Marked decrease in cytokines, especially IL-6**
- Ruxolitinib is a potent inhibitor of HIV-1 replication AND reactivation of latent HIV-1 in primary human lymphocytes and macrophages (*in vitro*)***



Ray Schinazi, PhD

Change in Cytokine Level, 6 Cycles of Therapy for Myelofibrosis



Christina Gavegnano, PhD



*Tam Expert Opin Invest Drugs 2013

**Verstovsek NEJM 2010 and 2012

***Gavegnano PLoS Pathog 2017

Objectives

- Primary Objectives

- Safety and tolerability of ruxolitinib in HIV-1 virologically suppressed PLWH, and changes in IL-6 while receiving ruxolitinib or continuing only ART (open label) – Phase 2a

- Key Secondary Objectives

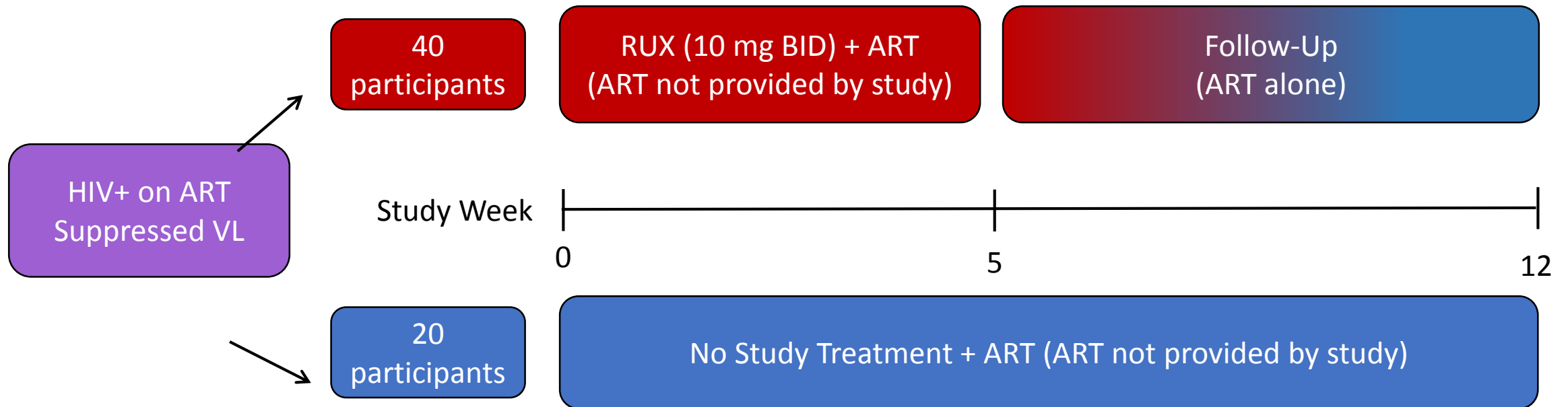
- Changes in T cell counts
- Changes in plasma HIV-1 RNA (single-copy assay)
- Changes in reservoir markers
- Changes in levels of other measures of inflammation and immune activation



