MidAtlantic AETC Webinar Wednesday Series Presents

Managing Comorbidities in People with HIV Over 50

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Objectives

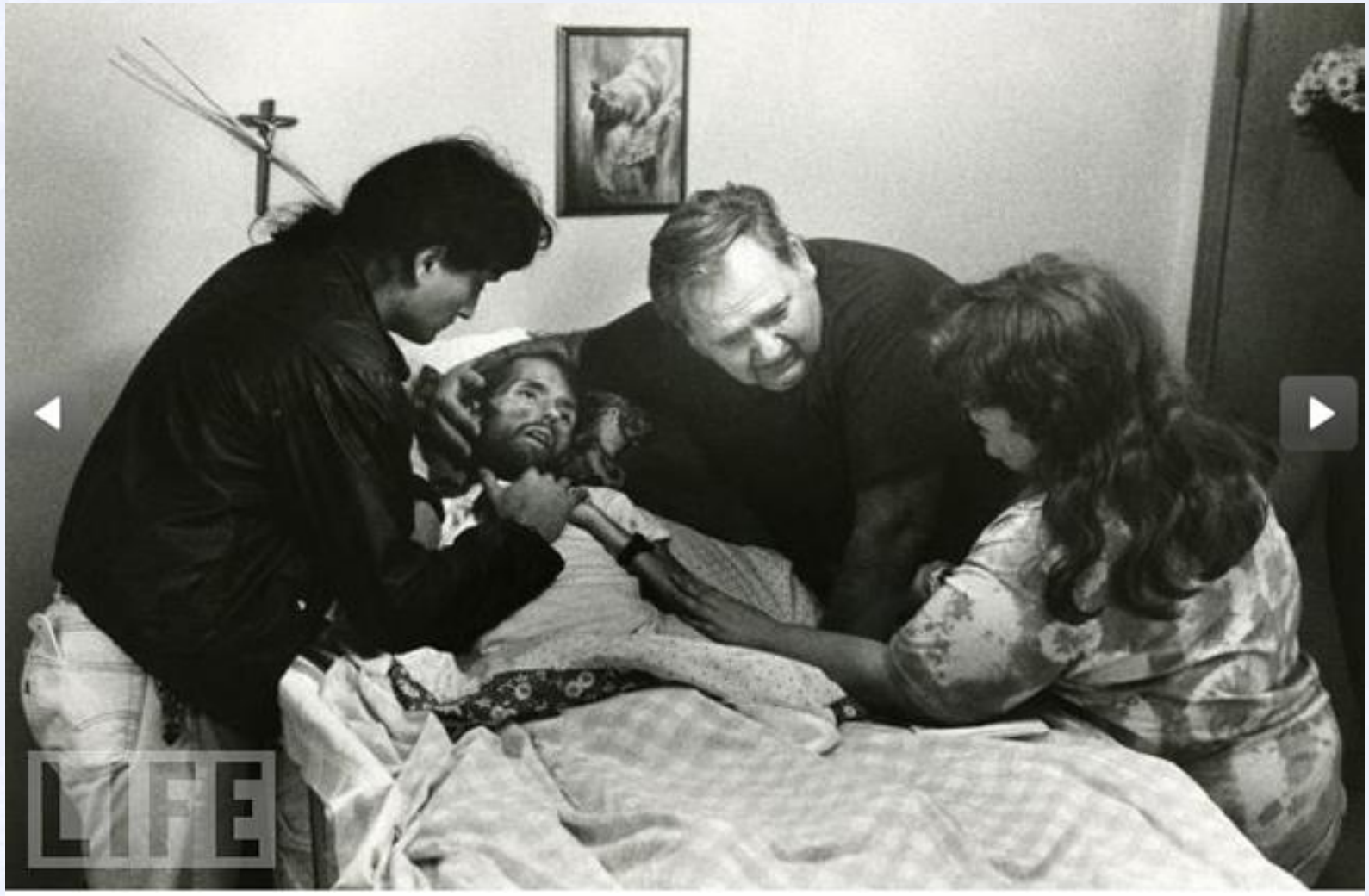
By the end of this program, participants will be able to:

- Discuss the management of age-related comorbidities in people with HIV.
- Describe the latest research related to treating comorbidities in persons with HIV over age 50.

Recommended Terminology Related to HIV

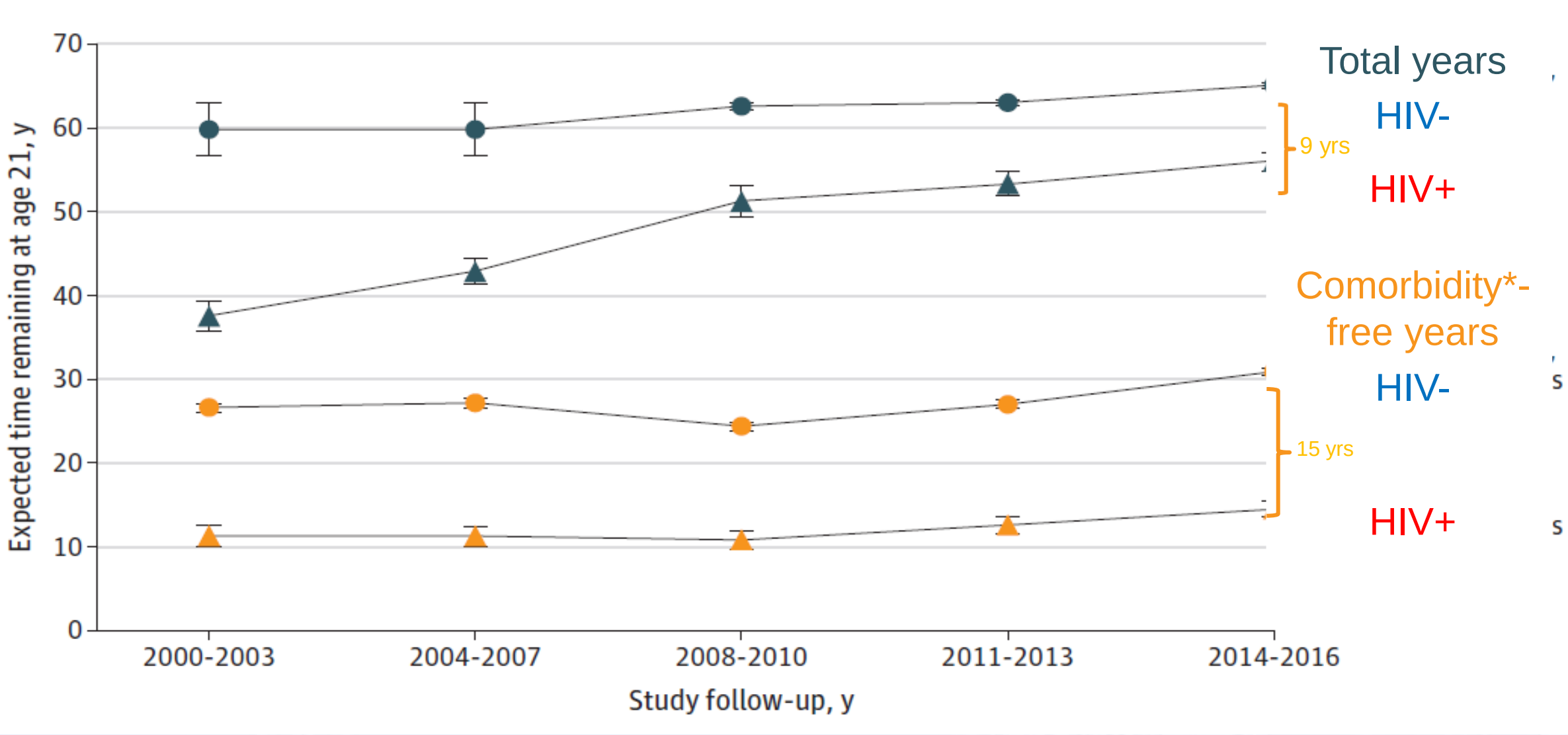
Stigmatizing	Preferred
HIV-infected person	Person living with HIV *or* Person with HIV (PWH)
AIDS Patient	
HIV Carrier	
AIDS Virus	HIV
Died of AIDS	Died of AIDS related complications
Full Blown AIDS	No medical definition for this use

HIV in 1982



Median survival was 8-15 months.

Life Expectancy and Comorbidity Gaps Persist



*Chronic liver, kidney, or lung disease; diabetes; cancer; cardiovascular disease

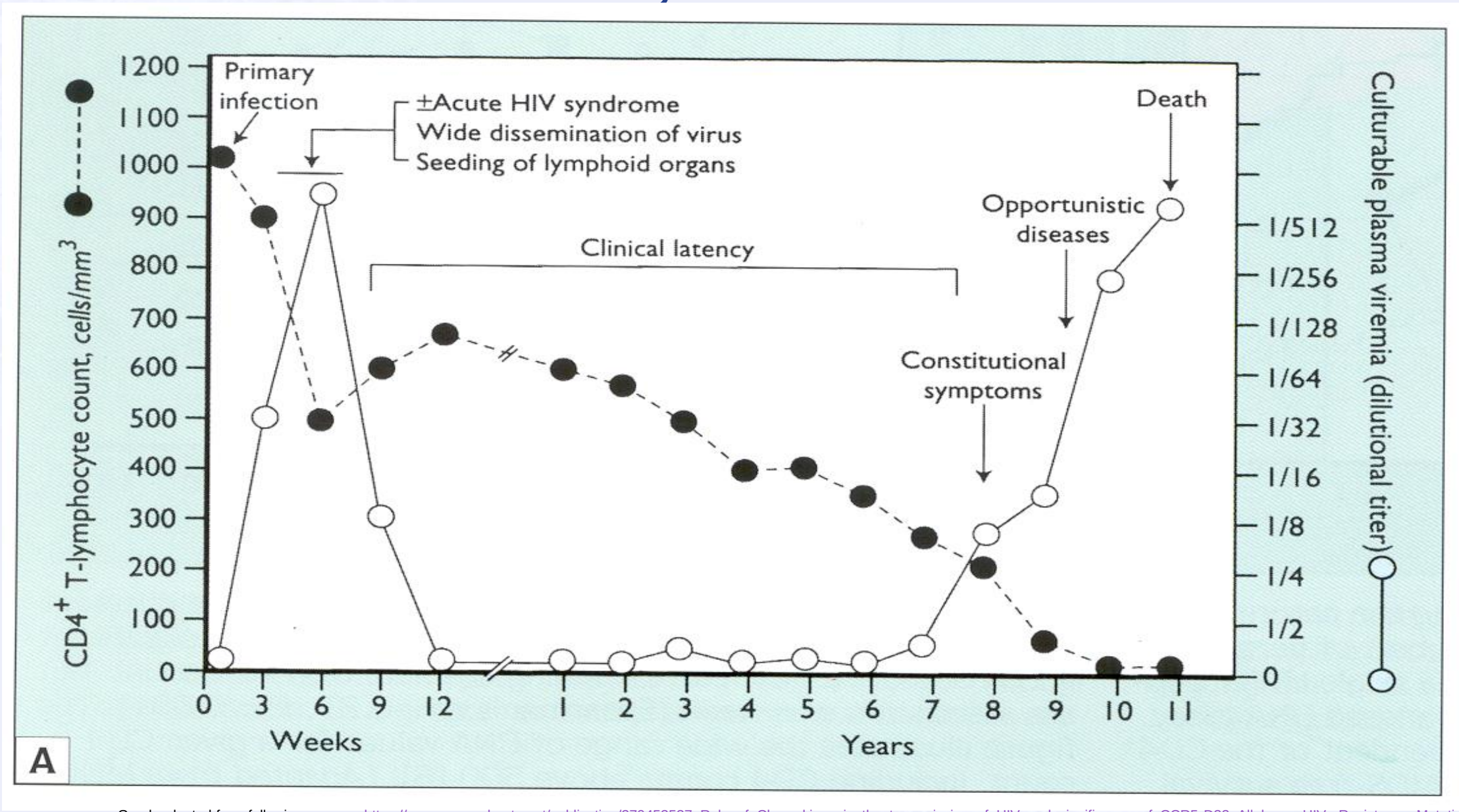
Source: Marcus JAMA Netw Open 2020

Introduction

- Improvements in antiretroviral therapy (ART) and HIV care have led to reductions in rates of nearly all major causes of death among adults with HIV on ART, particularly **AIDS-related deaths**
  - *Pneumocystis* jiroveci Pneumonia (PCP), Kaposi's Sarcoma, Cervical cancer
- The majority of mortality is now due to **non-AIDS causes**, mostly related to comorbidities, despite effective ART
  - Cardiovascular disease/stroke
  - Diabetes
  - Cancers: lung cancer, anal cancer, throat cancer, liver cancer

