DISCLOSURES

I have received speakers fees from Gilead Sciences, and travel/conference bursaries from ViiV Healthcare and Gilead Sciences
My institution has received funding from Gilead Sciences

Immune Dysregulation – a Remaining Challenge in HIV Medicine

Dr John Thornhill
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Consultant Physician, Barts Health NHS Trust

Non AIDS morbidity and mortality

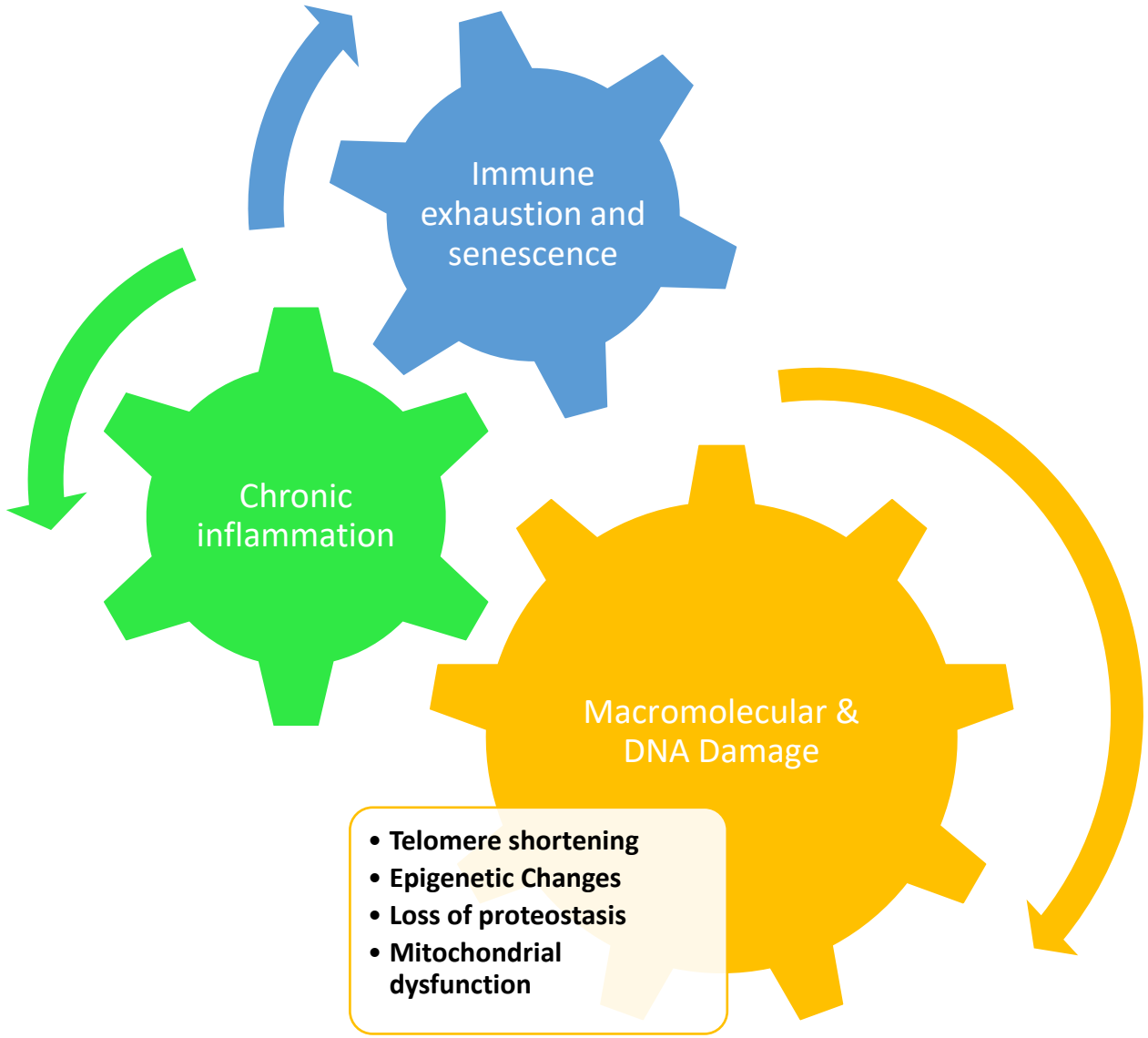
- Studies conducted in PLWH over the past decade or more have repeatedly reported an association of morbidity and mortality with blood biomarkers reflecting innate and adaptive immune responses as well as hypercoagulability

- Several of these biomarkers – including IL-6, hsCRP, and D-dimer – are consistently shown to be elevated in HIV infection, and further, remain elevated during ART