Jeffrey Lennox, MD

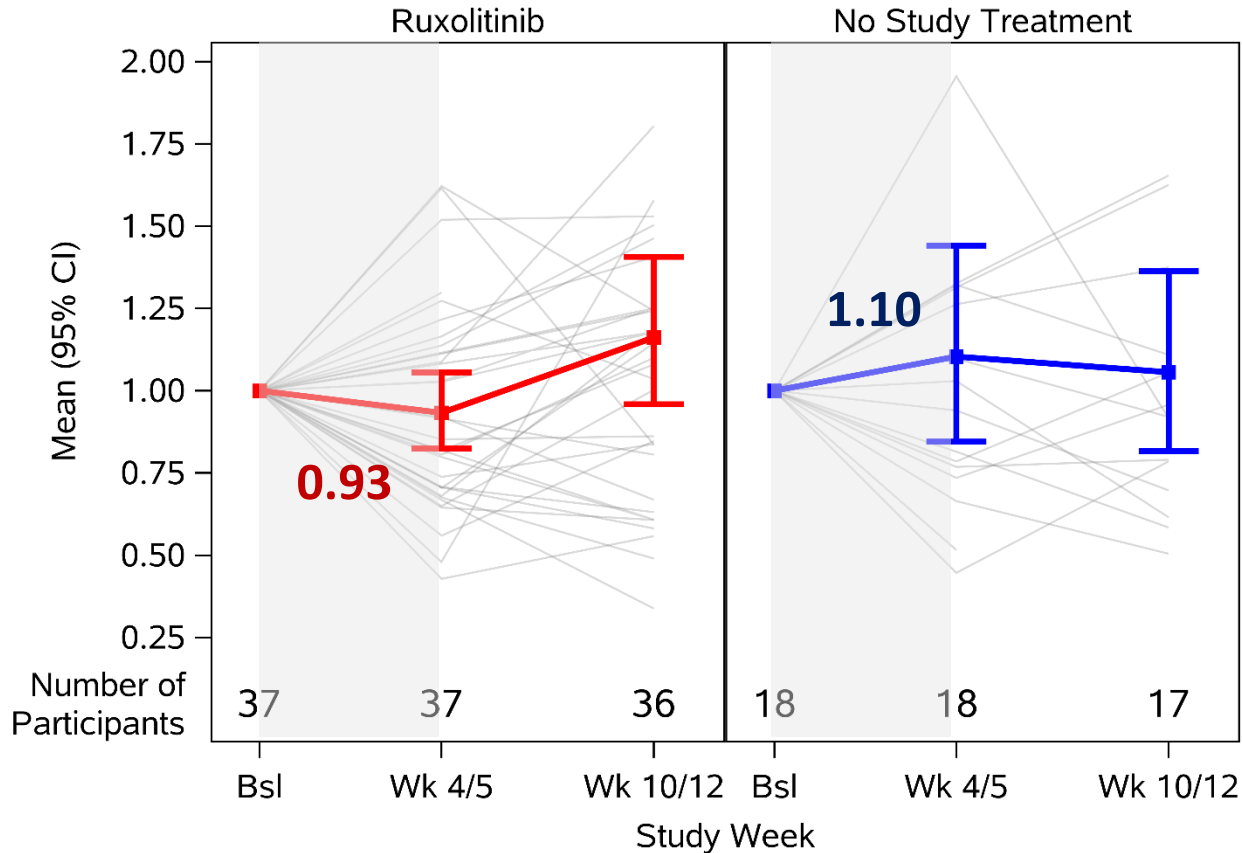
Study Population and Schema

- PLWH and ≥ 18 and < 75 years of age
- On NNRTI or INSTI (without cobicistat) containing ART ≥ 2 years, continuously virologically suppressed and CD4⁺ T cell count > 350 cells/mm³
- No history of, or current, significant medical condition other than HIV or hypertension

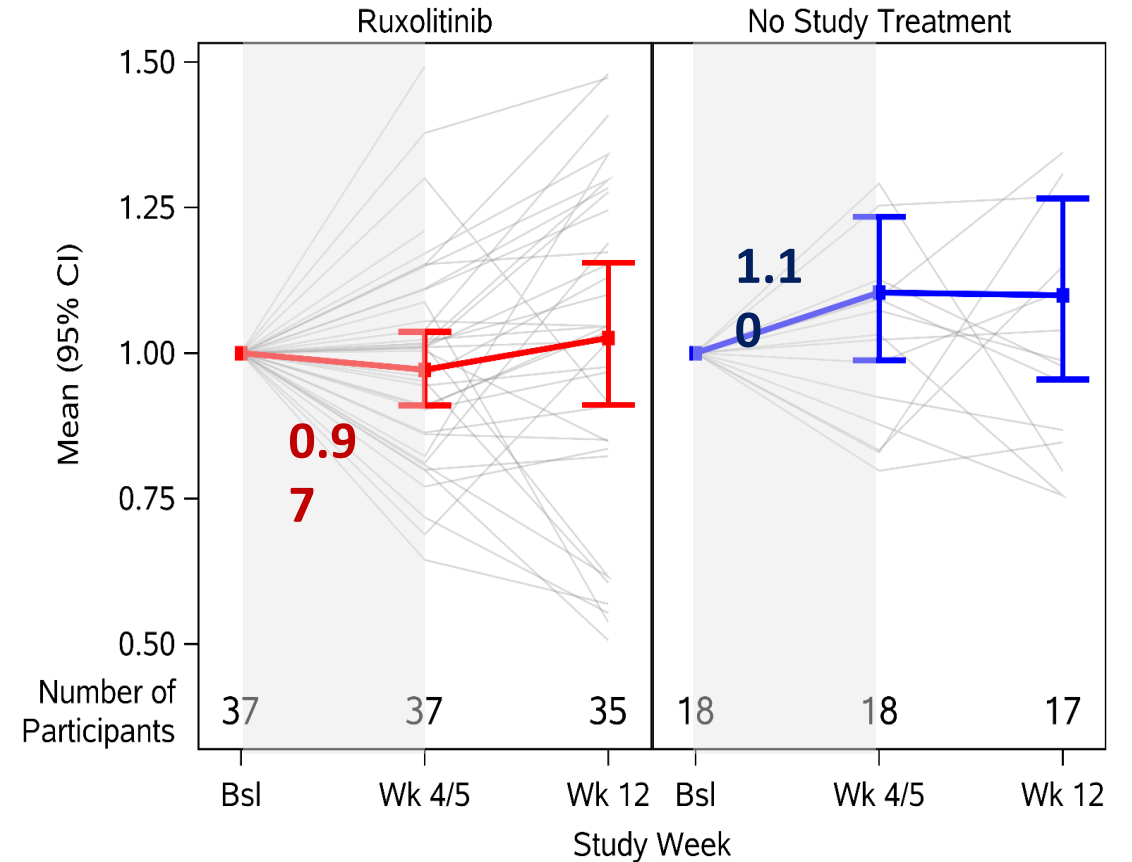


Results – IL-6 and sCD14

Fold Change in IL-6 (pg/mL)



Fold Change in sCD14 (ng/mL)



- No significant difference between arms
 - Mean (90% CI) relative fold change
 - 0.85 (0.69, 1.04)
 - P-value: 0.18