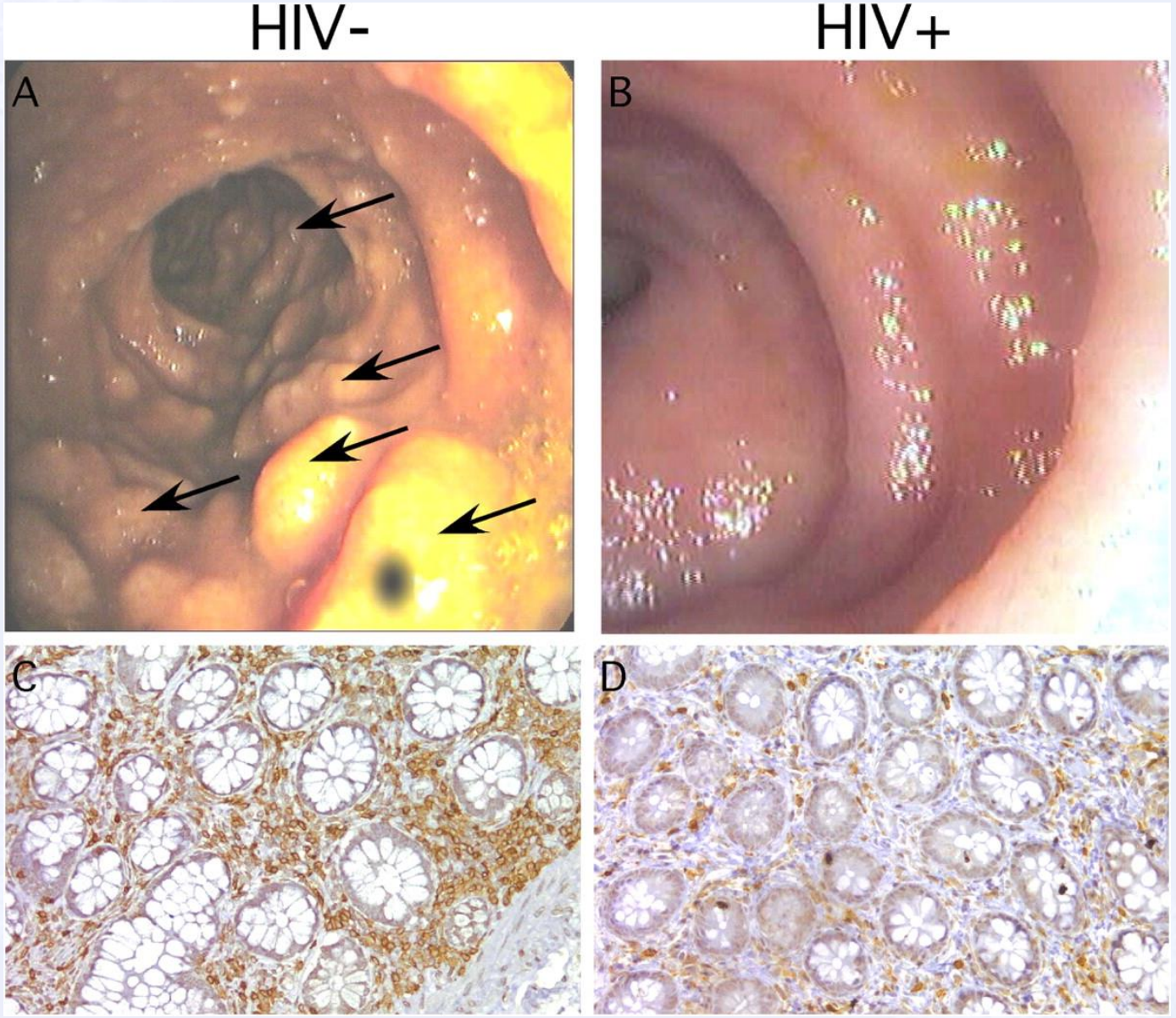
HIV Pathogenesis

Natural History of HIV-1 Infection

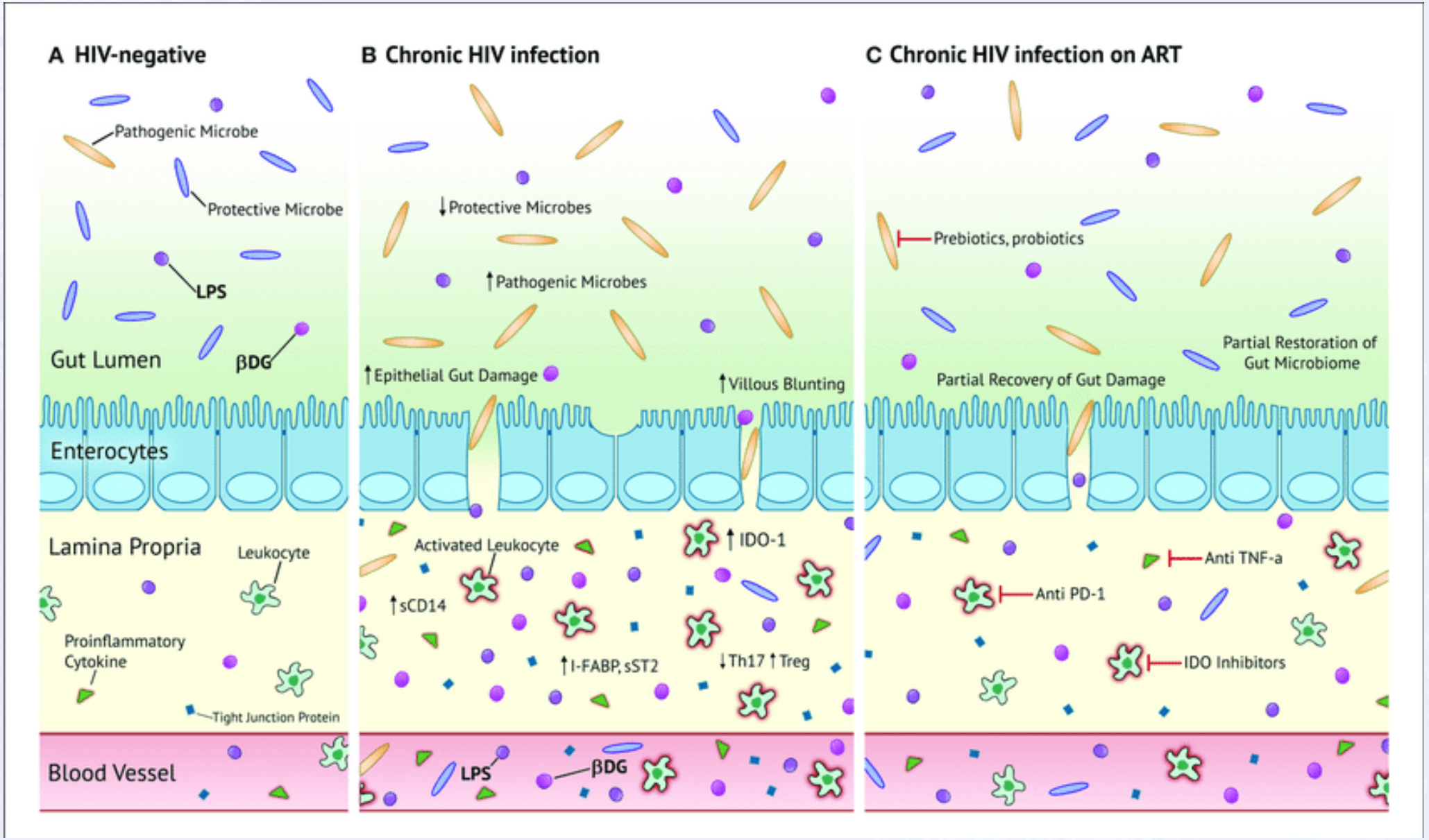


Graph adapted from following sources: https://www.researchgate.net/publication/270453537_Role_of_Chemokines_in_the_transmission_of_HIV_and_significance_of_CCR5-D32_Allele_as_HIV-_Resistance_Mutation and https://www.nejm.org/doi/full/10.1056/nejm199302043280508.

Gut is Area of Massive T Cell Loss



Translocation



Many Faces of Immune Activation: A Multifactorial Interconnection

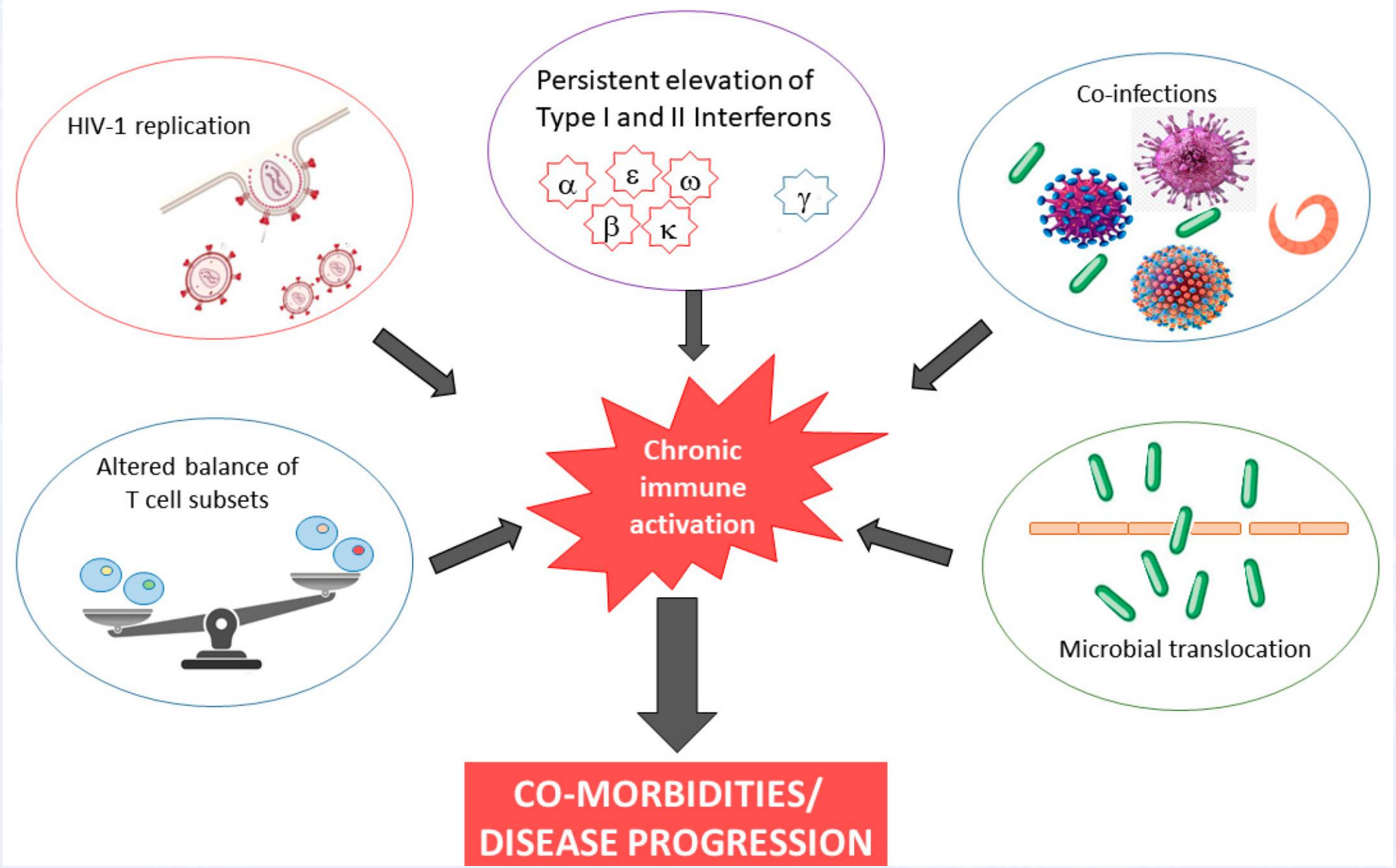

HIV-1 replication
Persistent elevation of
Type I and II Interferons
α
ε
ω
γ
β
κ
Co-infections
Altered balance of
T cell subsets
Chronic
immune
activation
Microbial translocation
CO-MORBIDITIES/
DISEASE PROGRESSION