Hunt PW et al J Infect Dis 2016
Younas M et al. HIV Med 2016

Armah KA et al. Clin Infect Dis 2012
Wada NI et al. AIDS 2015

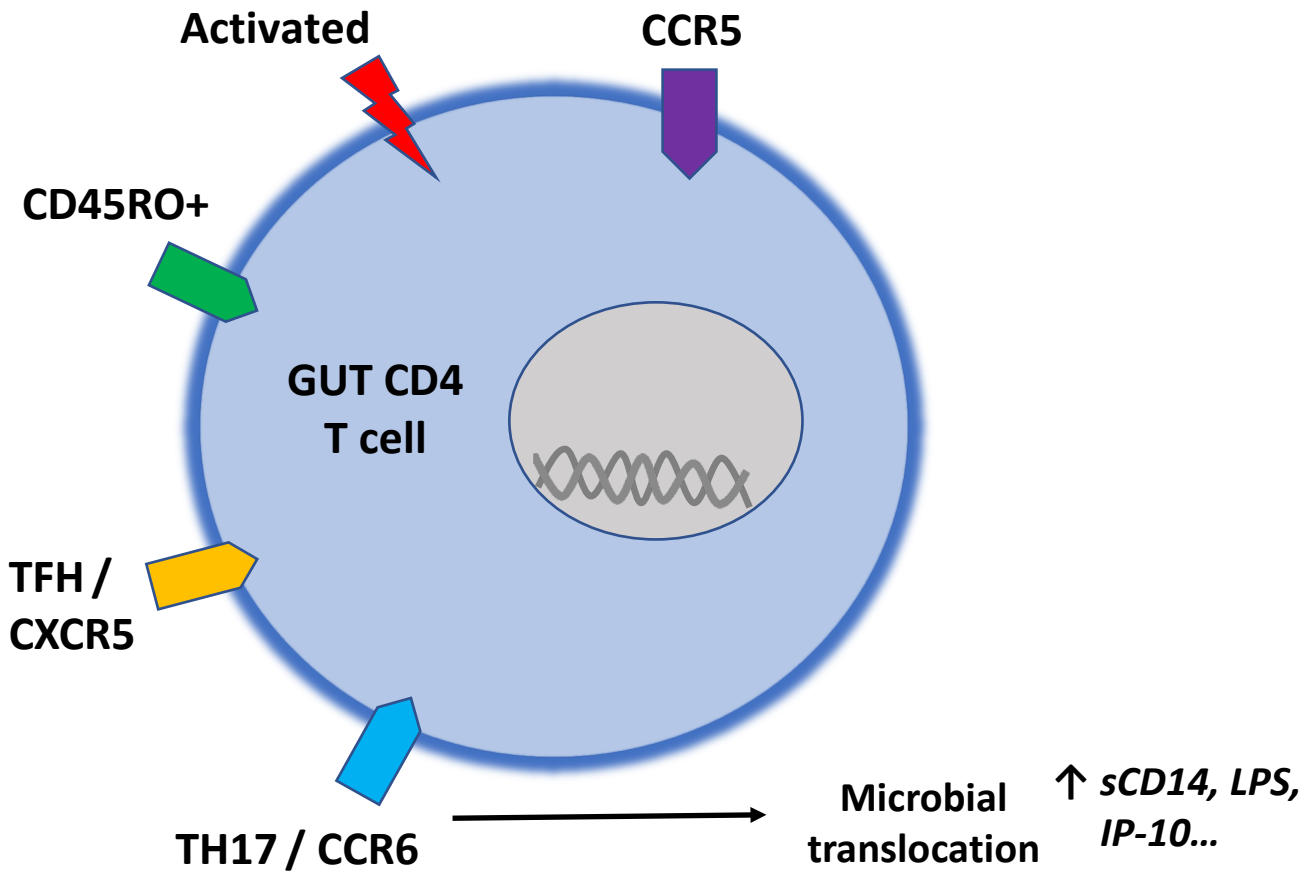
Mechanisms Immune Dysfunction on ART



Immune Senescence and Chronic Inflammation

Primary HIV infection & the gut

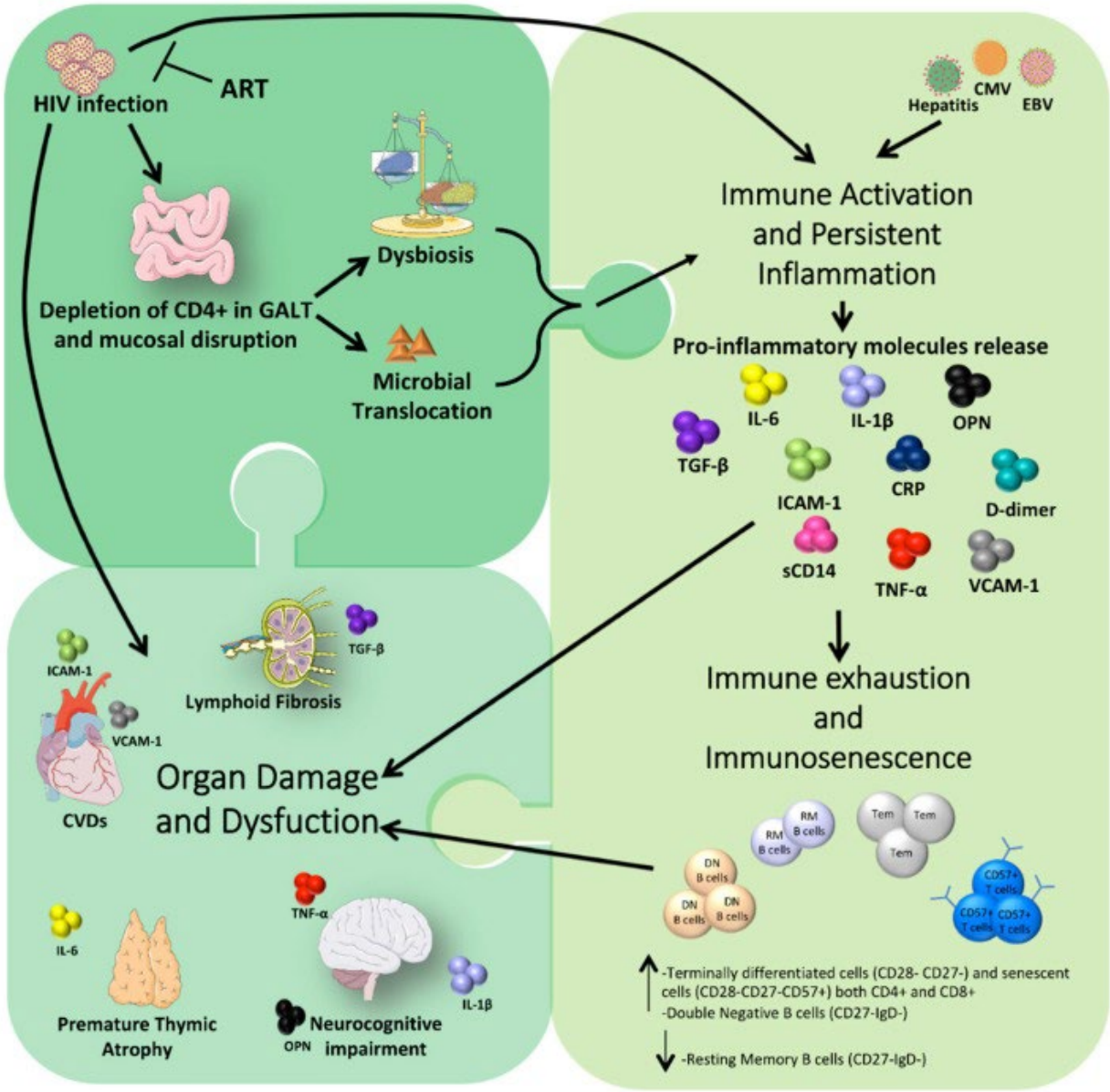
- The gut is a key site of infection and CD4 T cell depletion during primary HIV infection
- This is due to specific characteristics of CD4 cells in the gut, which allow for rapid and sustained infection of gut CD4 T cells
- This supports microbial translocation



Mechanisms of Immune dysfunction in HIV

- There are many potential mechanism of chronic inflammation & immune dysfunction on ART

- HIV infection causes both mucosal disruption and depletion of CD4+ T cells in GALT causing dysbiosis and bacterial translocation



Residual HIV-1 replication

Zicari S et al. Viruses. 2019.