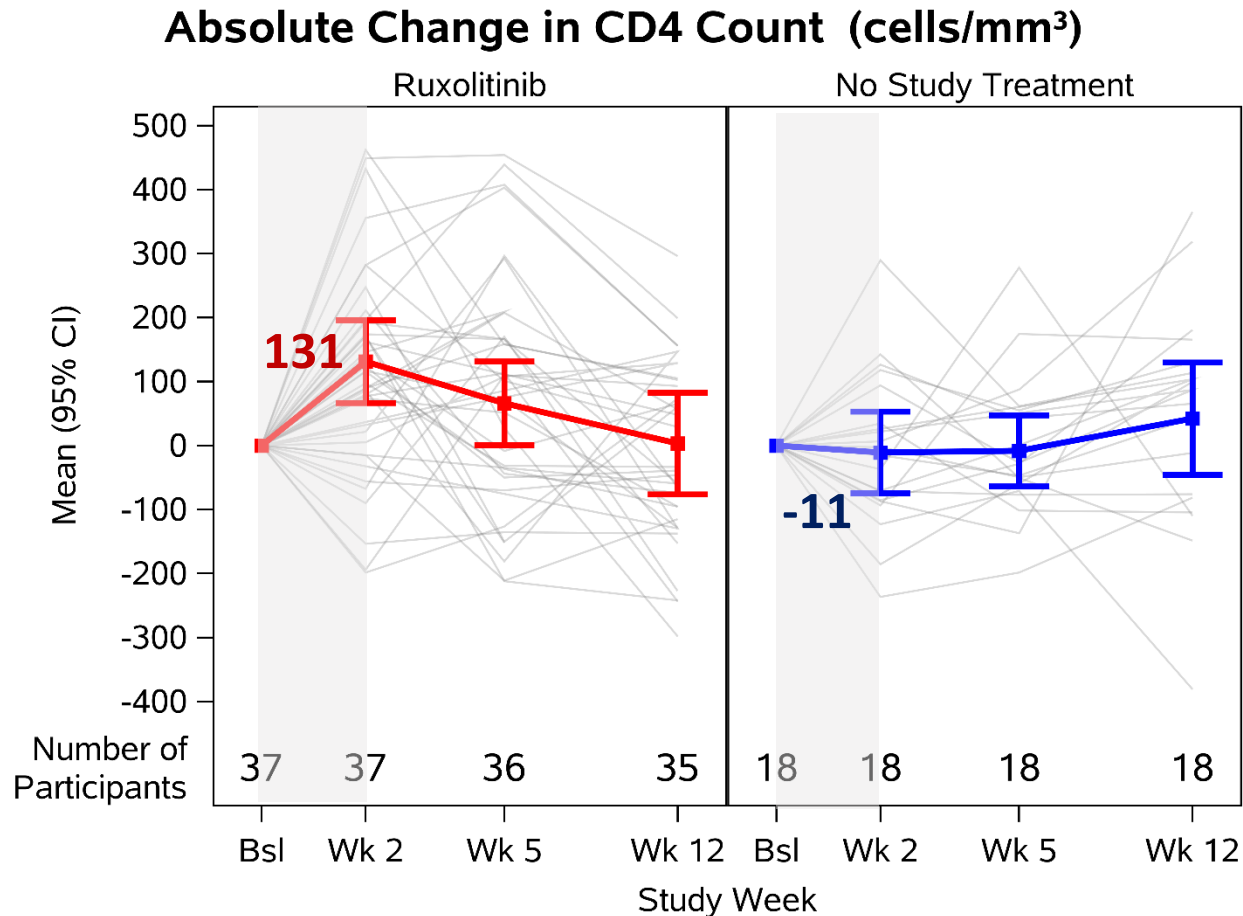
- Significant difference between arms
 - Mean (90% CI) relative fold change
 - 0.88 (0.80, 0.97)
 - P-value: 0.034

Marconi CROI 2019

Results – CD4 Counts



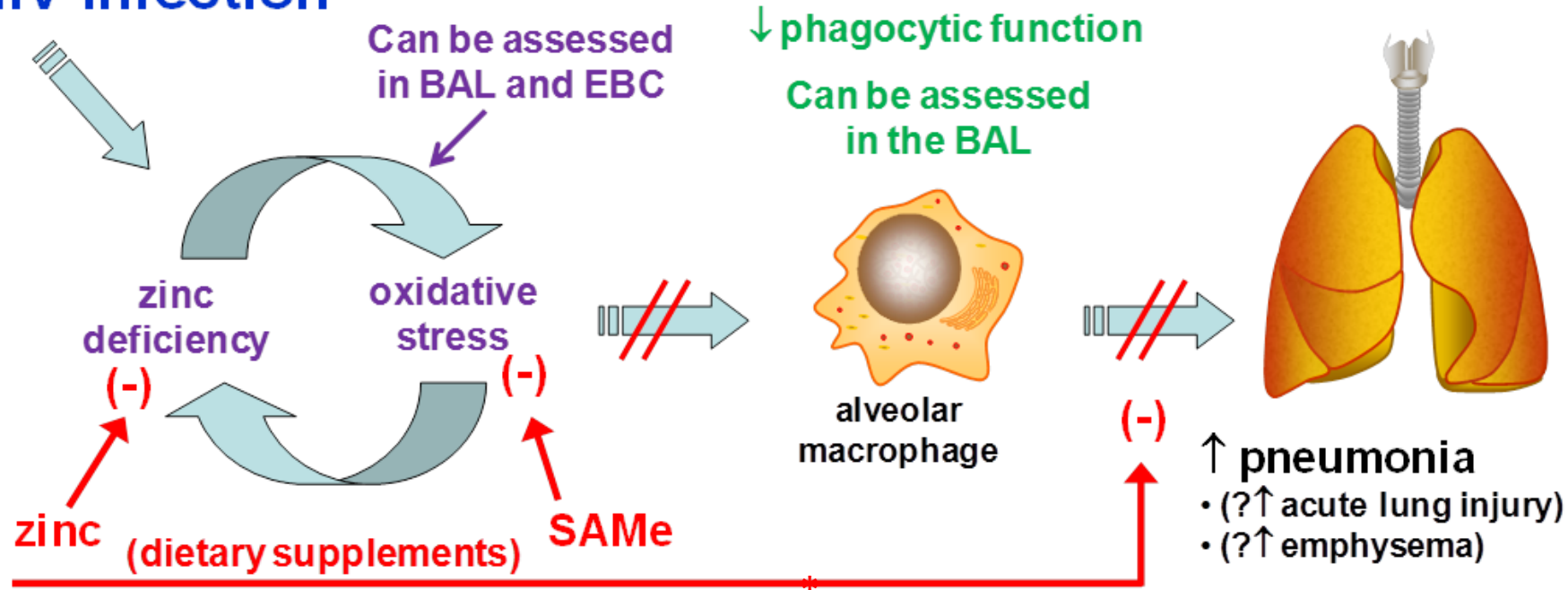
Michael Lederman, MD



- Significant differences between study arms at week 2
 - Mean Difference: 142.1 cells/mm³
 - P-value: 0.007
- Higher (non-significant) RUX differences observed at week 5
 - Mean Difference: 74.3 cells/mm³
 - P-value: 0.14