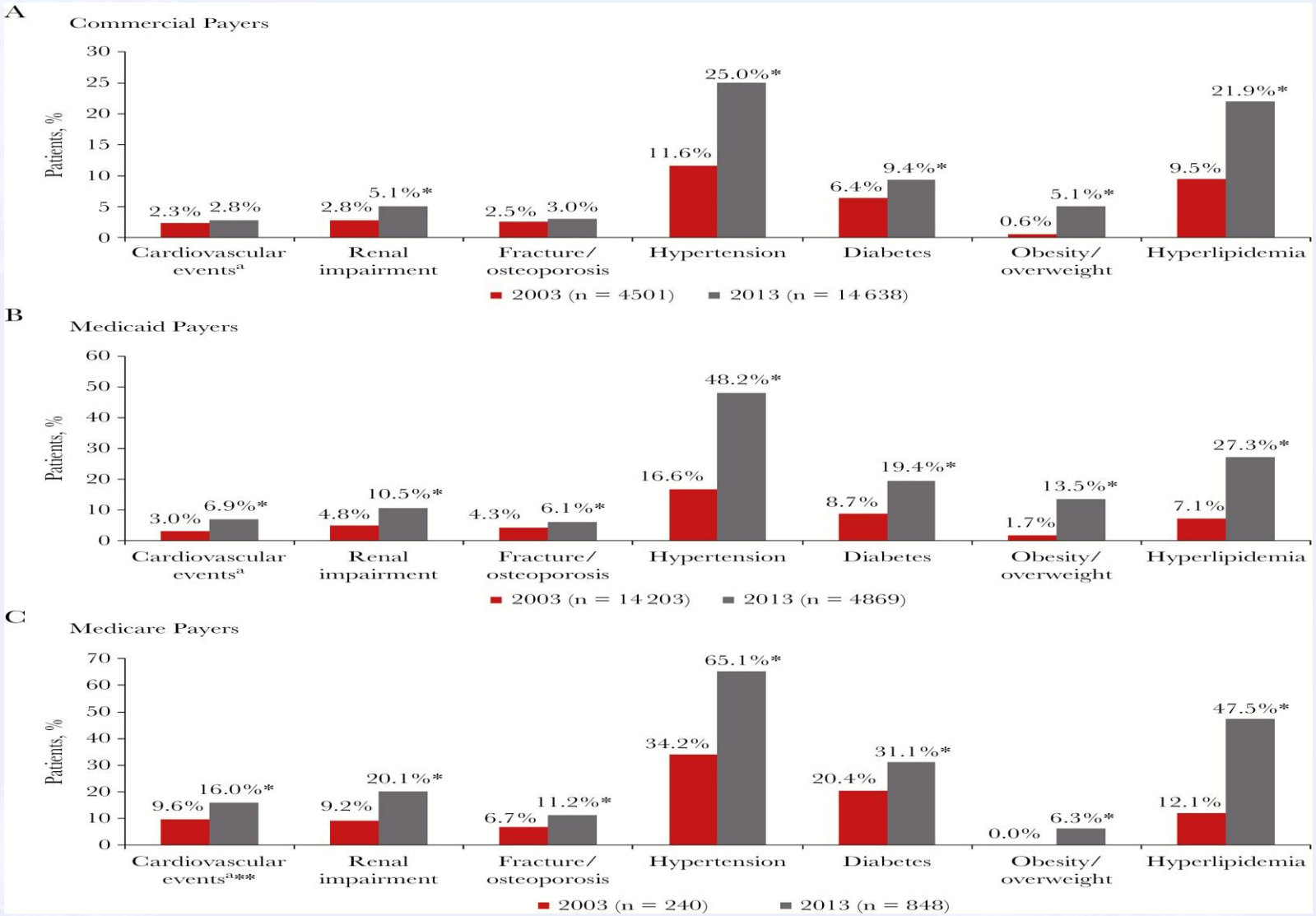
Table. Comparative Prevalence of Selected Comorbidities Among People With HIV Treated With Antiretroviral Therapy and Matched Controls Without HIV in the United States, 2003-2013[a]

	Commercial Insurance, No. (%)		Medicaid, No. (%)	
	HIV Cases (n = 20 519)	Controls (n = 46 763)	HIV Cases (n = 16 020)	Controls (n = 36 791)
Cardiovascular events	1375 (6.7)	1871 (4.0)	1666 (10.4)	2796 (7.6)
Kidney impairment	1806 (8.8)	1309 (2.8)	2435 (15.2)	2171 (5.9)
Fracture or osteoporosis	1559 (7.6)	2993 (6.4)	2083 (13.0)	3679 (10.0)
Liver disease	1272 (6.2)	1122 (2.4)	1810 (11.3)	1656 (4.5)
Cancer	1642 (8.0)	1917 (4.1)	1570 (9.8)	1545 (4.2)

[a] Adapted from Gallant et al.[2]

Source: Galant et al. J Infect Dis, Volume 216, Issue 12, 15 December 2017, Pages 1525–1533

Figure. Trends in comorbid conditions among patients with prevalent human immunodeficiency virus (HIV) infection, by ...



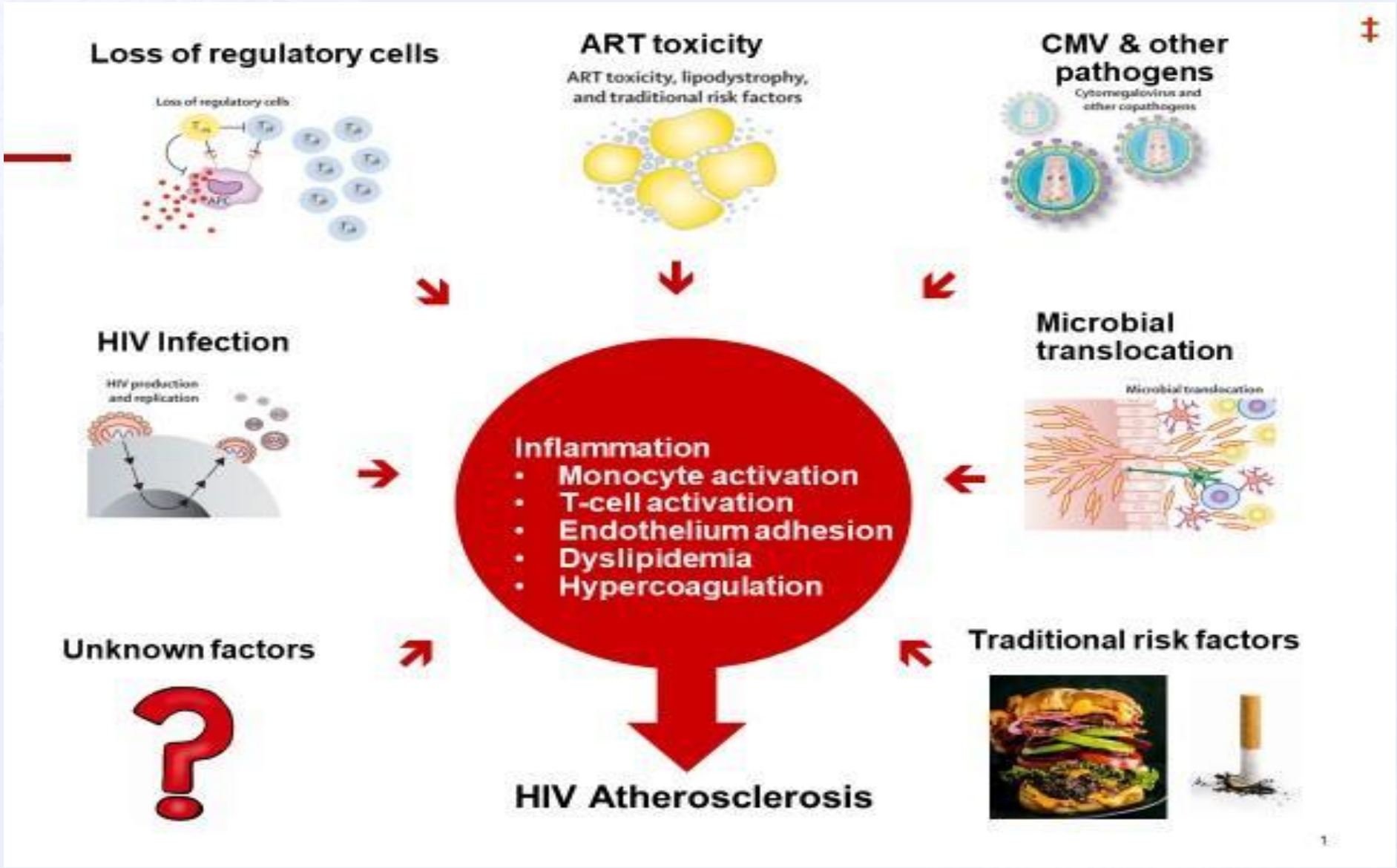
J Infect Dis, Volume 216, Issue 12, 15 December 2017, Pages 1525–1533, https://doi.org/10.1093/infdis/jix518

Common Comorbid Conditions

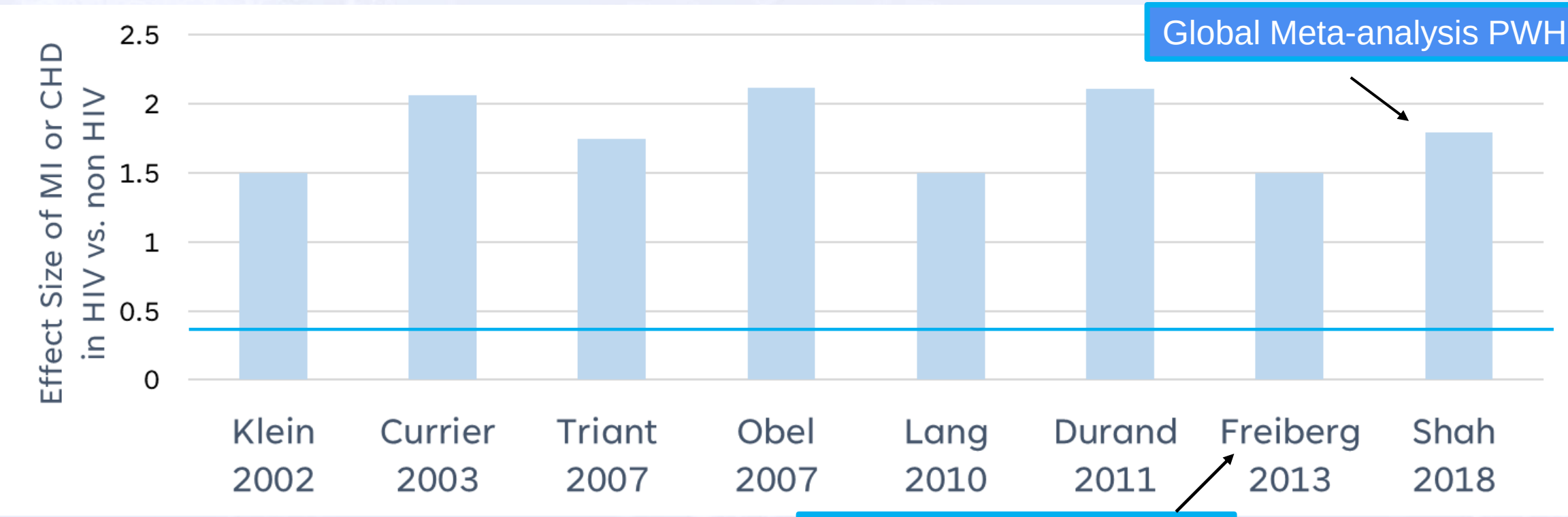
- Frailty
- **Cardiovascular disease**
- **Obesity**
- Diabetes mellitus
- Renal disease
- Osteoporosis
- Neurocognitive disorders
- **Cancers**