Even on ART – markers of gut barrier dysfunction and elevated immune activation is evident and associated with poor outcomes

Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection

Plasma gut epithelial barrier integrity markers (IFABP and zonulin-1 levels), soluble CD14 level, kynurenine/tryptophan ratio, sTNFR-I, hsCRP, and D-dimer level all strongly predicted mortality

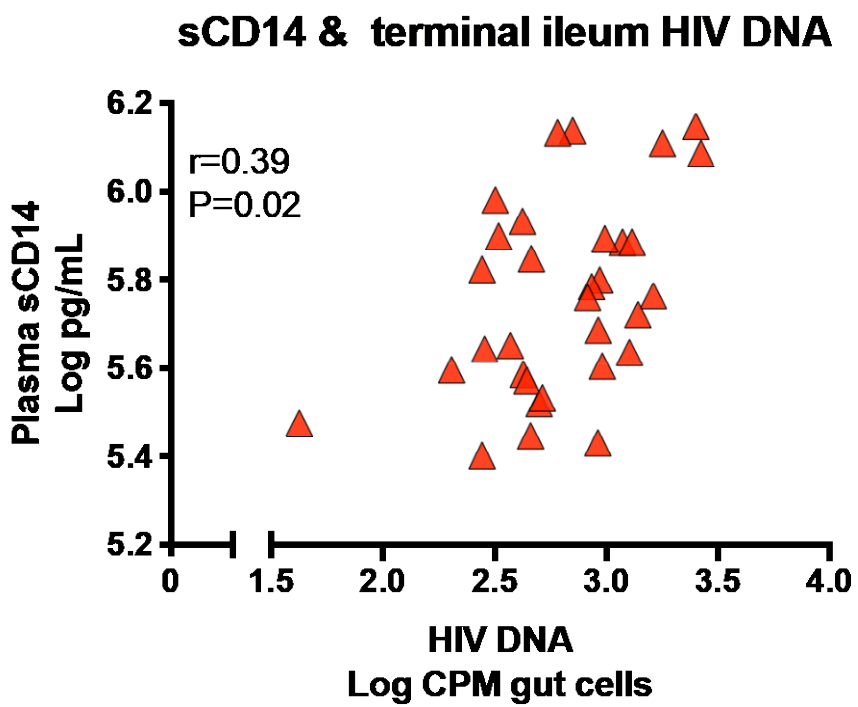
Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non–AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment

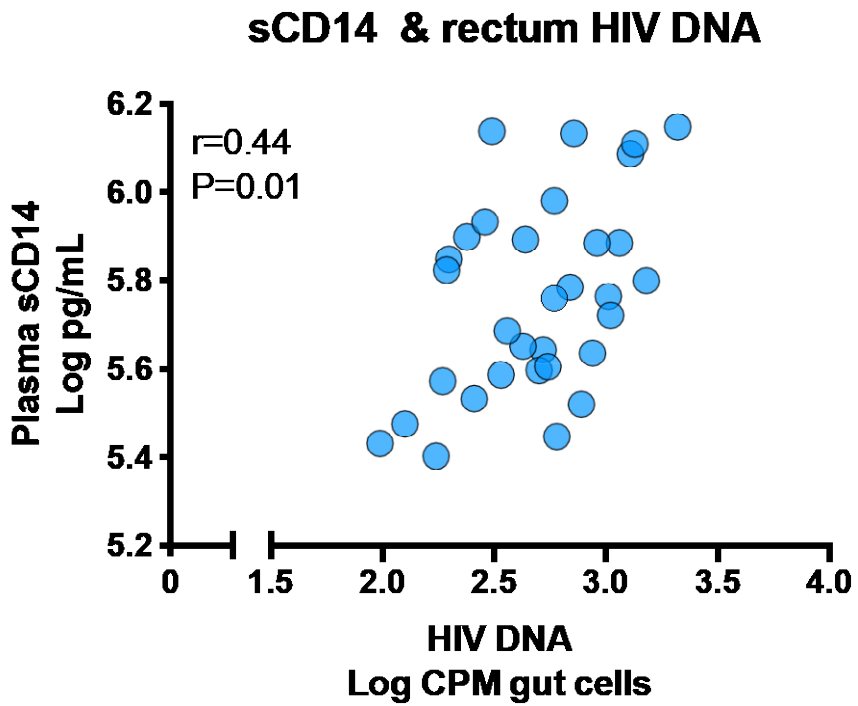
Higher IL-6 level, sTNFR-I level, sTNFR-II level, KT ratio, and D-dimer level at year 1 were associated with the occurrence of non–AIDS-events

Hunt PW et al. JID 2014

Tenorio AR et al. JID 2014

sCD14 - a marker of bacterial translocation is associated with HIV DNA in gut





Legend: ▲ T. Ileum ● Rectum

CPM, copies per million. HIV DNA expressed as copies per 10^6 gut cells
R=Spearman's rho

HEATHER
HIV RESERVOIR TARGETING WITH EARLY ANTIRETROVIRAL THERAPY

Thornhill J - unpublished

Macromolecular Damage

Mitochondrial dysfunction

Many historical NRTIs are well established to have effects on mtDNA [1]

A recent study has show than EVG & DLG use is associated with slow proliferation & impaired respiration with underlying mitochondrial dysfunction in CD4+ T cells. [2]

In-vitro & rodent studies suggest that certain HIV proteins cause mitochondrially toxicity, especially in neurons [3,4,5]

Epigenetic Changes

Significant epigenetic age acceleration (median 1.9– 4.8 years) &telomere length shortening were observed from pre-to post-HIV infection

These remained significant in three epigenetic measures after controlling for T cell changes.

No acceleration was seen in age- and time interval-matched HIV-uninfected controls. [6]

Telomere Shortening

In the context of chronic, treated HIV infection, shorter telomere length has been documented in the blood cells of people with HIV than in people without HIV [7,8]

JCI insight

Effect of HIV infection and antiretroviral therapy on immune cellular functions

Human Immunodeficiency Virus Type 1 gp120 and Tat Induce Mitochondrial Fragmentation and Incomplete Mitophagy in Human Neurons