RAISE/IMMUNE Zinc + SAMe

HIV infection



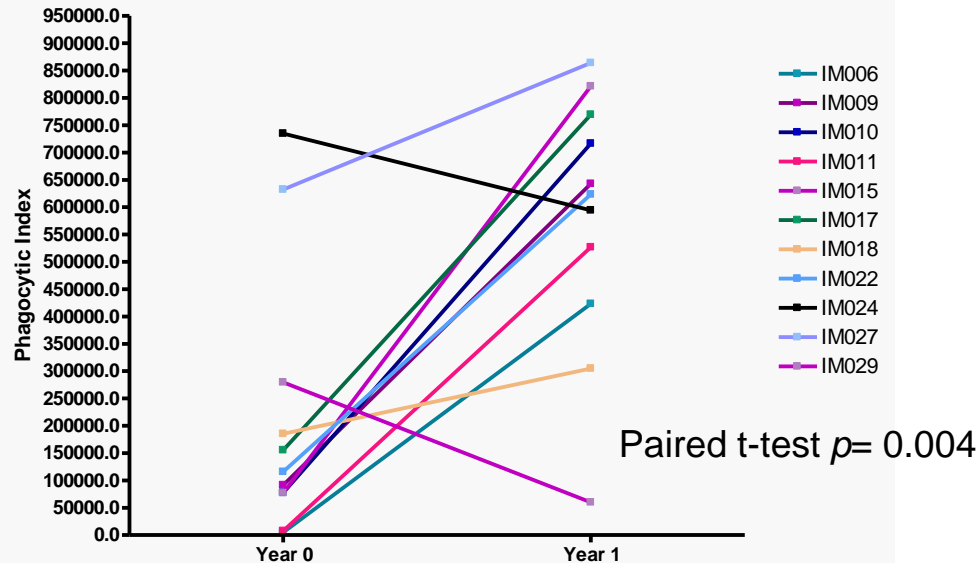
Sushma Cribbs MD

- Immune Non-Responders (20+40) followed 2 years
- S-adenosylmethionine – glutathione (thiol antioxidant) precursor

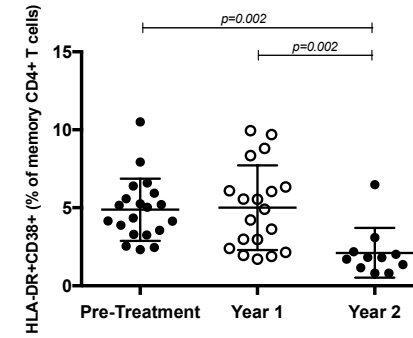
Results

- Large reduction in CD4 and CD8 T cell activation (HLA-DR+CD38+)
- Significant reduction in PD-1+ CD4 and CD8 T cells
- Significant reduction in CD4 proliferation (Ki-67+)
- Increased phagocytic activity

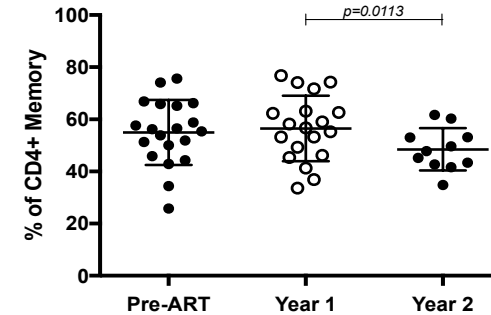
Average Phagocytic Index pre- and post-Zn and SAME oral supplementation



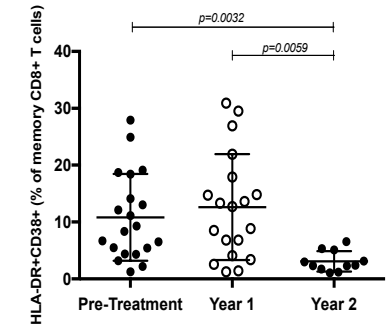
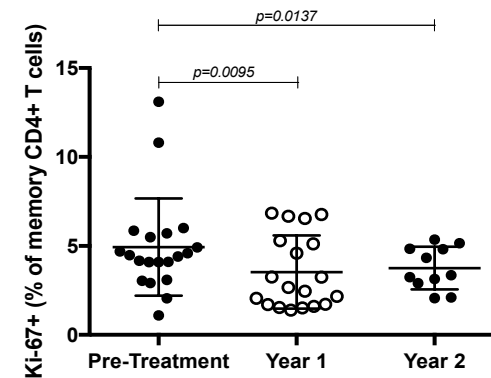
Activation (HLA-DR+ CD38+) in memory CD4+ T cells Activation (HLA-DR+ CD38+) in memory CD8+ T cells