Cardiovascular Disease

Cardiovascular Disease (CVD)

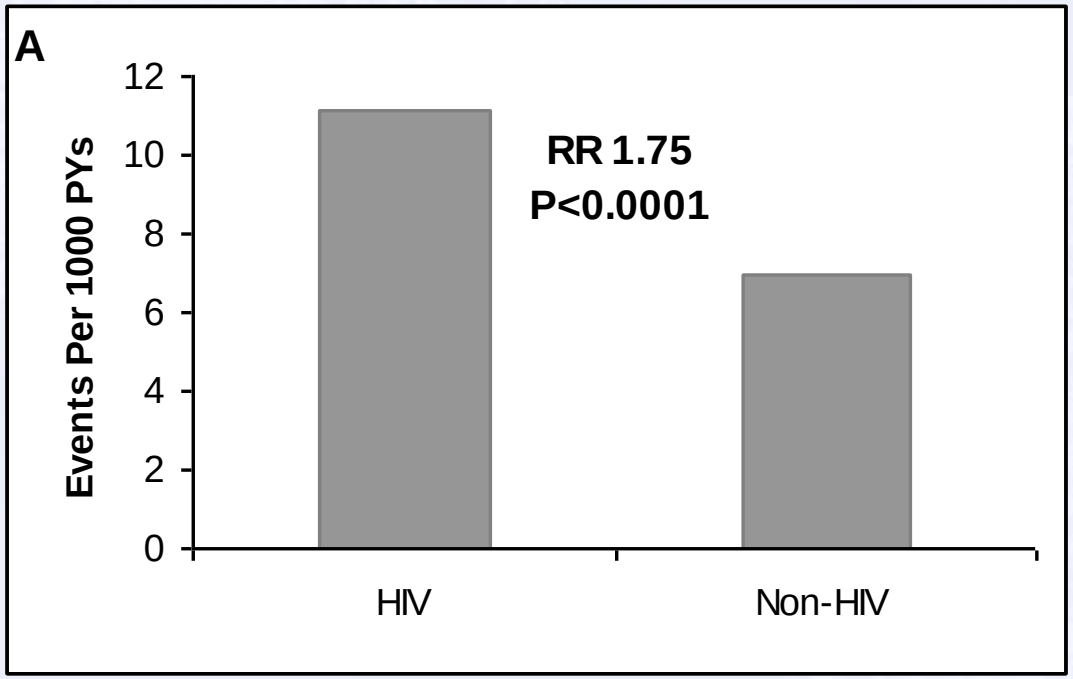


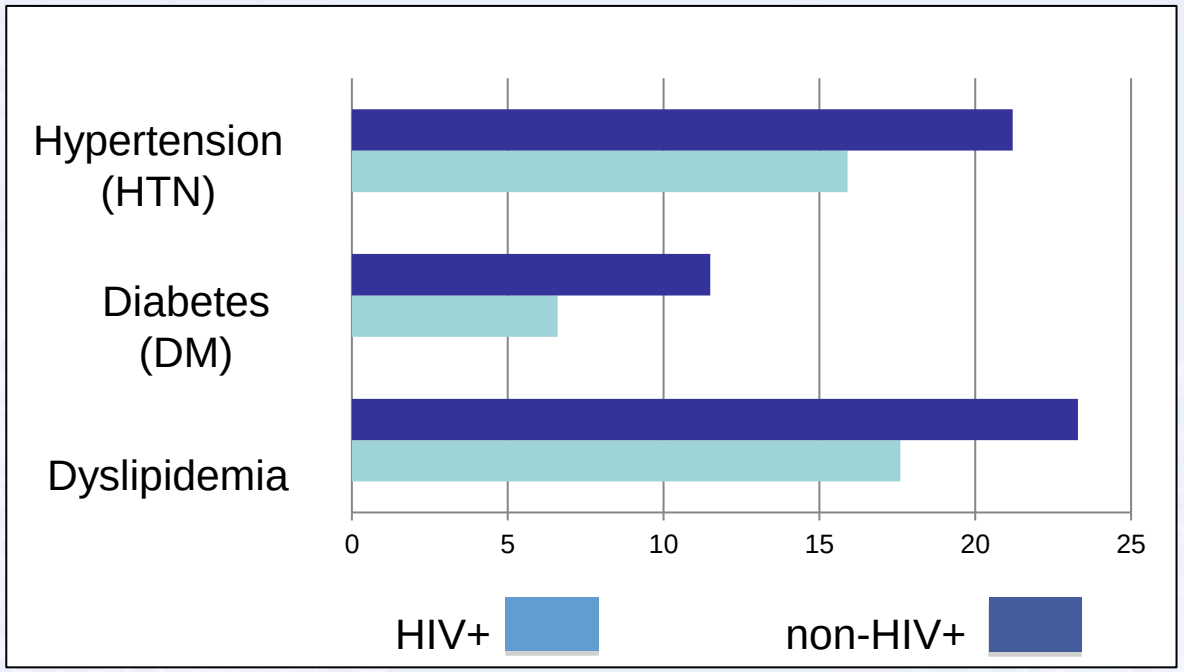
CVD Risk in PWH is Increased Beyond That Predicted by Traditional Risk Factors



In the VACS cohort, the HR of MI was 1.48 in HIV vs. non-HIV adjusting for FRS, and comorbidities, (95% CI 1.27-1.72).

Increased Traditional Risk Factors Account for Only a Portion of CVD Risk in HIV

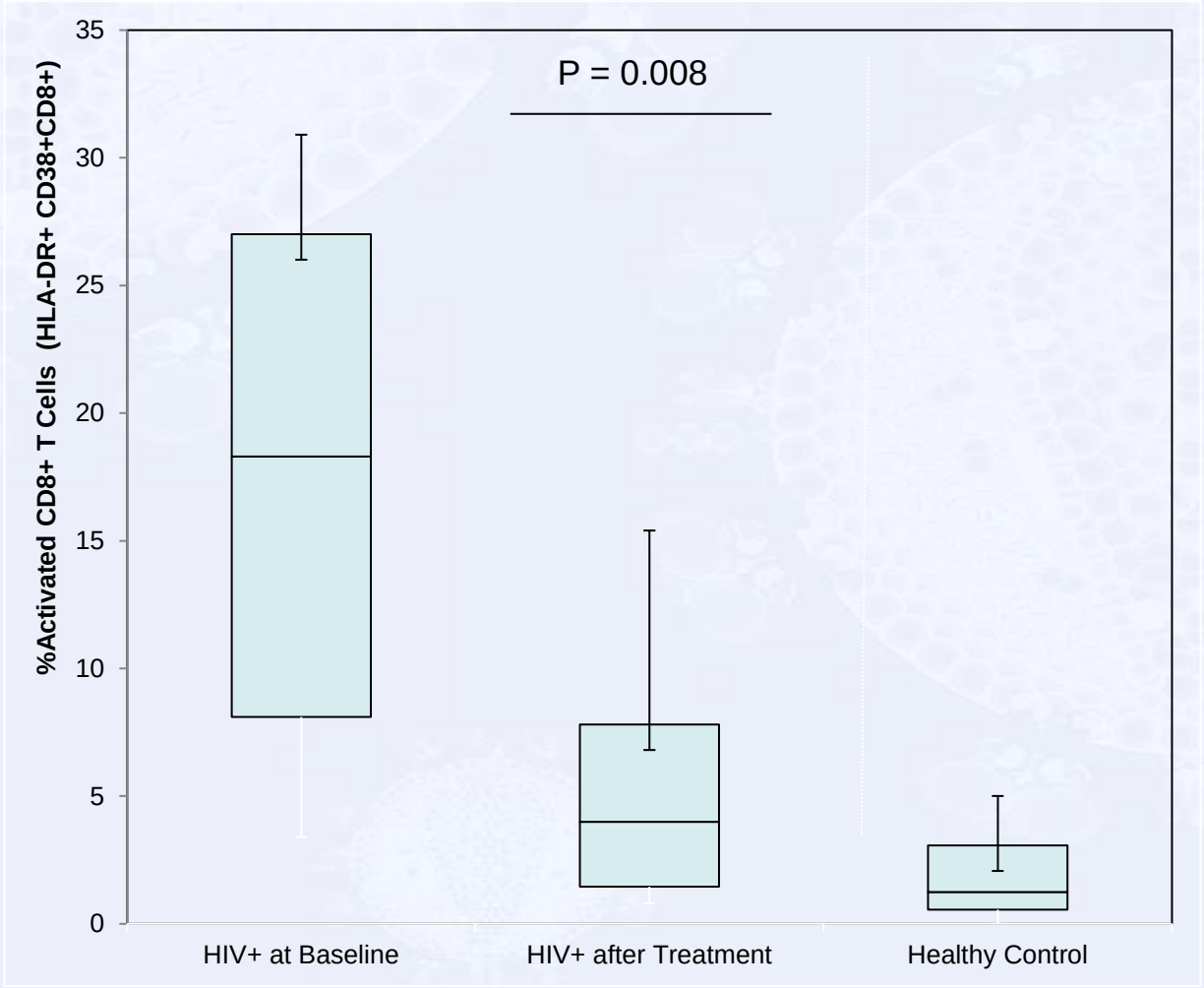


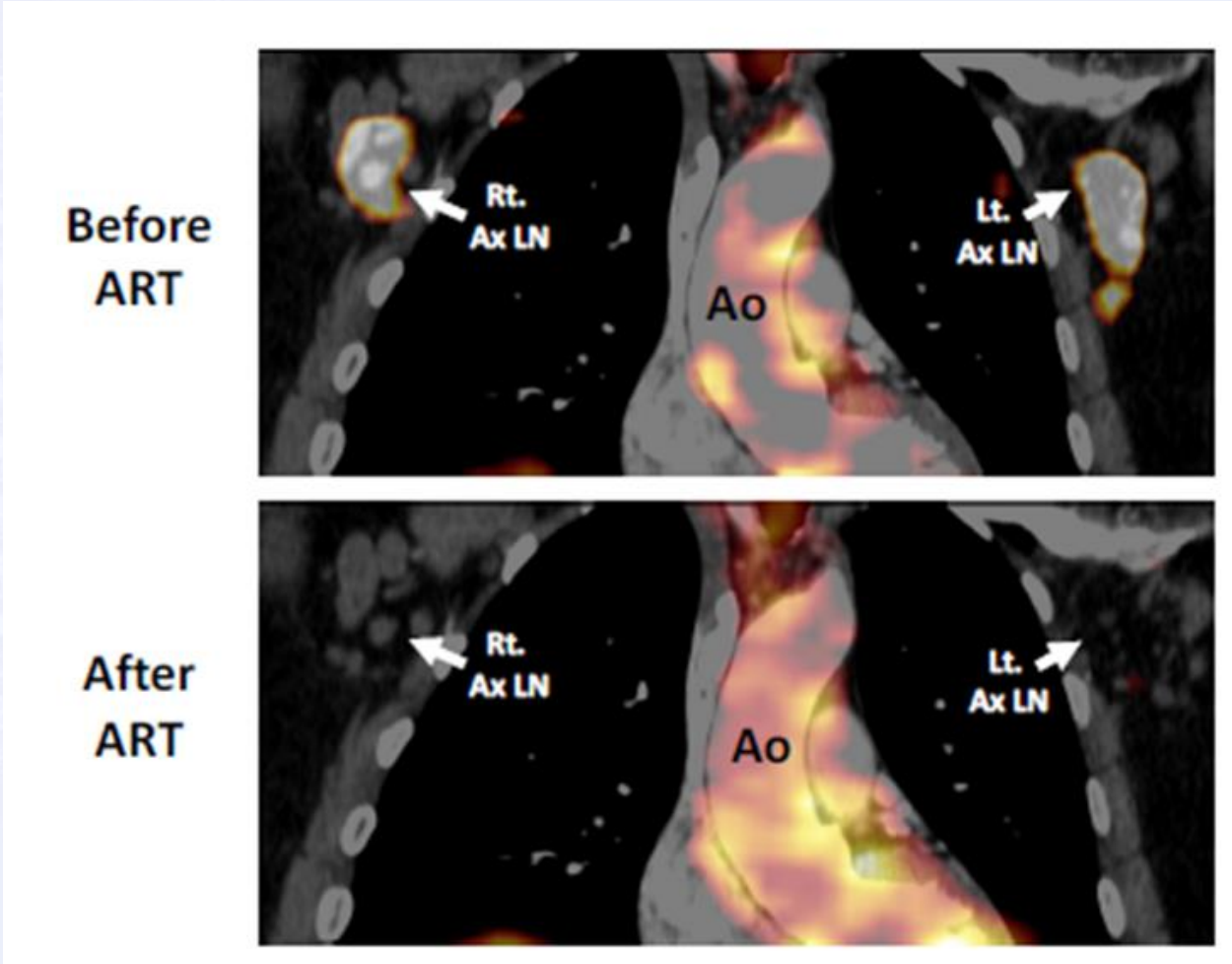


- DM, HTN, and dyslipidemia, though increased, accounted for 25% of excess risk.
- Newer studies suggest importance of inflammation and immune dysfunction, as non traditional risk factors.