iScience

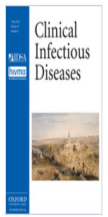
CellPress OPEN ACCESS

Article

Accelerated aging with HIV begins at the time of initial HIV infection

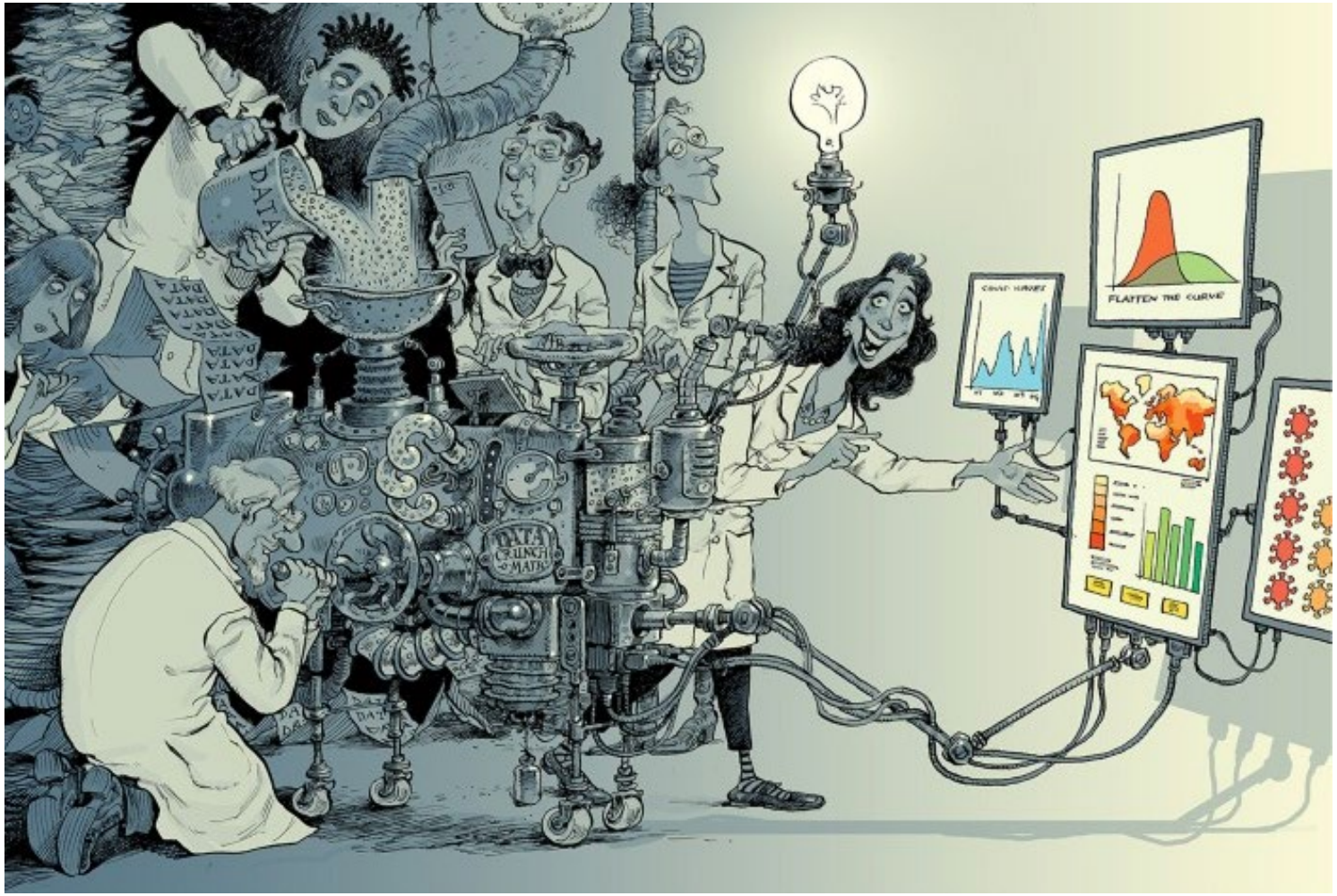
Epigenetic Features of HIV-Induced T-Cell Exhaustion Persist Despite Early Antiretroviral Therapy

Genevieve E. Martin[1,2], Debattama R. Sen[3,4], Matthew Pace[1], Nicola Robinson[1], Jodi Meyerowitz[1], Emily Adland[5], John P. Thornhill[1,6], Mathew Jones[1], Ane Ogbe[1], Lucia Parolini[1], Natalia Olejniczak[1], Panagiota Zacharopoulou[1], Helen Brown[1], Christian B. Willberg[1,7], Nneka Nwokolo[8], Julie Fox[9,10], Sarah Fidler[6,11], W. Nicholas Haining[4,12] and John Frater[1,7] on behalf of the CHERUB Investigators*



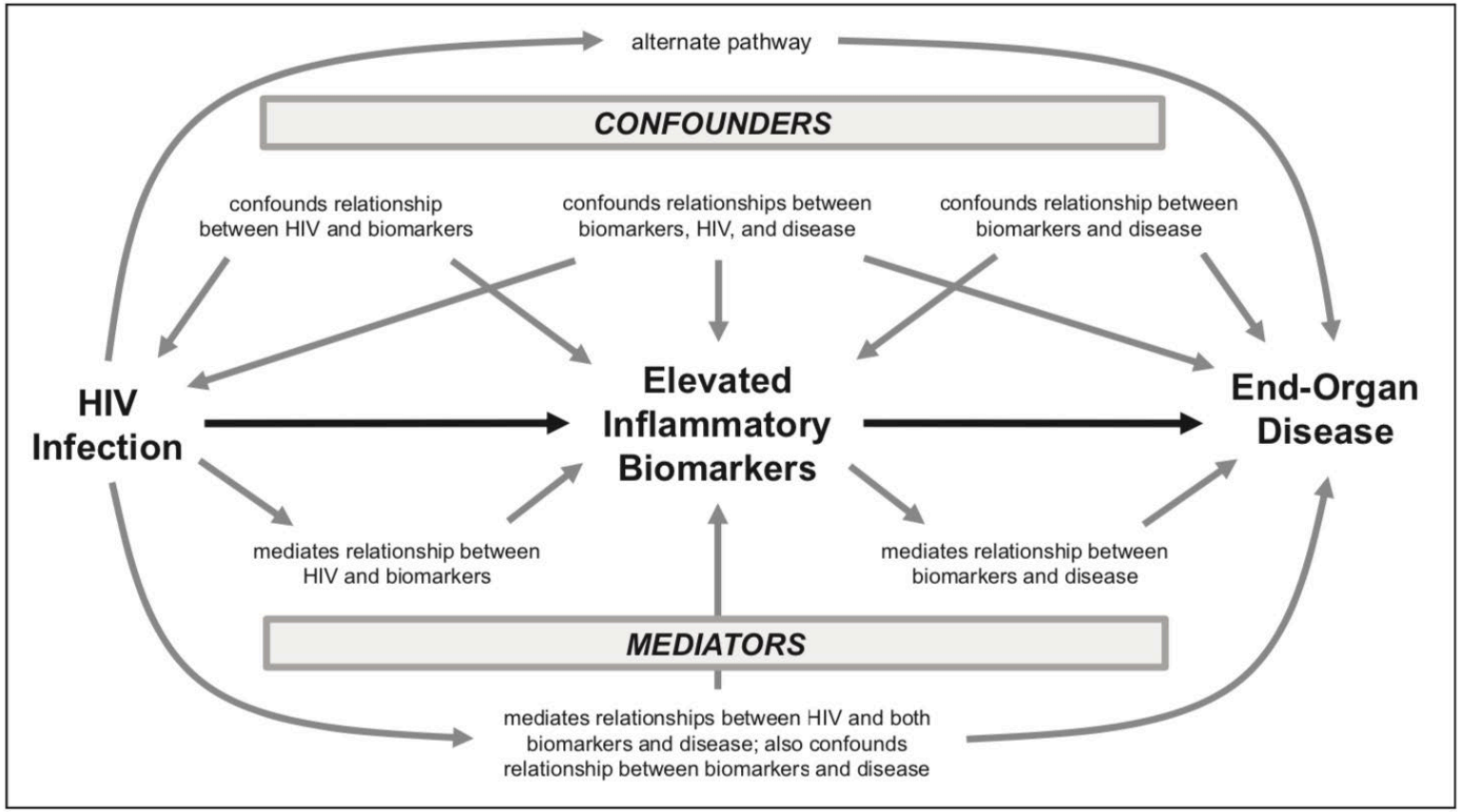
Association Between Short Leukocyte Telomere Length and HIV Infection in a Cohort Study: No Evidence of a Relationship With Antiretroviral Therapy

