Inflammaging: Discover the Fountain of Youth

Vincent Marconi, MD
Professor of Medicine
Emory University School of Medicine
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).
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
The Good and the Bad of Inflammation

Inflammatory trigger
- Infection
- Tissue injury
- Tissue stress and malfunction

Physiological purpose
- Host defence against infection
- Tissue-repair response
- Adaptation to stress, and restoration of a homeostatic state

Pathological consequences
- Autoimmunity, inflammatory tissue damage and sepsis
- Fibrosis, metaplasia and/or tumour growth
- Shift in homeostatic set points, development of diseases of homeostasis and/or autoinflammatory diseases

Medzhitov Nature 2008
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.

**THE SECRET KILLER**
Inflammation is linked to Alzheimer’s, cancer, depression, heart attacks and other diseases.
What can you do to fight it?
Inflammation is only part of the story

Medzhitov Nature 2008
Normal Stress Response

Body returns to normal

Adrenaline, noradrenaline and cortisol levels lower

Flight/Fight response activated

Adrenaline, noradrenaline and cortisol released

Acetylcholine released

Threat Removed

External threat by individual

- Heart rate increased
- Breathing increased
- Fats and Glucose released for energy
- Blood flow diverted from non-essential body areas to muscles and brain
- Perspiration increased
- Immune system suppressed

Visual
Auditory
Olfactory
Somatic
Gustatory
The Stress Response Influences Immunity and Inflammation

- Inflammation
- Type I interferon antiviral response
- Immunoglobulin G1 production

Cole Genome Biology 2007
Extreme Acute Stress

Social or Environmental Experience

CNS Interpretation

Neuroendocrine Function

Cell Signal Transduction

Transcription Factors

Protein Expression

Chronic Stress

Low SES

Social loss/bereavement

PTSD

Cancer Diagnosis

Social Threat

Loneliness

Social Instability

Chronic Stress

Low Social Rank

Caregiving for seriously Ill

Anxiety

Early life adversity

Epigenetic Modification Can Be Durable

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

H Palma-Guedel, A Córdova-Palomera, E Eliañez, M Deaschle, and L Fahranis

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

Kanherkar Front Cell Dev Biol 2014
Ancient Humans

Modern Humans

Perceived Threat?

Yes

Inflammation

End-organ disease
Susceptible to infections
Autoimmune disorders

No

Interferon type 1
Immunoglobulins

Less end-organ disease
Resistant to infections
Increased longevity

Goal

Ideally

Practically

Cole PLoS Genetics 2014
HIV as a Model for Aging
Improved Life Expectancy*, but Gap Persists: HIV vs. HIV-

Gap only 6y if CD4 nadir >500 and no smoking, EtOH or hepatitis

Gap ~20y if CD4 nadir <350 (Samji, PLoS One, 2013)

Deaths per 100,000 person-yrs

Est. Years of Life Remaining

*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]

CD4 Recovery Predicts End-Organ Disease

Number at Risk
1322
1100
839
693
497
432
280
240
143
143
96
97

Patient Characteristic
All Patients
Non Responders
Responders

Cumulative Composite Rate (95% CI)
5 years on study
9.0% (7.7% - 10.4%)
10.0% (8.3% - 12.0%)
8.1% (6.4% - 10.3%)

10 years on study
21.2% (18.6% - 24.3%)
25.9% (21.9% - 30.5%)
15.7% (12.6% - 19.5%)

Sol Aldrete, MD

1. Nonresponders (CD4 slope ≤100/year)
2. Responders (CD4 slope>100/year)
• 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)
Microbial Translocation

Gastrointestinal

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

Hunt 2008

Periodontal/Oral

Increased proliferation but no increase in sCD14

Noguera-Julian *Medicine* 2017
DNA methylation (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 DNA methylation age

Methylated sites were associated with inflammatory genes

VPS37B significant: vesicular trafficking protein involved in HIV budding and transport

Yan Sun, PhD

Nelson AIDS 2017
Interventions
Aging Interventions

Decrease the antigenic load
- Increase the antibody production
- Use of virosomal vaccine
- Improve the adjuvants (lipopeptide, IL-7)

Restore thymic output
- Thymus graft
- Stem cell
- IL-7 → Appearance of lymphomas in mice