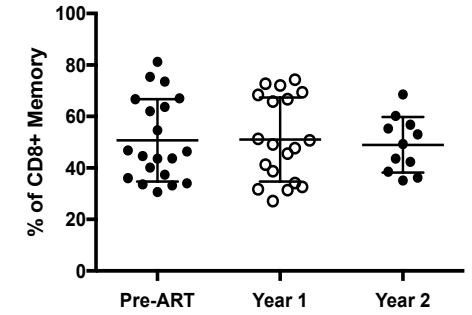
PD1 Expression in CD4+ Total Memory



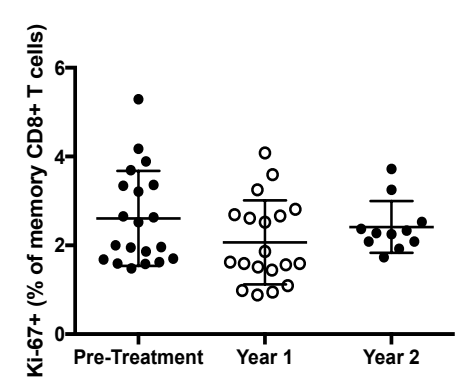
Ki-67 expression in memory CD4+ T cells



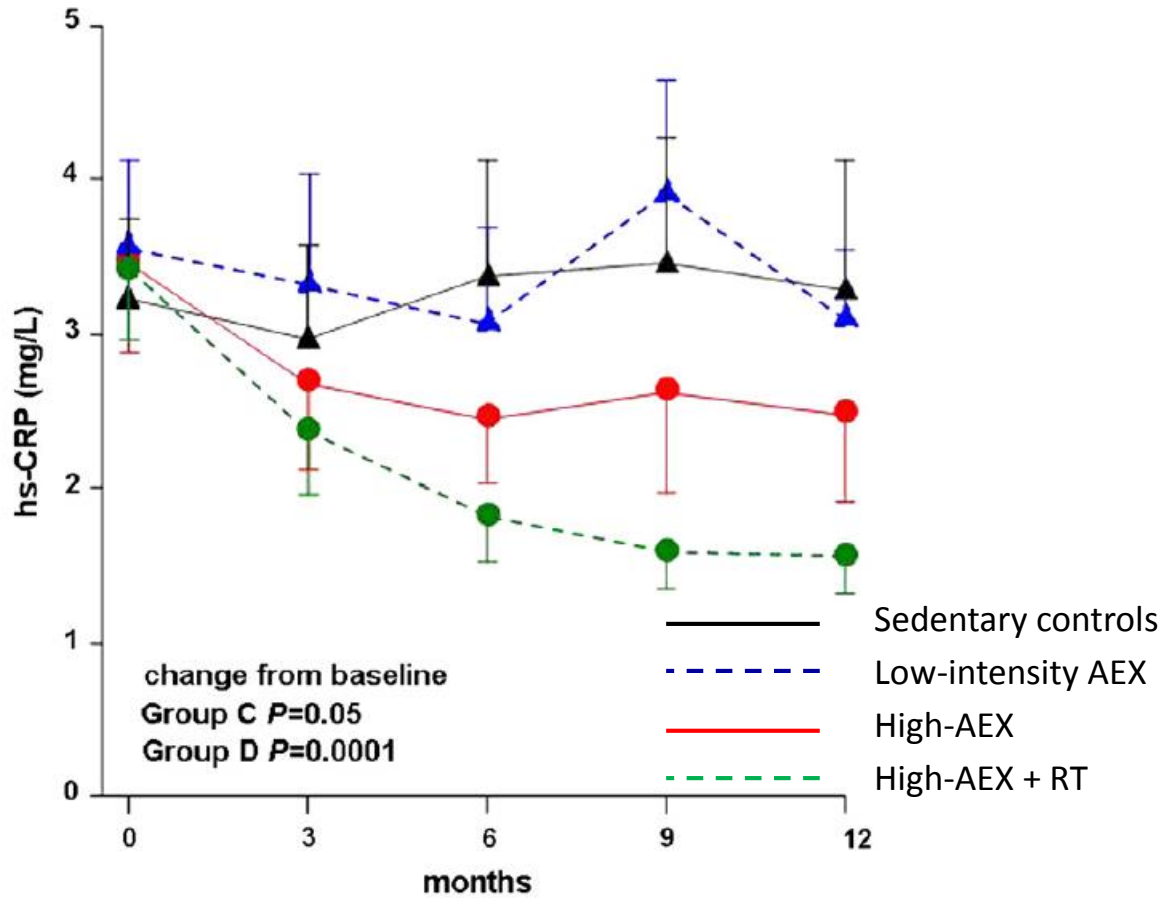
PD-1 Expression in Total CD8+ Memory



Ki-67 expression in memory CD8+ T cells

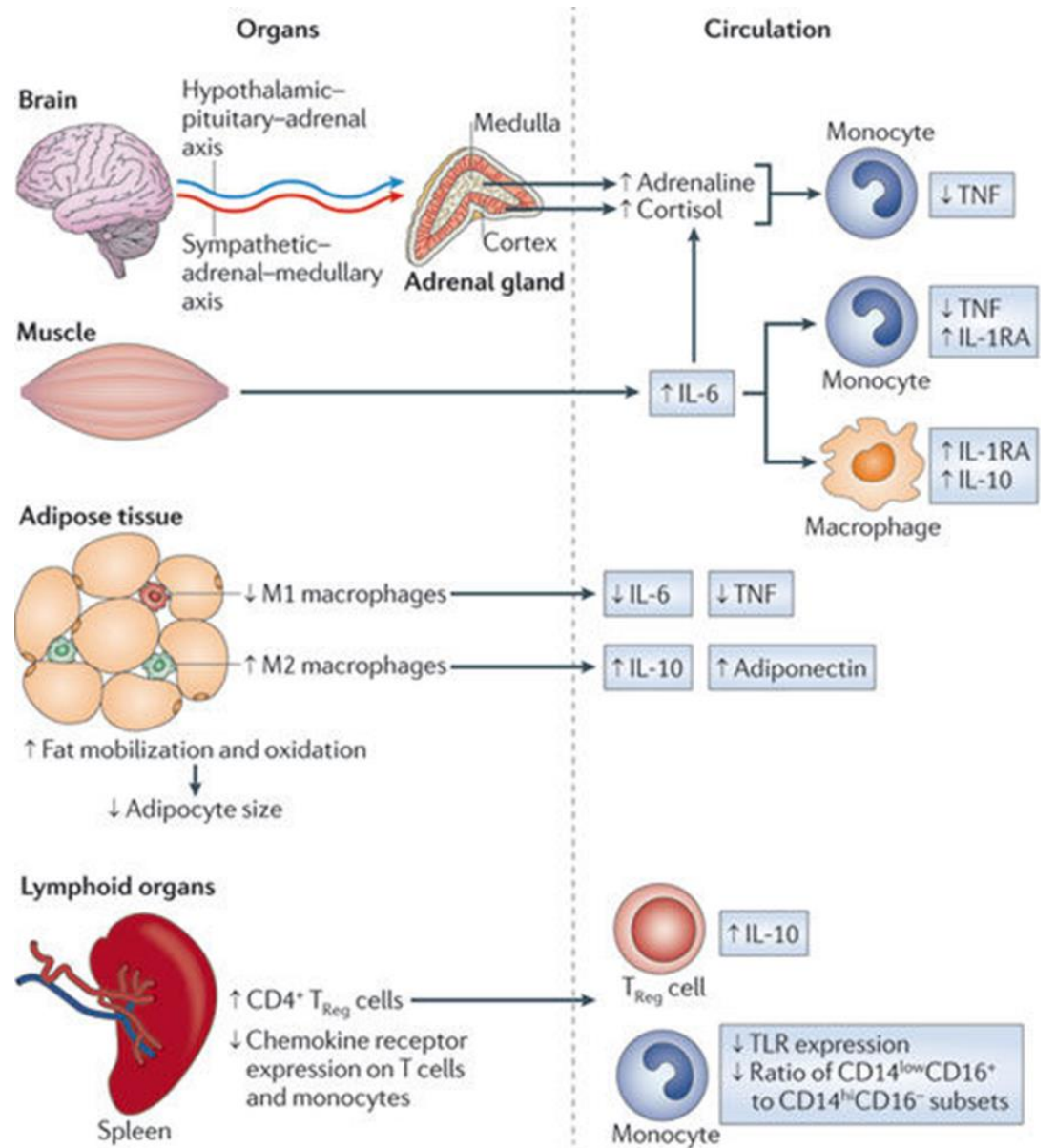


Effects of exercise on systemic inflammation



S. Balducci *Nut, Metab & CVD* 2010

Oursler MD



Gleeson M, 2011

Effects of exercise on inflammation in younger HIV+

- Mod-AEX + RT in 89 HIV+ adults, mean age 48 yr¹
 - No change hsCRP (even stratified by compliance)