1. Lim SE et al. J Biol Chem 2001
2. Korencak M et al. JCI Insight. 2019
3 Cotto B et al. Prog Neurobiol 2019
4. Cheung al. J Cell Physiol 2019
5. Teodorof-Diedrich C et al. J Virol 2018
6. Breen et al. iScience 2022
7, Effros RB et al. AIDS
8 Zanet DL et al. Clin Infect Dis 2014



Lots of cohort data!

Analytical considerations for observational studies evaluating inflammation and end-organ disease among PWH.



- Highlights the challenges interrupting the current literature on inflammation and end-organ disease

Peterson, T; Baker, JV. Assessing inflammation and its role in comorbidities among persons living with HIV. Current Opinion in Infectious Diseases: February 2019

Non AIDS morbidity & Mortality

- Cardiovascular disease
- Cancer
- Lung Disease
- Metabolic diseases
- Low Bone Mineral Density

1. Ambrosioni J et al. Lancet HIV. 2021
2. https://www.bhiva.org/updated-statement-on-considerations-for-critical-care-for-people-with-HIV-during-COVID-19

Cardiovascular Disease

- **Cardiovascular disease is increased 2-fold in people living with HIV** [1]
- **Potential mechanisms include endothelial dysfunction and arterial inflammation** [2]

- PWH have higher levels of biomarkers reflecting inflammation and innate immune activation which correlate with imaging measures of atherosclerosis
  - carotid intima–media thickness, coronary artery calcium
  - risk of CVD events

- Higher biomarkers of monocyte and macrophage activation have shown the most consistent effects across studies
  - e.g. sCD163 and sCD14 [3,4]

- As have Higher measures of more general systemic inflammation
  - e.g. IL-6, hsCRP, sTNFR-1, and sTNFR-2 [5,6]

- Association between CVD and ART (Abacavir and bPI)

1. Shah ASV et al. Circulation. 2018
2. Subramanian S et al *JAMA.* 2012
3. Burdo TH et al. J Infect Dis 2011
4. Hannna DB et al . J Infect Dis 2017
5. Duprez DA et al. PLoS One 2012
6. Triant VA et al, JAIDS 2009

REPRIEVE

Randomized Trial to Prevent Vascular Events in HIV

- NIH Funded RCT Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in Adults living with HIV (REPRIEVE)

lipoprotein-associated phospholipase A2 (LpPLA2), and oxidized low-density lipoprotein (oxLDL)
Hoffmann et al. *JAMA Netw Open.*

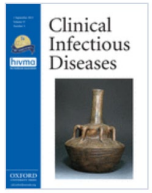
JAMA Network Open

Original Investigation | Cardiology

Assessment of Coronary Artery Disease With Computed Tomography Angiography and Inflammatory and Immune Activation Biomarkers Among Adults With HIV Eligible for Primary Cardiovascular Prevention

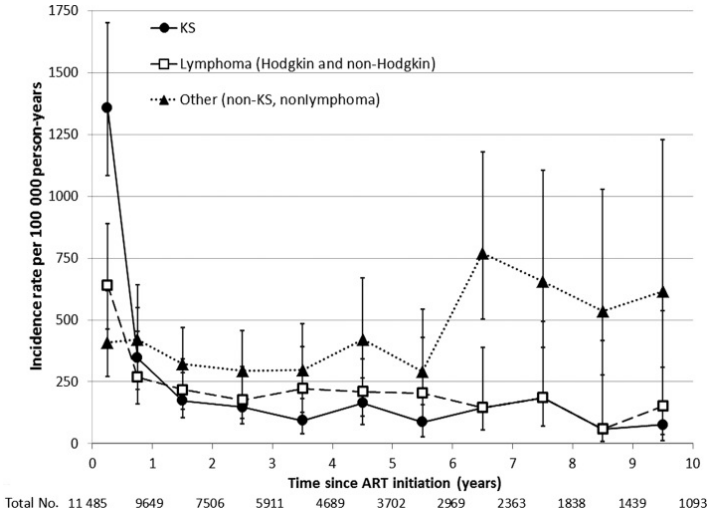
- 755, aged 40 to 75 years, without known CVD, receiving stable antiretroviral therapy, and with low to moderate atherosclerotic cardiovascular disease (ASCVD) risk
- Critical stenosis was rare, but higher-risk plaque features, including vulnerable plaque and high Leaman scores, were seen in approximately one-fifth of participant
- plaque indices were associated with ASCVD risk scores and, independently, indices of inflammation and immune activation.
- IL-6, LpPLA2, oxLDL, and MCP-1 levels were higher in those with plaque compared with those without
- LpPLA2 and IL-6 levels were associated with plaque in adjusted modeling, independent of traditional risk indices and HIV parameters (

Cancer



Incidence and Timing of Cancer in HIV-Infected Individuals Following Initiation of Combination Antiretroviral Therapy

- KS and lymphoma rates were highest following ART start, particularly in those low CD4 cell counts
- Whereas other cancers increased with time on ART



Yanik EL et al. Clin Infect Dis. 2013

AIDS

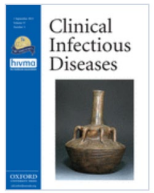
Predicting risk of cancer during HIV infection

the role of inflammatory and coagulation biomarkers

- PWH on continuous ART in the control arms of three randomized trials (*N* = 5023)
- 24 000 person-years of follow-up
- 172 patients developed cancer (70 infection-related; 102 infection-unrelated).
- **The risk of developing cancer was associated with higher levels (per doubling) of IL-6, CRP, D-dimer**
- **Only IL-6** (hazard ratio 1.29, *P* = 0.003) remained associated with cancer risk **after adjustment**