Triant JCEM 2007

Immune Activation Improves with ART but Does not Normalize and Inflammation Persists





Zanni JAMA Cardiology 2016

ART-Specific Implications

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)
  - Older drugs (didanosine, stavudine): mitochondrial toxicity
  - TDF: nephrotoxicity
  - TAF: increased cholesterol, LDL, weight gain
  - Abacavir: conflicting data (higher risk in observational studies)
- Protease inhibitors (PIs): initial concern for a class effect but now drug specific
  - Boosted darunavir-progressively increased risk
  - Boosted atazanavir-not associated with an increased risk
- Integrase strand transfer inhibitors (INSTIs)
  - Weight gain, Diabetes, HTN
  - Neutral to lower CVD risk

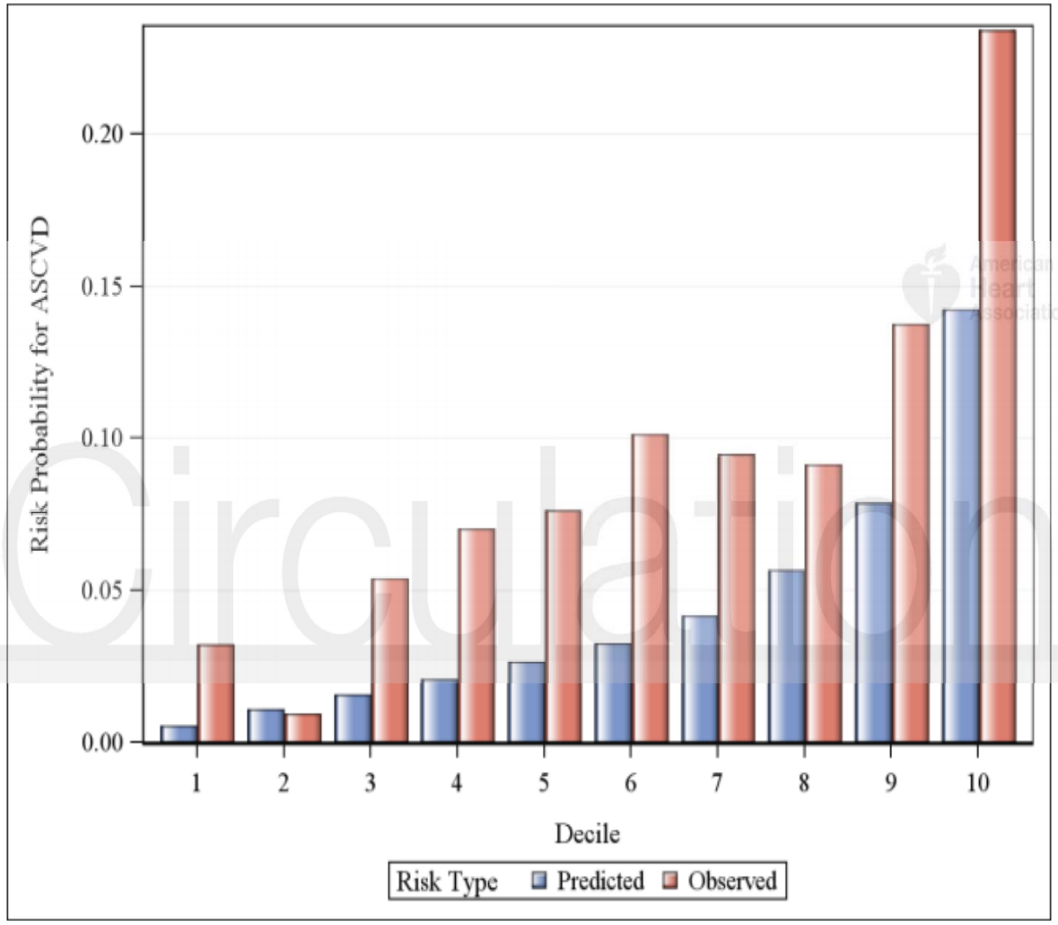
Current Challenges in Preventing and Treating CHD in HIV

- Identifying patients with disease: current risk identification strategies are not adequate
- Understanding the optimal timing and use of ART to maximize effects on immune function and minimize metabolic effects
- Developing a safe and effective strategy for primary prevention, especially for those not identified by current algorithms, but with substantial subclinical disease
- Developing an intervention that addresses both traditional and immune-related risk factors

Circulation
Volume 137, Issue 21, 22 May 2018; Pages 2203-2214
https://doi.org/10.1161/CIRCULATIONAHA.117.028975

ORIGINAL RESEARCH ARTICLE

Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection



Clinical Perspective

What Is New?

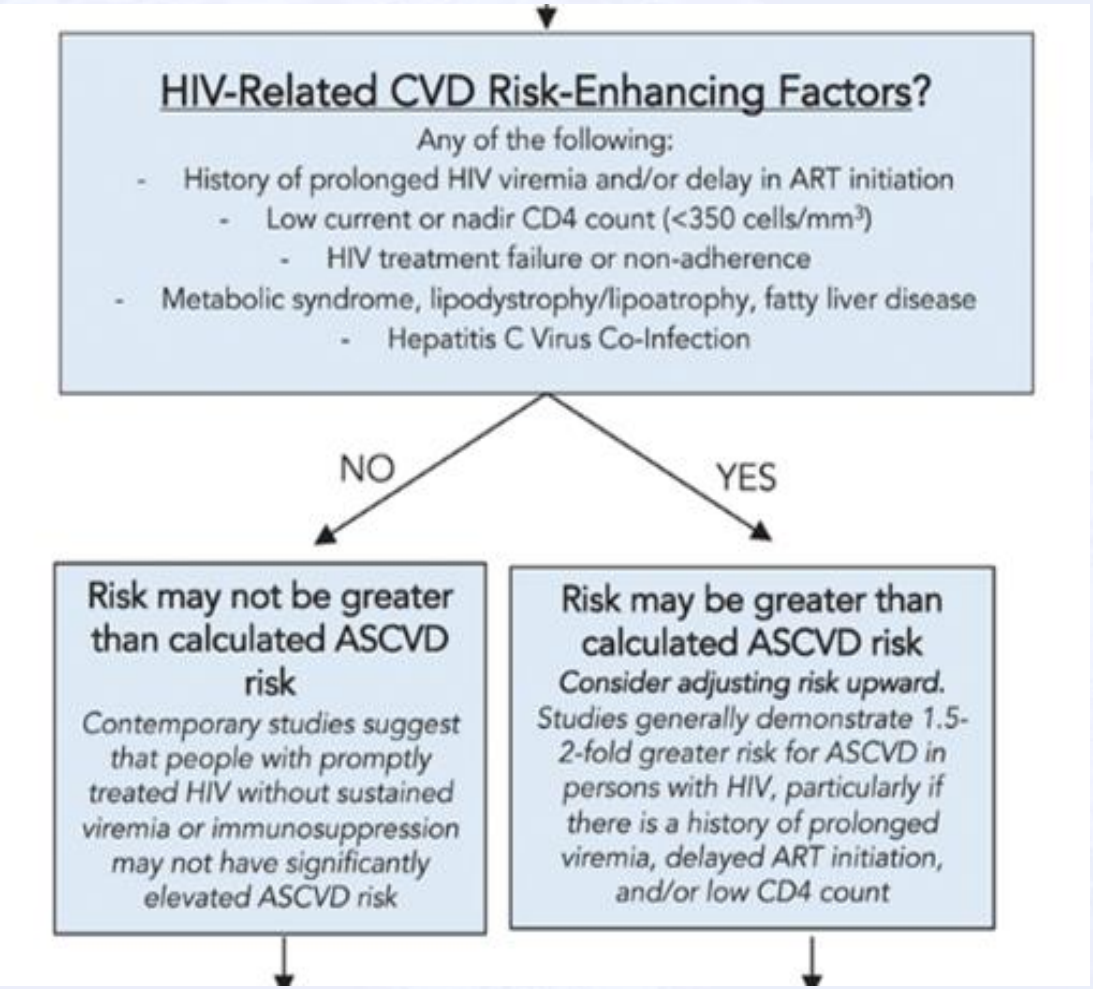
- In this study evaluating cardiovascular disease (CVD) risk prediction in HIV populations, established CVD risk prediction functions were shown to underestimate risk in HIV-infected men and poorly discriminate between individuals who experience an outcome from those who do not.
- The study adds new knowledge by evaluating several risk functions in parallel for the first time, including the FHS (Framingham Heart Study) function for hard coronary heart disease and 2 functions that predict atherosclerotic CVD, the American College of Cardiology/American Heart Association function and an adapted FHS global CVD function.

What Are the Clinical Implications?

- Our findings suggest that established CVD risk functions may not accurately estimate risk in the setting of HIV disease and may fail to identify men at elevated CVD risk who would benefit from aggressive risk reduction.
- The incorporation of HIV-specific variables into current CVD risk prediction algorithms may be necessary to accurately predict risk for this population that is already at heightened risk.
- Tailored CVD risk prediction strategies may apply to other high-risk populations with chronic inflammatory conditions.

Triant VA, et al. *Circulation* 2018;137:2203-14

Interim Approach to Primary Prevention



LOW-MODERATE RISK APPROACH

LIFESTYLE OPTIMIZATION
(Particularly Smoking Cessation)
+
YEARLY RE-ASSESSMENT OF RISK
Consider high risk approach if patient-clinician discussion determines potential benefit > risk and patient preference for high risk approach

HIGH RISK APPROACH

Consider referral to cardiologist; patient-clinician discussion re: benefit vs. risk, patient preference

LIFESTYLE OPTIMIZATION
(Particularly Smoking Cessation)
+
LIPID LOWERING DRUG THERAPY
*Atorvastatin 10-80 mg**
*Rosuvastatin 5-40 mg**
Pitavastatin 2-4 mg

Statin Dosing: START LOW, GO SLOW
Decrease dose or discontinue if severe myalgia or unexplained muscle weakness, LFTs >3x the upper limit of normal, or CK >10x the upper limit of normal

Feinstein MJ et al. *Circulation* 2019;140(2):e98-e124.