 - Modest change VO_2 peak (2.2 mL/kg/min, p=0.07)
- Mod-AEX +/- RT in 35 HIV+ adults, median age 48 yr²
 - Significant change hsCRP and biomarkers inflammation
 - 30% receiving statins (at entry and during intervention)
- Is high-intensity AEX/RT needed to improve VO_2 peak, systemic inflammation and aging?



HAL MAYFORTH



Kris Ann Oursler, MD

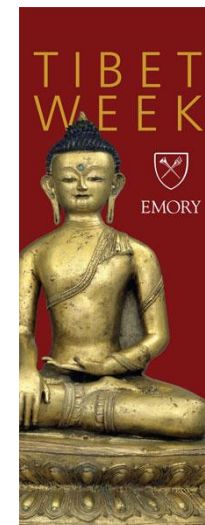
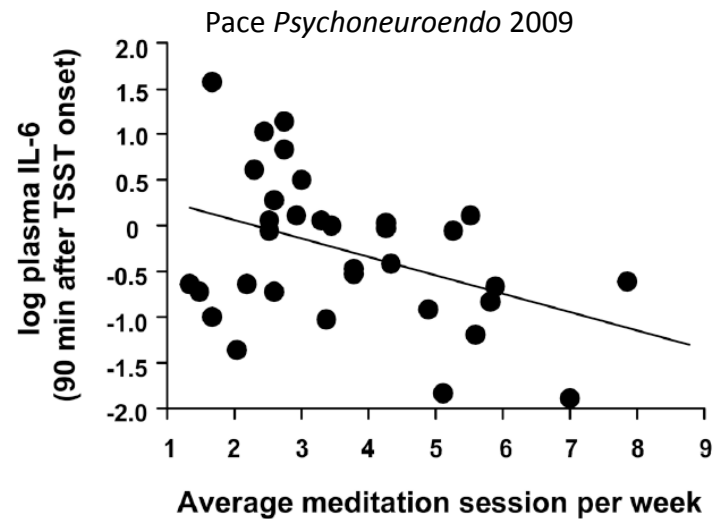
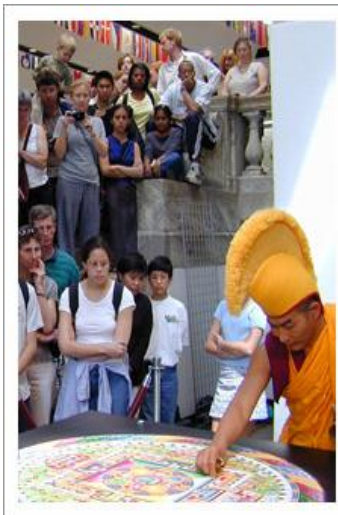
¹ SE Cutrono *AIDS Behav* 2016

² M Bonato *BMC ID* 2017

Cognitively-Based Compassion Training (CBCT)