Modulate T cell functions
- Use of blocking antibodies (IL-1, IL-6, TNFα)
- Use of statins, NSAID
- Maintenance of telomeres
- Injection of autologous T cells

Exercise
- Intensity
- Type
- Frequency
- Intensive exercise is immunosuppressive

Nutrition
- Caloric restriction
- Antioxidant
- Omega-3 PUFA → Immunosuppressive effects
- Zinc → High doses are toxic
- Selenium
- Modulation of leptin levels
- Linoleic acid
- Decreased sugar/salt

Hormones
- Oestrogen → Some toxic effects
- Insulin
- Vitamin D
## Current Inflammation Strategies

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

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-1α/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
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)***

* Tam Expert Opin Invest Drugs 2013  
** Verstovsek NEJM 2010 and 2012  
*** Gavegnano PLoS Pathog 2017

Ray Schinazi, PhD

Christina Gavegnano, PhD
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
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

HIV+ on ART Suppressed VL

- 40 participants
- RUX (10 mg BID) + ART (ART not provided by study)
- Follow-Up (ART alone)

Study Week
0 5 12

- 20 participants
- No Study Treatment + ART (ART not provided by study)

Marconi CROI 2019
Results – IL-6 and sCD14

- No significant difference between arms
  - Mean (90% CI) relative fold change
    - 0.85 (0.69, 1.04)
  - P-value: 0.18
  Marconi CROI 2019

- Significant difference between arms
  - Mean (90% CI) relative fold change
    - 0.88 (0.80, 0.97)
  - P-value: 0.034
Results – CD4 Counts

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

BAUM CID 2010
Asdamongkol Jpn J ID 2013
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

Paired t-test $p = 0.004$
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 yr\(^1\)
  – 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 yr\(^2\)
  – 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?

\(^1\) SE Cutrono AIDS Behav 2016
\(^2\) M Bonato BMC ID 2017
Cognitively-Based Compassion Training (CBCT)
### Results

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

- 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)
Perceived Threat?

Yes

Inflammation

JAK-Stat
Zn/SAMe
Exercise

Interferon type 1
Immunoglobulins

No

Less end-organ disease
Susceptible to infections
Autoimmune disorders

Goal

Resistant to infections
Increased longevity

Ancient Humans

Modern Humans

End-organ disease
Cole PLoS Genetics 2014

Stress

Time

Stress

Time

Inflammation

JAK-Stat
Zn/SAMe
Exercise

Interferon type 1
Immunoglobulins

Goal
Spirit
Mind
Body
Community/Family
Nature
Meditate
Participate
Breathe
Sleep
Nourish
Move
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
Acknowledgments

Exercise Study (VA 5I01RX000667)
- Kimberly Birkett
- Theron Clark-Stuart
- Julia Gallini
- Chani Jain
- Ngoc-Anh Le
- Kathryn Meagley
- Joe Nocera
- Kris Ann Oursler
- Alice Ryan
- Yan Sun
- Ernest Tate

TCM INR (R01 AI110334 NIAID)
- Sol Aldrete
- Nicolas Chomont
- Keith Delman
- Kirk Easley
- Jake Estes
- Justin Harper
- Anum Khan
- Michael Lowe
- Darius McDaniel
- Luca Micci
- Elena Morales
- Mirko Piaiartini
- Amelie Pagliuza
- Ericka Patrick
- Maria Pino
- Jonathan Pollock
- Emily Ryan
- Rafick Sekaly
- Theron Stuart
- Tanisha Sullivan
- Cameron Tran

ACTG 5336 (NIAID/NIH)
- Carlos del Rio
- Steve Deeks
- Charlie Flexner
- Christina Gavegnano
- Selwyn Hurwitz
- Amy Kantor
- Jeff Lennox
- Carlee Moser
- Ray Schinazi
- Guido Silvestri
- Atho Tsibris

Zn/SAMe (R01 HL125042 NHLBI)
- Sushma Cribbs
- David Guidot
- Igho Ofotokun

CBCT (EMCF)
- Gene Farber
- Kathryn Meagley
- Christina Mehta
- Mehul Tejani
- Thaddeus Pace
Special thanks to the participants and staff from the Emory HIV Clinical Sites

Atlanta VAMC
1,900 patients

Grady Hospital
6,000 patients

Emory Midtown
1,900 patients