Need for a Large RCT to Inform Clinical Practice

- HIV patients with low traditional risk scores are at increased risk for CVD with subclinical plaque and inflammation

- ART alone is not enough to prevent CVD in PWH

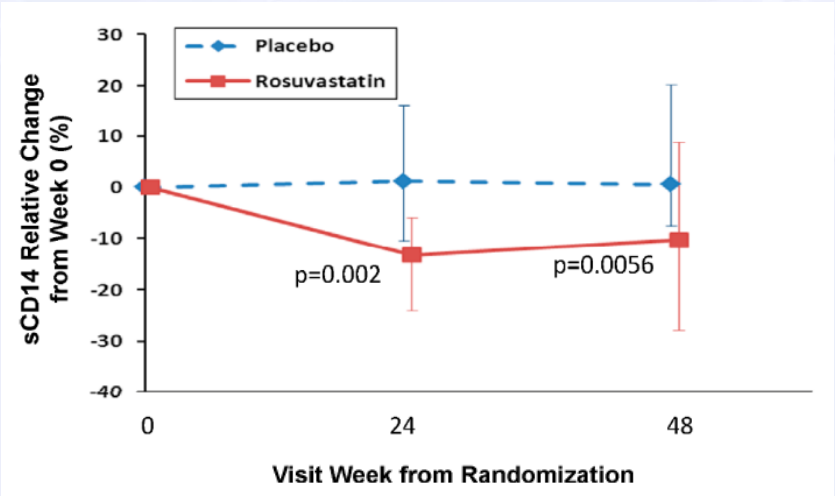
Statins Address Both Traditional & Immune Risk Factors in HIV

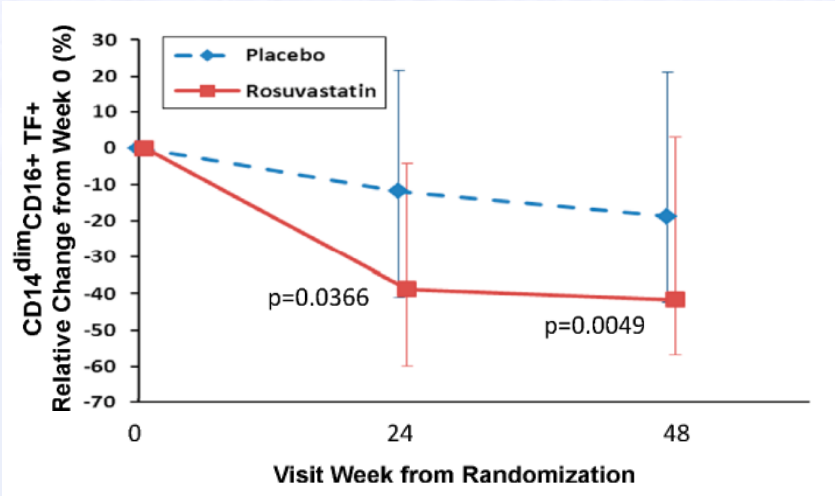
LDL Lowering:

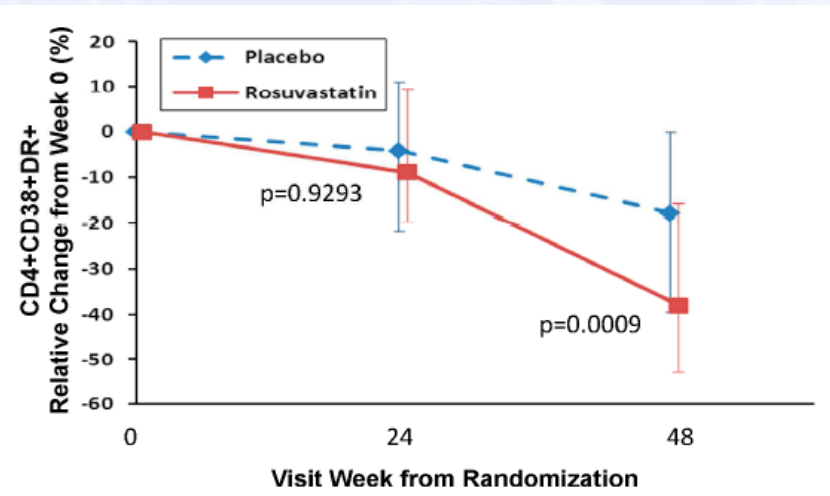
- Statins lower LDL by similar amounts in patients with and without HIV: (HIV-infected: -26.2%; HIV-uninfected: -26.9%)

Dampening of Immune Activation:

- Decrease monocyte activation reflected in decreased circulating levels of sCD14 and the macrophage-derived phospholipase Lp-PLA2







Silverberg Ann Int Med 2009, McComsey CROI 2013, Funderburg JAIDS ePUB

Main question REPRIEVE aimed to answer:

Will statin therapy prevent atherosclerotic cardiovascular disease (ASCVD)-related major adverse cardiovascular **EVENTS** (MACE) among PLHIV on ART *who may not be already receiving statin therapy clinically* based on their traditional CVD risk score and LDL-c level?

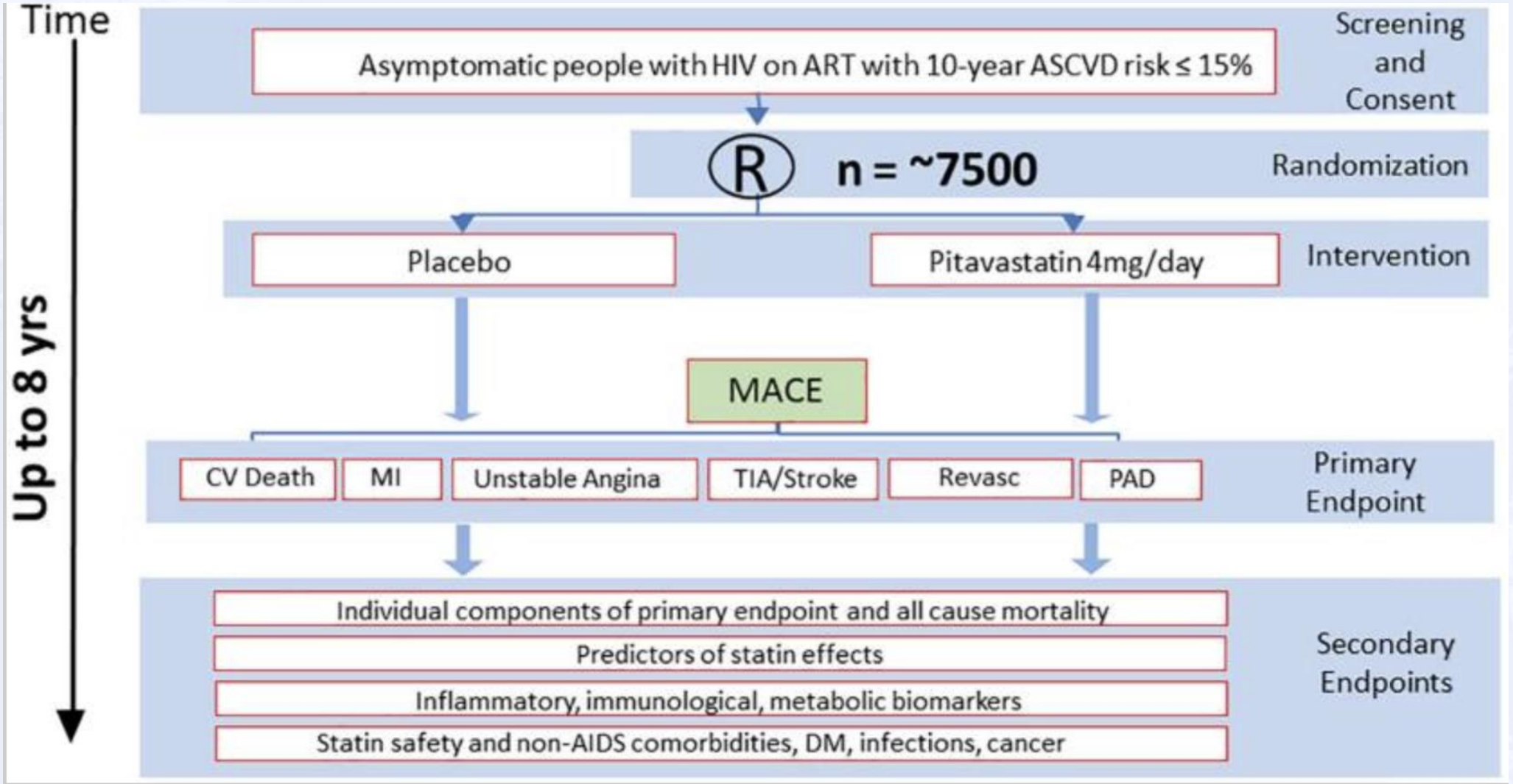
NIH National Heart, Lung, and Blood Institute