Cognitively-Based Compassion Training



Results

Self-reported Scale	Measurement	Control	Intervention	P-value
GWB score	Median (Q1, Q3) baseline score	76.5 (66, 85)	70 (53, 89)	
	Median (Q1, Q3) change in score	0 (-6, 8)	+10 (1, 18)	0.023
ICQ Acceptance	Median (Q1, Q3) baseline score	19 (14, 22)	19 (15,21)	
	Median (Q1, Q3) change in score	+1.5 (-1.5, 4)	+3 (1, 9)	0.041

- CBCT increased psychological well-being and overall acceptance of their HIV illness in comparison to controls
- Less VF in CBCT than control (9.7% vs 18.8%, NS)

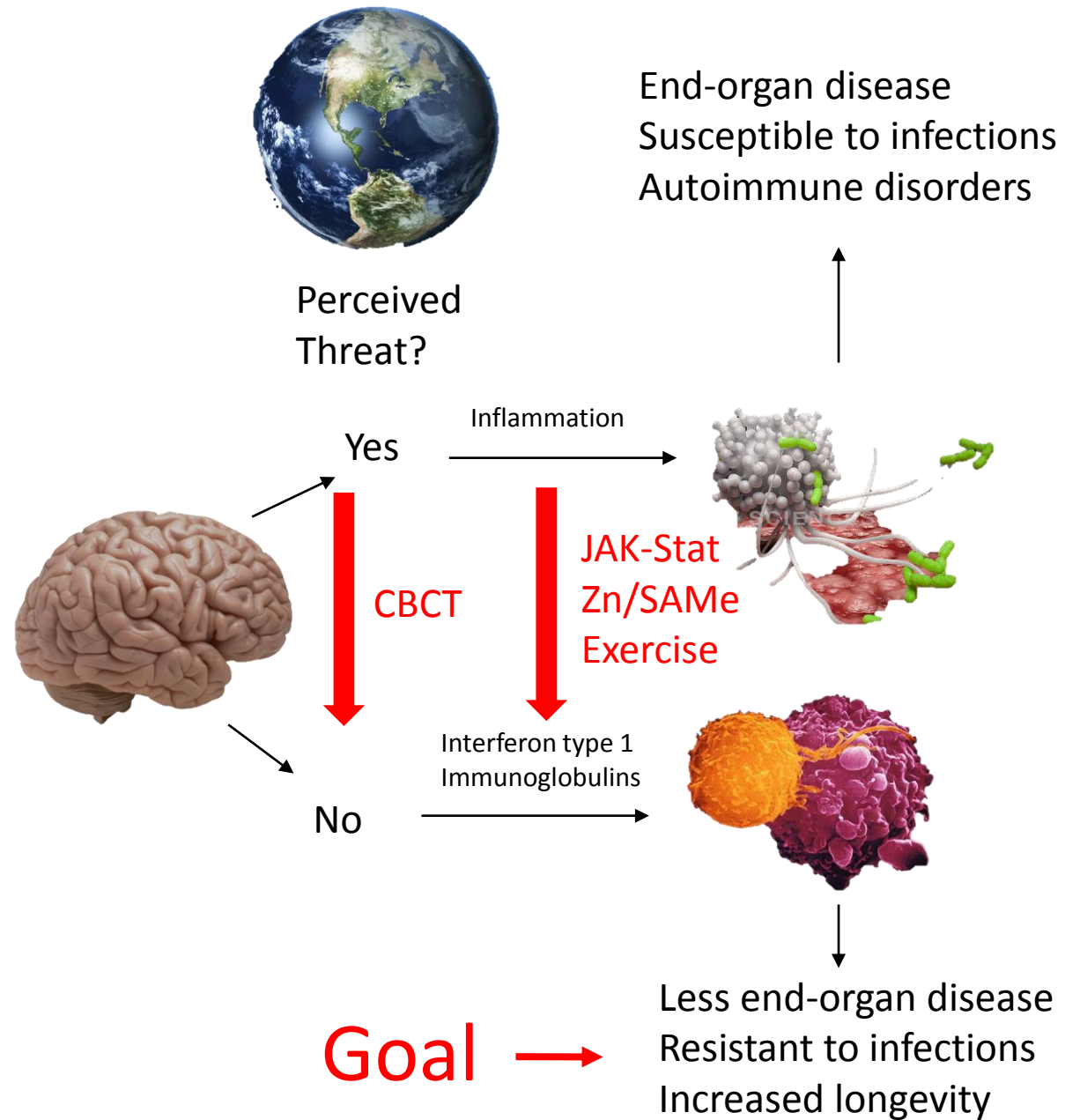
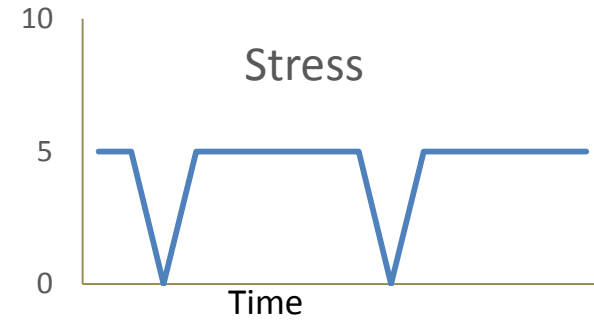