Borges A´ H et al. AIDS 2013

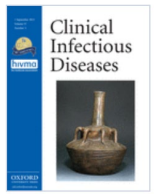
Cancer



Immediate Antiretroviral Therapy Reduces Risk of Infection-Related Cancer During Early HIV Infection

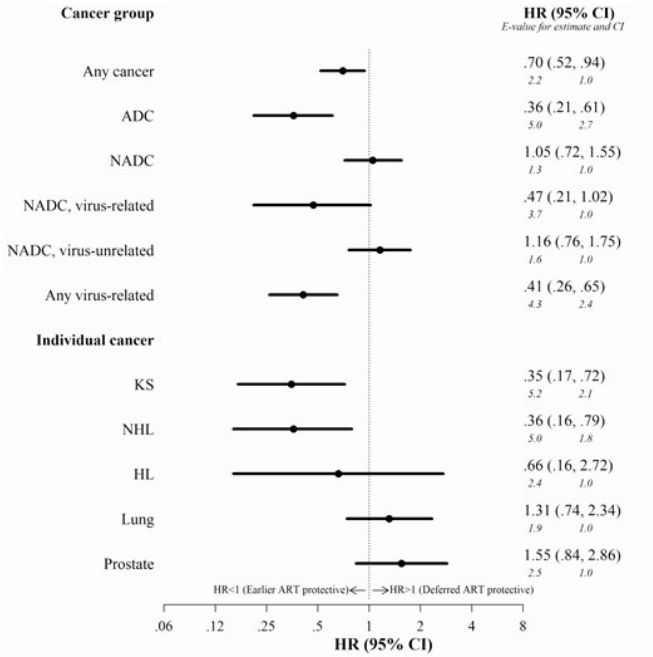
- START trial cohort
- Immediate ART initiation significantly reduces risk of cancer.
- The benefit does not appear to be solely attributable to HIV RNA suppression and may be also mediated by other mechanisms.
- **Baseline CD8 count was a predictor for infection-related and unrelated cancer development**

Borges ÁH et al. Clin Infect Dis. 2016



Timing of Antiretroviral Therapy Initiation and Risk of Cancer Among Persons Living With Human Immunodeficiency Virus

- NA-ACCORD cohort
- **Protective results for earlier ART were found for any cancer**

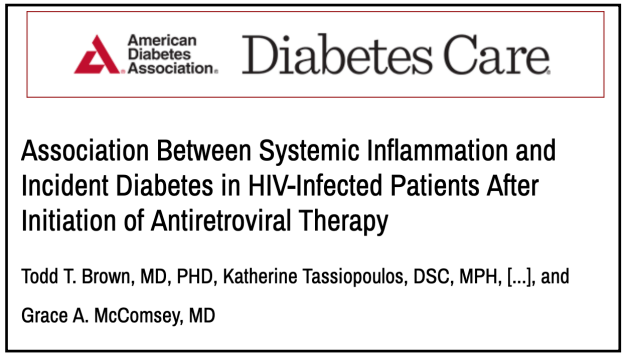


Silverberg MJ et al. Clin Infect Dis. 2021

Other Co-morbidities

Metabolic diseases

Immune dysfunction may be drivers of T2DM and NAFLD in PWH


American Diabetes Association. Diabetes Care

Association Between Systemic Inflammation and Incident Diabetes in HIV-Infected Patients After Initiation of Antiretroviral Therapy

Todd T. Brown, MD, PHD, Katherine Tassiopoulos, DSC, MPH, [...], and Grace A. McComsey, MD

- Nested case control study (n=55)
- **Inflammatory markers 48 weeks after ART initiation were associated with increased risk of diabetes**.

Brown TT et al. *Diabetes Care* 2010

Neurocognitive Disorders


AIDS (London, England)

Author Manuscript HHS Public Access

Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection

Tricia H. Burdo, Allison Weiffenbach, [...], and Kenneth C. Williams

- All patients were on ART with VL<50
- **Patients with Neuro impairment had significantly higher plasma sCD163 than those with asymptomatic impairment (*P* = 0.04) or controls**