NIH National Institute of Allergy and Infectious Diseases

REPRIEVE

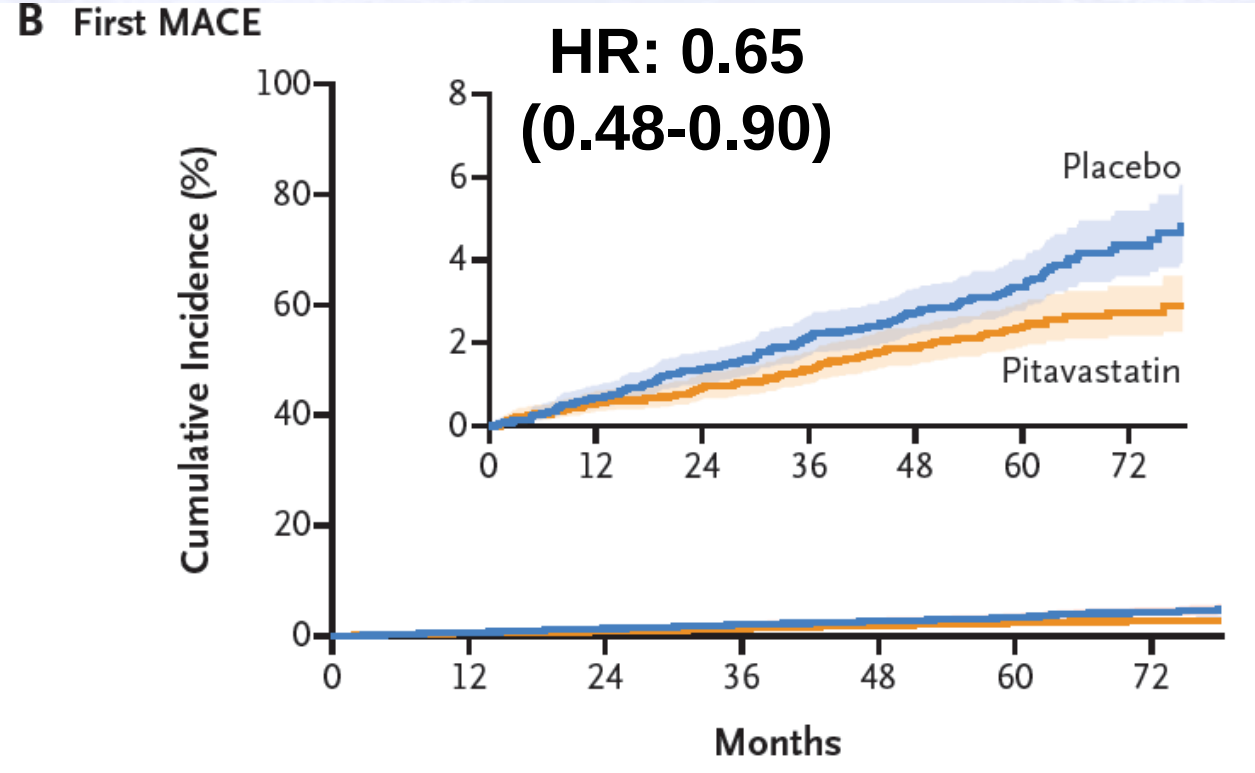
ACTG AIDS CLINICAL TRIALS GROUP

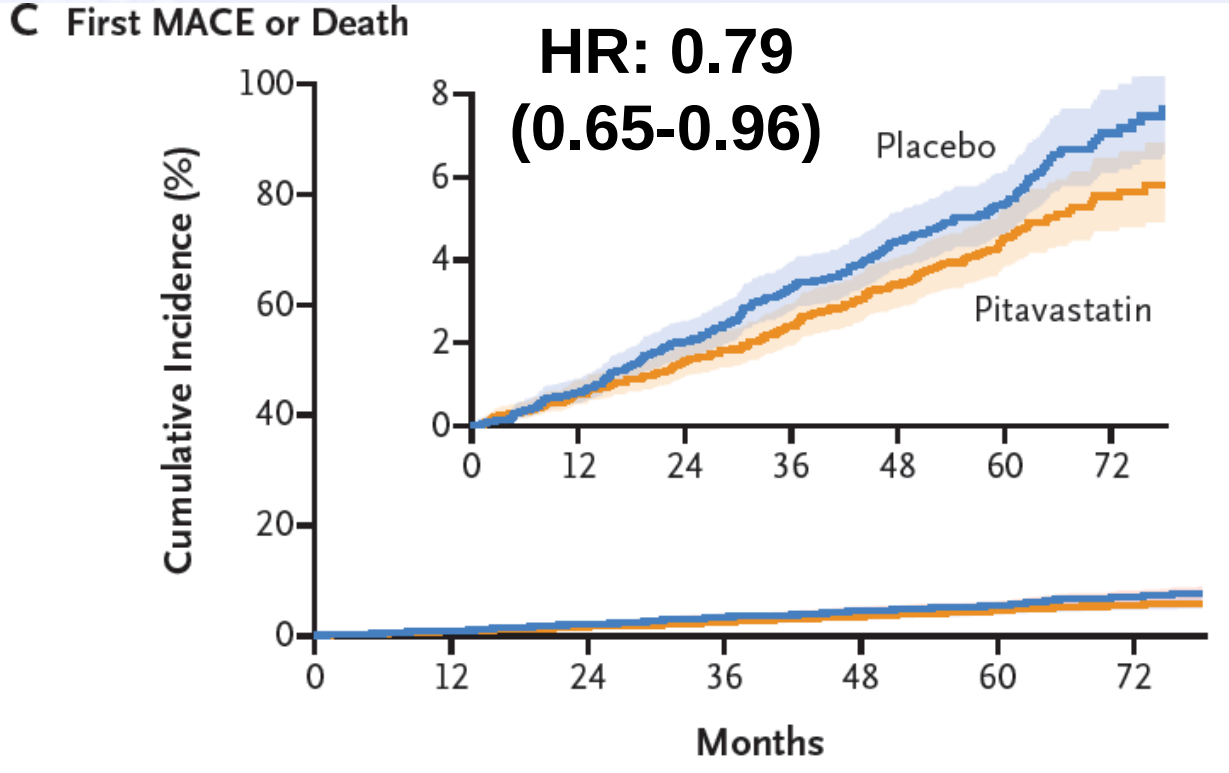
REPRIEVE Trial Schema



Grinspoon, Am Heart Journal 2019

REPRIEVE: Main Outcomes





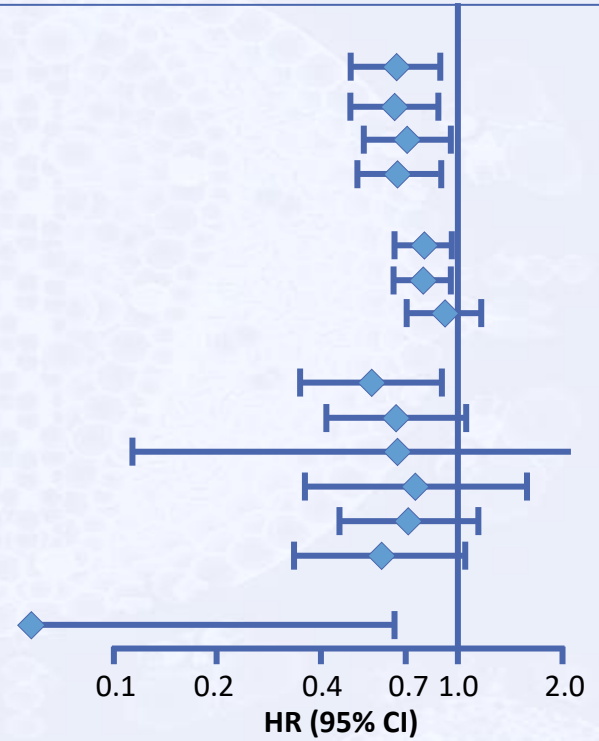
Grinspoon, NEJM, 2023

Topline Data

- The Data Safety Monitoring Board (DSMB) found a **robust signal for efficacy with a 35% reduction in MACE (strokes, heart attacks, revascularizations, peripheral ischemia, and cardiac related death)** relative to placebo and voted to close the trial for efficacy.
- There was a 21% reduction in MACE plus all cause death vs. placebo.
- The study was presented IAS conference in July and published at the same time in the NEJM.

REPRIEVE: First Major Cardiovascular Event and Individual MACE Components

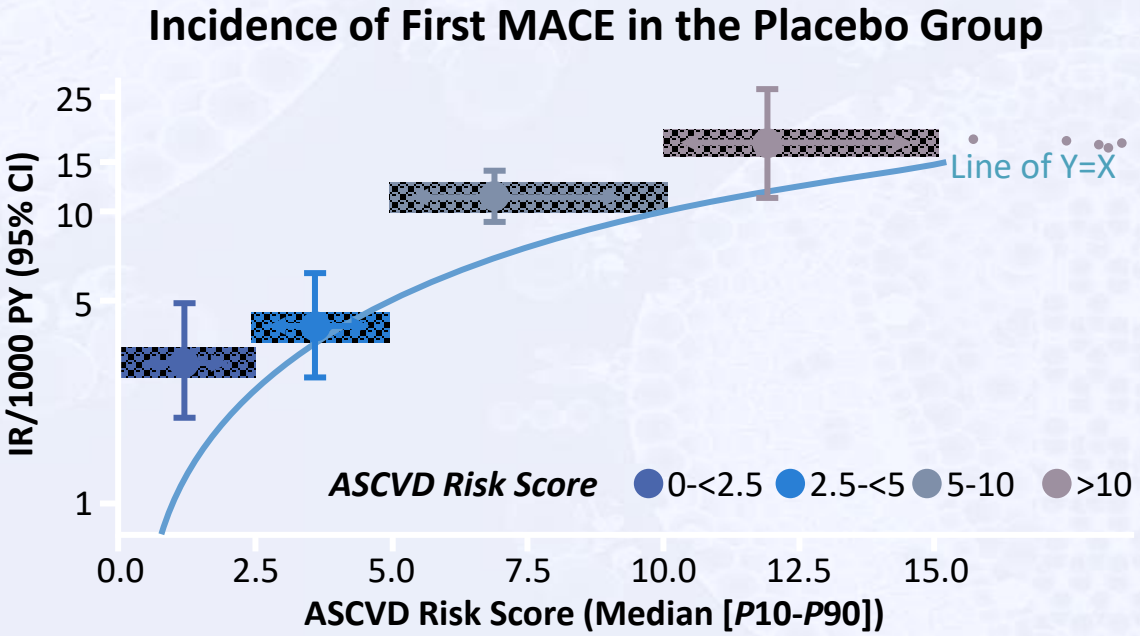
	Pitavastatin no./1000 PY (n events)	Placebo no./1000 PY (n events)	HR (95% CI)	Nominal *P* Value
Primary endpoint and supporting analyses				
First MACE	4.8 (89)	7.3 (136)	0.65 (0.48-0.90)	.002
First Confirmed MACE	3.8 (71)	5.9 (110)	0.65 (0.48-0.87)	.004
First MACE (as-treated analysis)	4.4 (77)	6.3 (107)	0.71 (0.53-0.95)	.021
First MACE (per-protocol analysis)	4.5 (80)	6.8 (120)	0.67 (0.50-0.89)	.005
Secondary endpoints and supporting analyses				
First MACE or death	9.2 (170)	11.6 (216)	0.79 (0.65-0.96)	.021
First MACE or death including viral status follow-up	9.1 (173)	11.7 (222)	0.78 (0.64-0.95)	.014
Death (all-cause)	6.2 (116)	6.8 (129)	0;.90 (0.70-1.16)	.42
Individual components of MACE				
First cardiac ischemia or MI	1.4 (26)	2.5 (47)	0.56 (0.34-0.90)	.017
First cerebrovascular (stroke or TIA)	1.6 (29)	2.4 (44)	0.66 (0.41-1.05)	.080
First Peripheral Arterial Ischemia	0.1 (2)	0.2 (3)	0.67 (0.11-4.02)	.66
CV death	0.6 (12)	0.9 (16)	0.75 (0.36-1.59)	.45
CV or undetermined death	1.6 (30)	2.2 (42)	0.71 (0.45-1.14)	.16
First cardiac catheterization or revascularization	1.0 (18)	1.7 (31)	0.59 (0.33-1.05)	.073
First carotid or cerebrovascular revascularization	0 (0)	0 (0)		
First peripheral arterial revascularization	0 (0)	0.3 (6)	0 (0-0.66)	.99

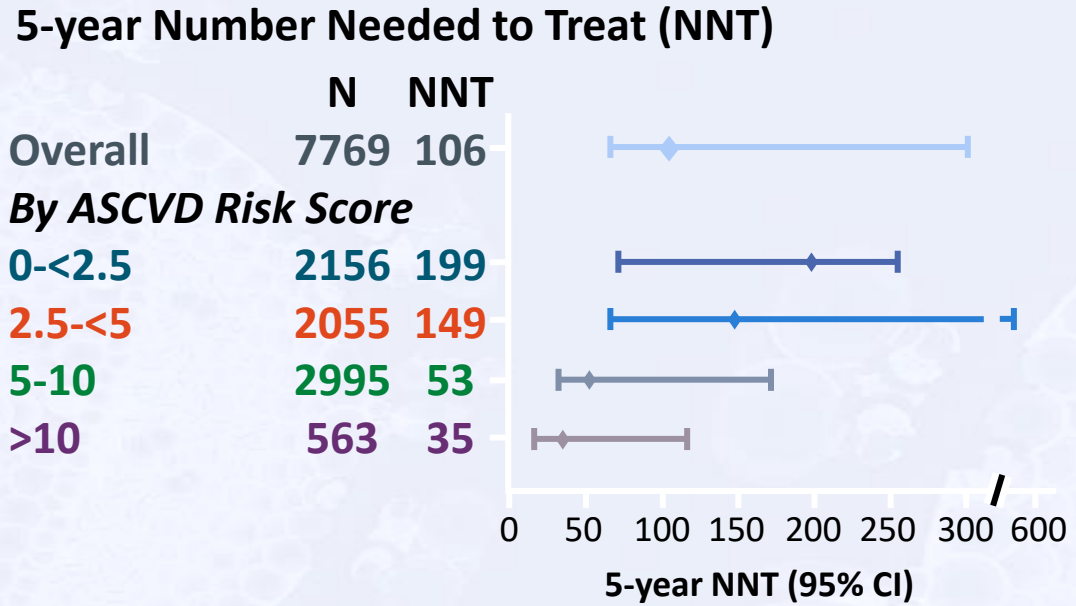


- Pitavastatin effect consistent across major subgroups, including LDL, age, sex, race, GBD region, CD4 count, ART duration
- LDL cholesterol decreased by 30% in pitavastatin group; no change with placebo

Grinspoon. IAS 2023. Abstr SY06. Grinspoon SK. NEJM. 2023;[Epub].

REPRIEVE: First Major Cardiovascular Event By ASCVD Risk Score





- 5-yr NNT of 106 (95% CI: 64-303) compares favorably with a range of 80-160 for HTN treatment in other studies
- Event rates increased with increasing risk categories for ASCVD, suggesting greater benefit among the participants at higher CV risk at baseline

Grinspoon. IAS 2023. Abstr SY06. Grinspoon SK. N Engl J Med. 2023; Epub.

JAMA Network™

Daily Statin Trial for People With HIV Halted Early for Clear Benefit

POZ™

Statin Reduces Cardiovascular Risk for People With HIV

By Liz Highleyman Large trial finds that pitavastatin lowered the risk for major cardiovascular events by 35%. Read the full article here.