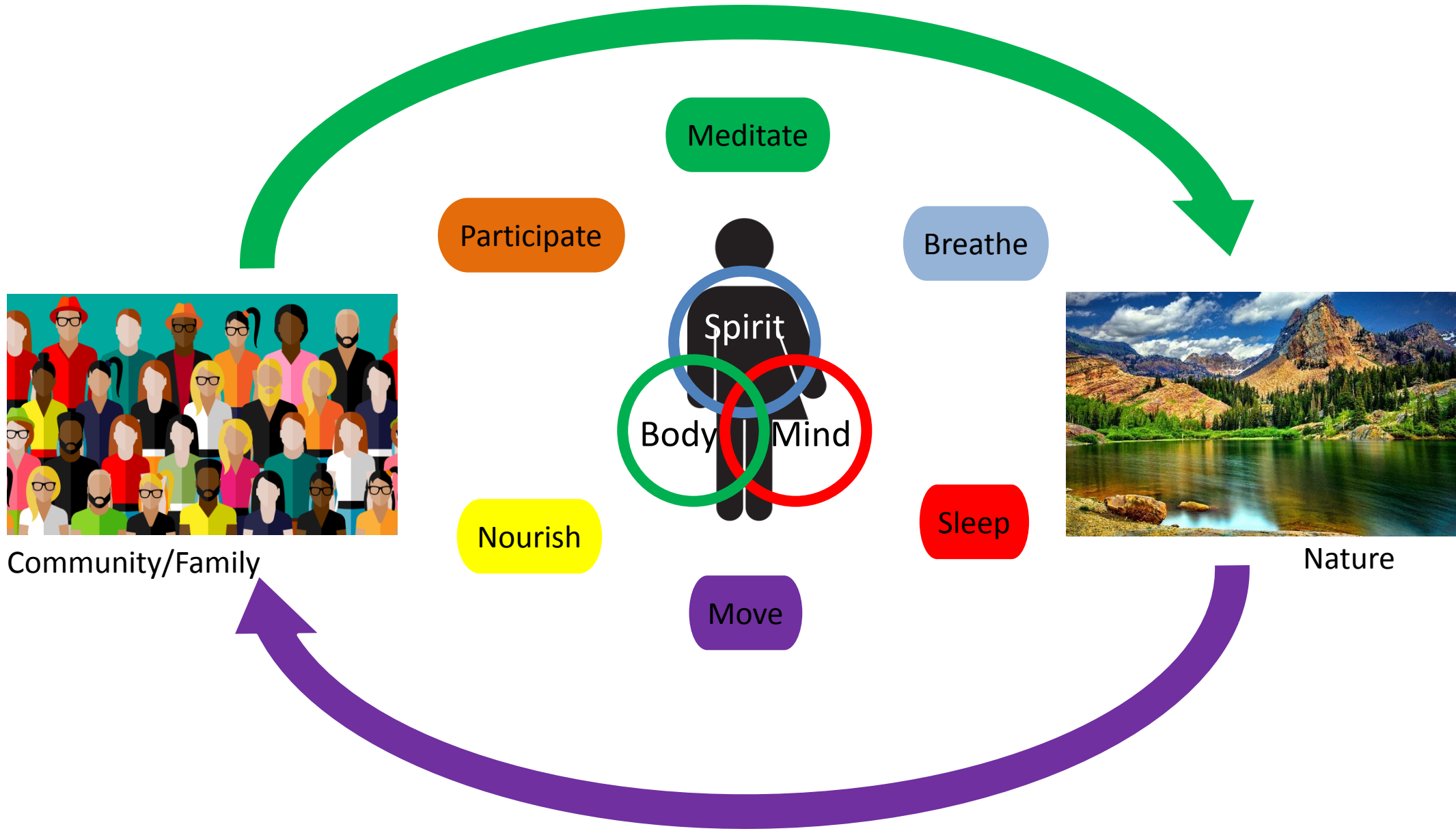
Mehul Tejani MD

Ancient Humans



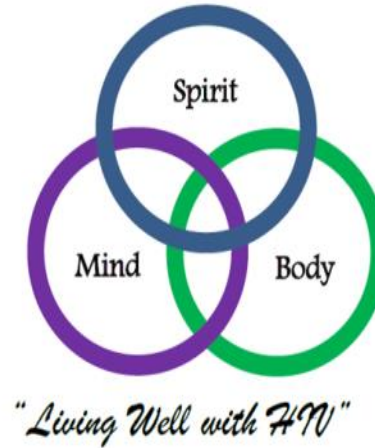
Modern Humans





Mind Body Spirit Health & Wellness Program

- Regular Yoga
- Taiji and Qigong
- Dance Yoga
- Fashion Show
- Soul Yoga
- Meditation
- Movies at Ponce
- Men's Group
- Belly Dancing
- Women's Support/Wellness
- Nutrition
- Mandala
- Healthy Relationships
- Skills Wellness
- Library use, Money Wellness
- Oncology
- Performance
- Art/Interpretive Dance
- Music Therapy
- Aroma Therapy
- Art Therapy
- Relationships
- Meditation
- Belly Dancing
- Laughter Yoga
- APD Safety
- Students Summer Health Fair
- Money Wellness
- Gardening
- Pet Wellness
- Wellness Improv
- Legal Assistance
- Literacy Action and The Atlanta Urban League
- Managing Holiday Stress/Eating
- Zumba
- Diabetes
- Wellness Workshops
- Disability/Social Security Workshop
- Affordable Care Act
- GED
- Tea Therapy
- African Dance
- Botanical Garden trip
- Addiction movie
- Sign Language and Pilates
- Numerology
- Mindfulness



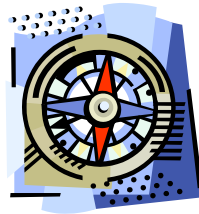
Conclusions

- Non-communicable diseases are the leading cause of death in high income countries
- Inflammation is a primary driver of NCDs and aging
- Stress and social isolation increase inflammation and decrease cell-mediated immunity
- HIV infection exacerbates age-related NCDs via inflammation
- JAK-STAT inhibition appears to reduce inflammation
- Zinc-SAMe reduces inflammation and improves lung health
- Further exploring exercise and meditation practices

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Atlanta VAMC

1,900 patients



Grady Hospital

6,000 patients



Emory Midtown

1,900 patients