Burdo et al. AIDS 2013

Strategies to prevent or reduce immune dysfunction

Early ART initiation

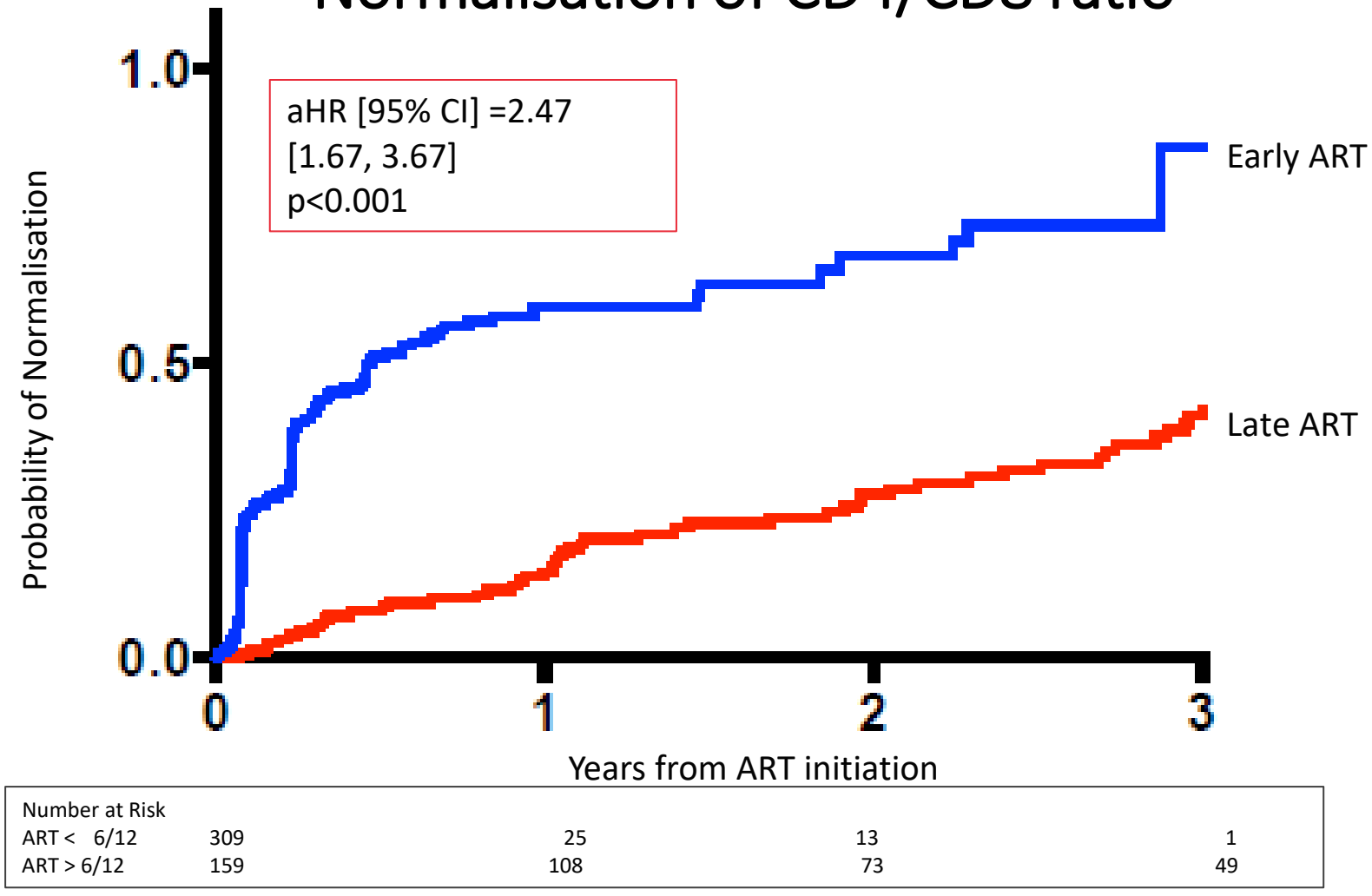
Clinical Infectious Diseases

Persistent, Albeit Reduced, Chronic Inflammation in Persons Starting Antiretroviral Therapy in Acute HIV Infection

- **Early ART was associated with normalization of TNF, sIL-6R, and D-dimer levels.**
- **CRP, sCD14, and HA levels decreased during ART but remained elevated compared with HIV-uninfected participants.**

Sereti I et al. CID 2017

Time from ART initiation to Normalisation of CD4/CD8 ratio

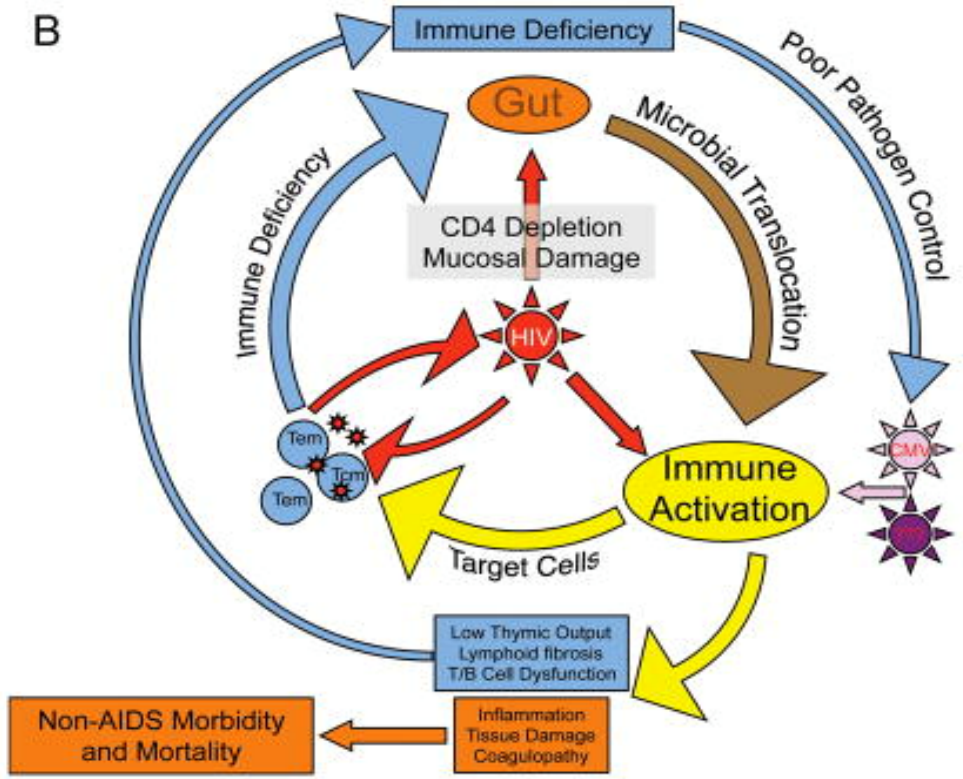


Thornhill J et al. JAIDS 2015

Gut immune recovery on ART

- **Initiation of ART in primary HIV infection (PHI) has been used as strategy to enhance immune recovery and limit HIV reservoir**
  - *Ananworanich J et al. EBioMedicine 2016*

- **However, reversing HIV-associated mucosal immune activation & damage remains a challenge**
  - Very early ART (Fiebig I/II) preserved mucosal Th17 and reversed immune activation RV254/RV304
    Schuetz A et al. Plos Path 2014
  - ART initiated 4 months after infection did not normalize gut immune activation in rectum
    Kim et al AIDS 2017



Interventions to reduced inflammation

Journal of acquired immune deficiency syndromes (1999)
Author Manuscript HHS Public Access

Rosuvastatin reduces vascular inflammation and T cell and monocyte activation in HIV-infected subjects on antiretroviral therapy

Journal of the American College of Cardiology
Author Manuscript HHS Public Access

IL-1β Inhibition Reduces Atherosclerotic Inflammation in HIV Infection

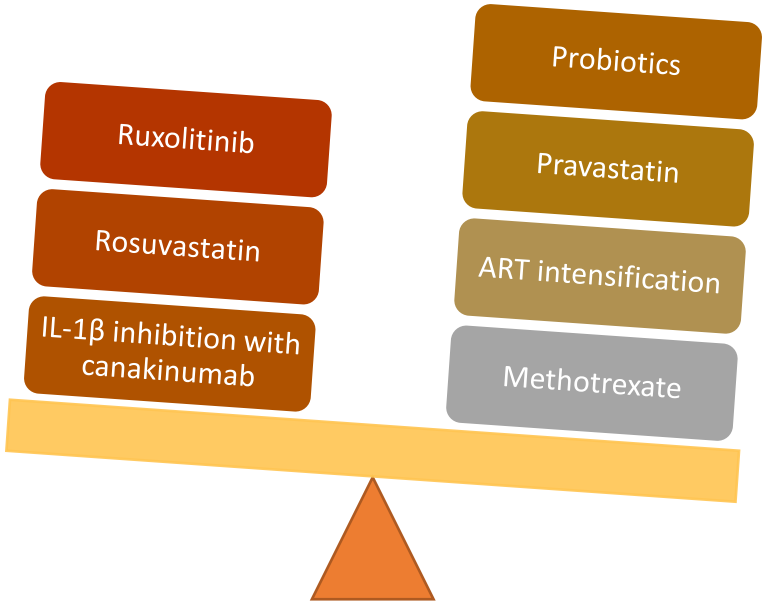
? Venetoclax
Bcl-2 antagonist

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

Maintenance of the HIV Reservoir Is Antagonized by Selective BCL2 Inhibition

Decreases markers of inflammation

No Impact



The lancet. HIV
Author Manuscript HHS Public Access

Effects of Statin Therapy on Coronary Artery Plaque Volume and High Risk Plaque Morphology in HIV-Infected Patients with Subclinical Atherosclerosis: a Randomized Double-Blind Placebo-Controlled Trial

Clinical Infectious Diseases

Safety and Impact of Low-dose Methotrexate on Endothelial Function and Inflammation in Individuals With Treated Human Immunodeficiency Virus: AIDS Clinical Trials Group Study A5314

Hsue PY et al. J Am Coll Cardiol 2018
Hsue PY et al. Clin Infect Dis 2019
Lo J et al. Lancet HIV 2015
Cummins et al. J Virol 2015

2 Drug regimen versus 3 Drug regimen

Long-Term Changes of Inflammatory Biomarkers in Individuals on Suppressive Three-Drug or Two-Drug Antiretroviral Regimens

Frontiers in Immunology

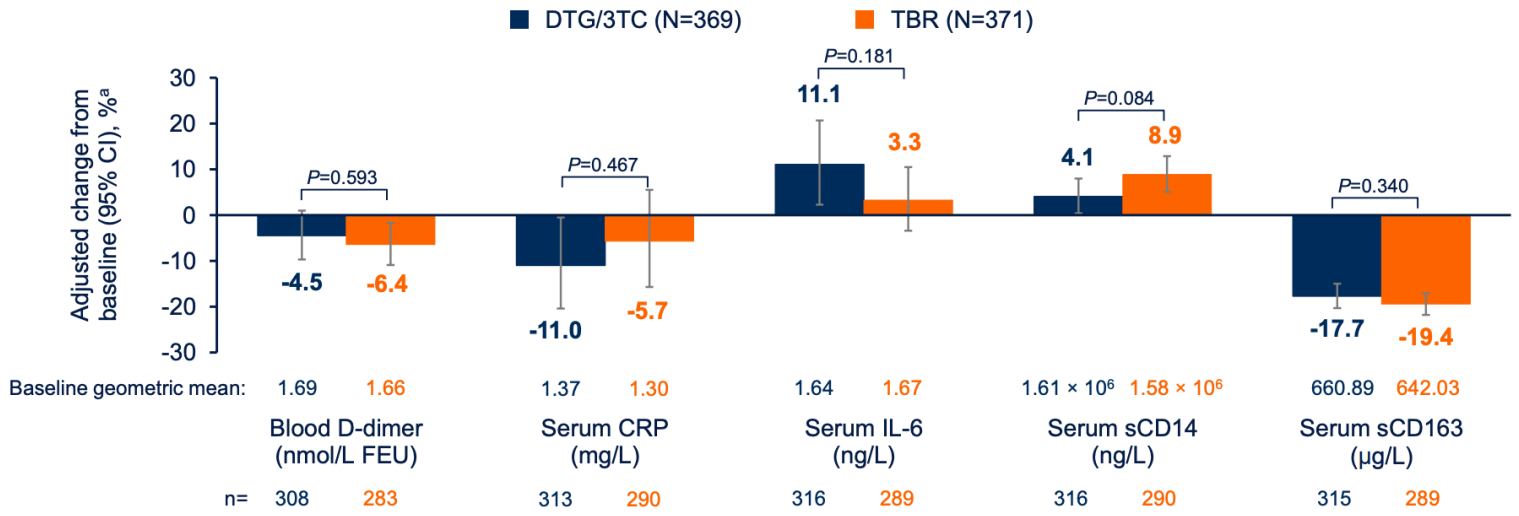
- In contrast, compared to 3DR, switching to 2DR was associated with increases in IL-6 (p=0.001), hs-CRP (p=0.003), and D-dimer (p=0.001) after year 3 from virologic suppression.

- 2DR was associated with a higher risk of hs-CRP quartile increase (aOR 3.3, 95%CI 1.1-10) and D-dimer quartile increase (aOR

Serrano-Villar S et al. Front. Immunol 2022

TANGO study – Change From Baseline to WK96 in Inflammation Markers

2 Drug regimen
versus
3 Drug regimen



- There were small and comparable changes in inflammation markers across the 2 treatment arms

CRP, C-reactive protein; FEU, fibrinogen-equivalent units; IL-6, interleukin-6; s, soluble.
[a]Percent change from baseline based on the estimated ratio (WK96 to baseline) in each arm calculated using mixed-model repeated measures applied to change from baseline in $\log_e$-transformed data adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, body mass index (continuous), smoking status, hepatitis C virus co-infection status, $\log_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. *P* values are for treatment comparison.

11th IAS Conference on HIV Science; July 18-21, 2021; Virtual

Wang et al. IAS 2021; Virtual. Slides OAB0301.

Wang et al. IAS 2021

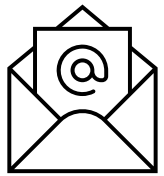
Summary

- Immune dysfunction is evident in PWH on ART
- The aetiology is complex and multifaceted
- Studies conducted in PWH over the two decades have repeatedly reported an association of morbidity and mortality with blood biomarkers reflecting innate and adaptive immune responses
- Several of these biomarkers – including IL-6, hsCRP, and D-dimer – are consistently shown to be elevated in HIV infection, and further, remain elevated during ART
- However, most data is observational and use surrogate biomarkers of inflammation and immune dysfunction rather than clinical endpoints

Summary

- These elevated biomarkers suggests the anti-inflammatory effect from ART treatment alone is incomplete.
- It follows that contemporary PWH may benefit from novel anti-inflammatory treatment strategies given in addition to ART
- However many of the strategies investigated to date to manage HIV-related inflammation have limited applicability to current clinical practice.
- Practical steps to controlling inflammation in PLHIV should be considered:
  - (a) ART should be initiated as soon as possible
  - (b) prevention and treatment of coinfections
  - (c) clinicians should screen for & treat any comorbid condition

Questions ?



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