A planned interim analysis of data from the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study found that participants who took pitavastatin calcium, a daily statin, **lowered their risk of major adverse cardiovascular events by 35% compared with those receiving a placebo.**

Sources: https://jamanetwork.com/journals/jama/fullarticle/2804471 and https://www.poz.com/article/statin-reduces-cardiovascular-risk-people-hiv

Implications for Care of PWH

- Statin therapy with lifestyle counseling, should be considered for PWH, even those with low-moderate risk predicted traditional risk to reduce major cardiovascular events and death

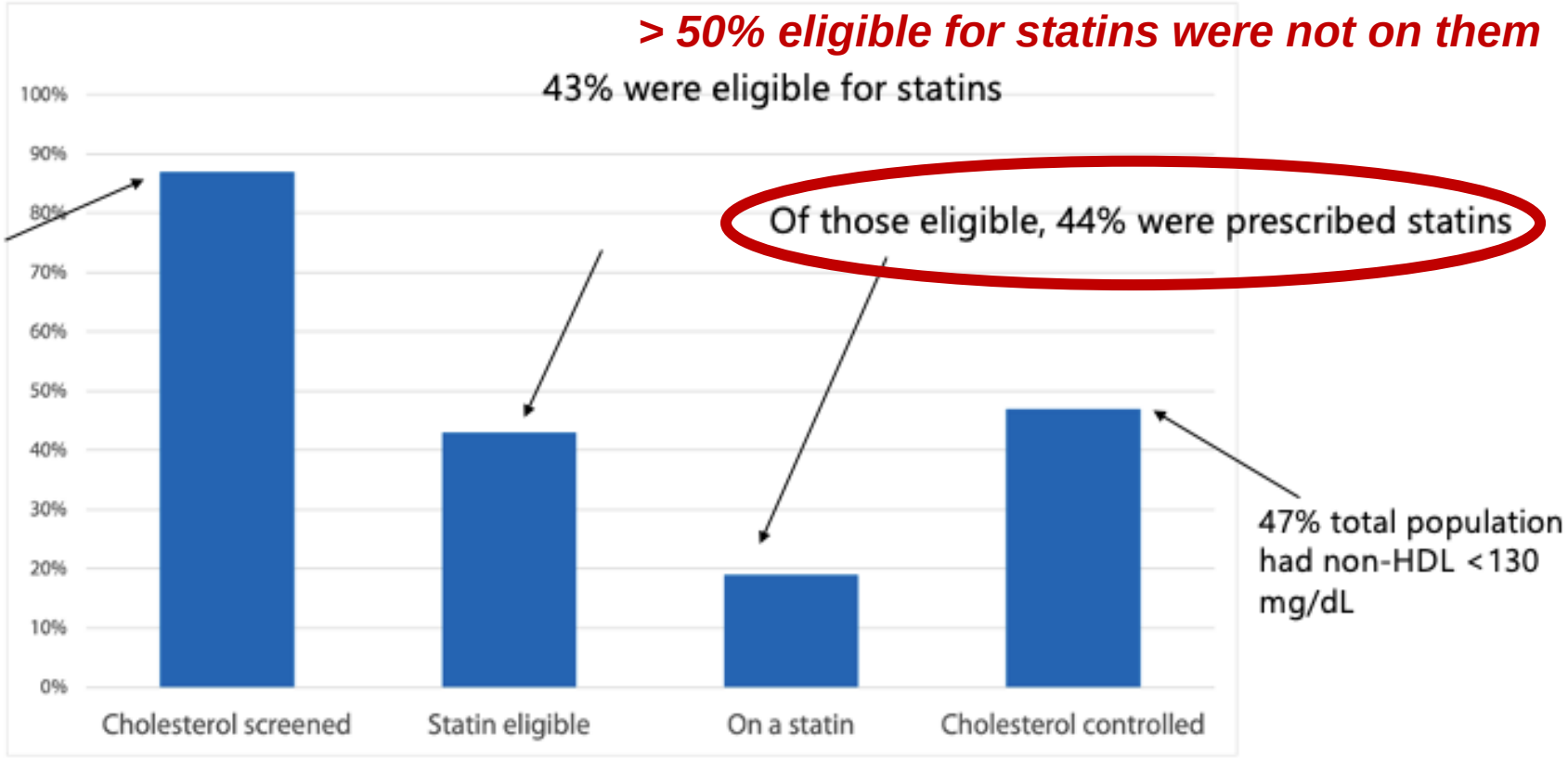
- For PWH, the decision to take a statin should be individualized
  - Shared decision making between the individual and the clinician
  - All relevant factors including statin risk and benefits should be considered, including but not limited to the results of REPRIEVE. This may include drug interactions, metabolic factors, and patient preferences.
  - All considerations about risk should emphasize a healthy lifestyle, ideal diet, counseling on smoking, blood pressure, dyslipidemia, and other CVD risks

Next Steps for REPRIEVE

- Assess CVD mechanisms across global burden of disease regions and effects in key groups by race, sex, and region and by underlying CVD rates.
- Assess mechanism of MACE reduction, LDL lowering vs. effects on inflammation.
- Identify statin effects on non-CVD events including COVID-19 and HIV related cancer.
- Assess accuracy of pooled cohort equation.

Opportunities for Improvement in Statin Use Among People with HIV

> 50% eligible for statins were not on them



REPRIEVE results are an important reminder to all clinicians to think about statins in PWH who meet criteria; even before the study results, PWH were undertreated.

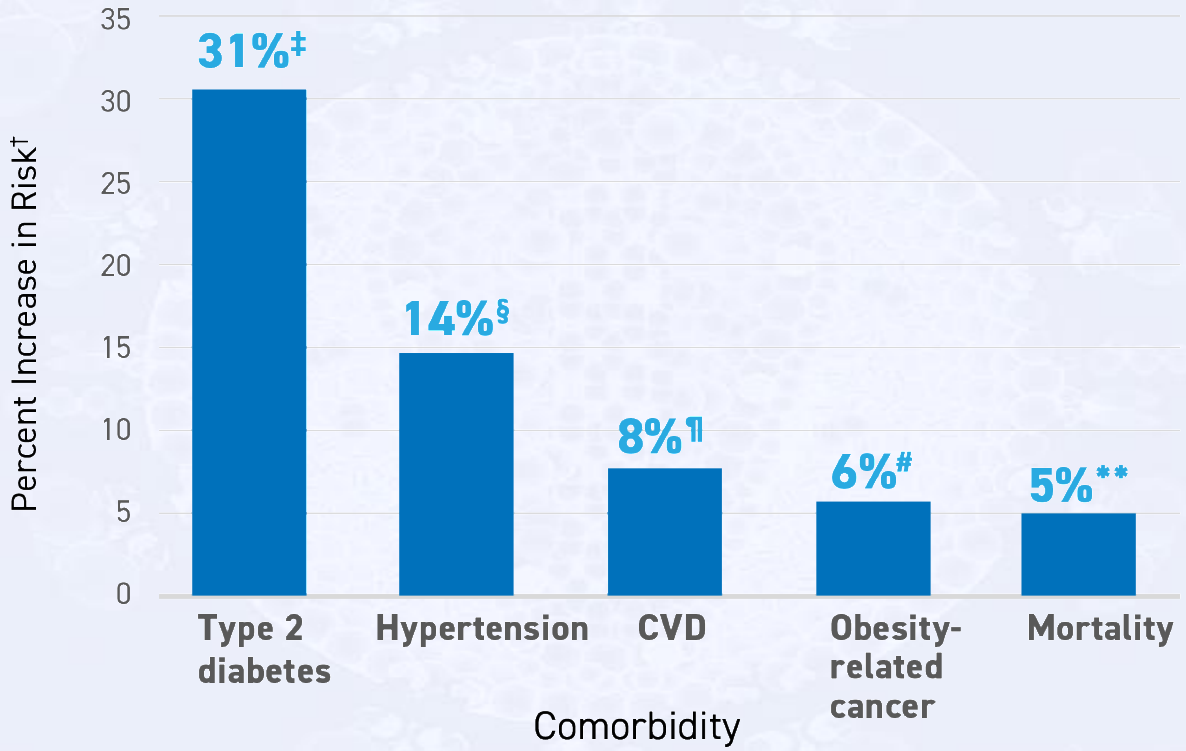
10-year ASCVD risk ≥ 7.5%, LDL-C ≥190 mg/dL, or age 40-75 years with diabetes

Megan Mclaughlin AIDS 2023

Obesity

Negative Outcomes Are Associated With Even a Moderate Weight Gain in the General Population

Meta-analysis* for comorbidity risk† due to weight gain
For each 5 kg (11 lb) of weight gain:



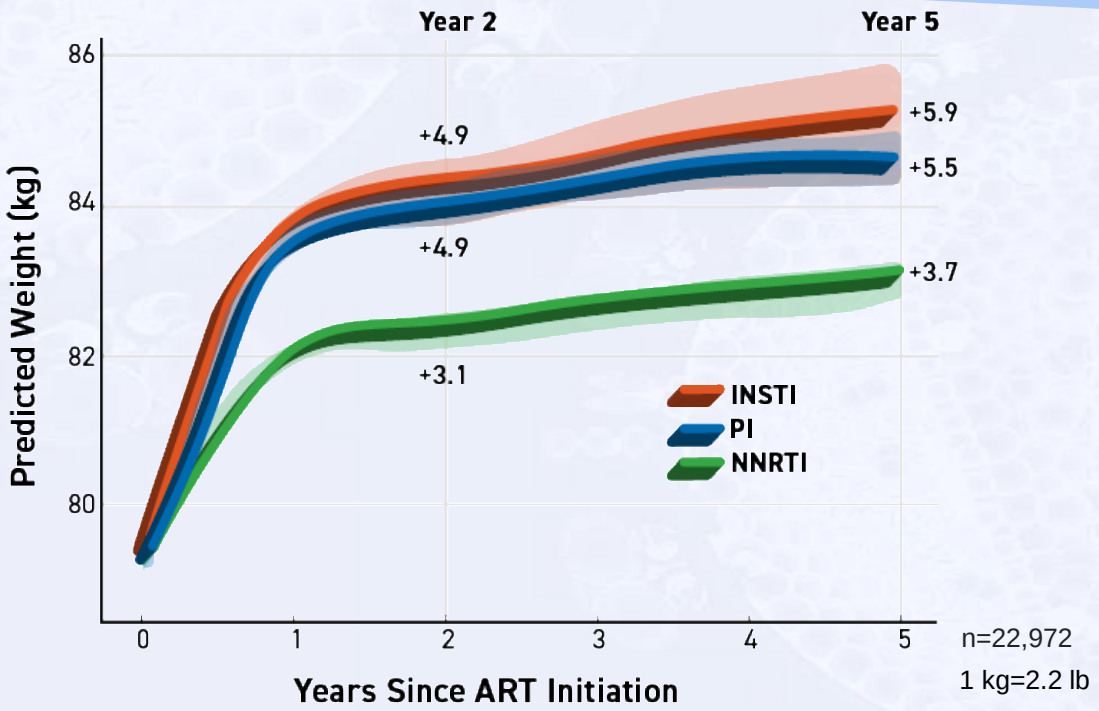
*Analysis of US women from the Nurses' Health Study and US men from the Health Professionals Follow-Up Study. †Increase in risk is based on the incident rate ratios for major health outcomes. ‡1.31 (95% CI: 1.28-1.33). §1.14 (95% CI: 1.10-1.17). ¶1.08 (95% CI: 1.08-1.09). #1.06 (95% CI: 1.02-1.09). **1.05 (95% CI: 1.04-1.07).

CVD=cardiovascular disease.

Reference: Zheng Y, et al. *JAMA.* 2017;318(3):255-269.

Weight Gain Was Greater in Treatment-naïve Patients Who Started Therapy on Specific ARV Regimens

Predicted Weight Changes Within 5 Years of ART Initiation by ART Class[1]



n=22,972

1 kg=2.2 lb

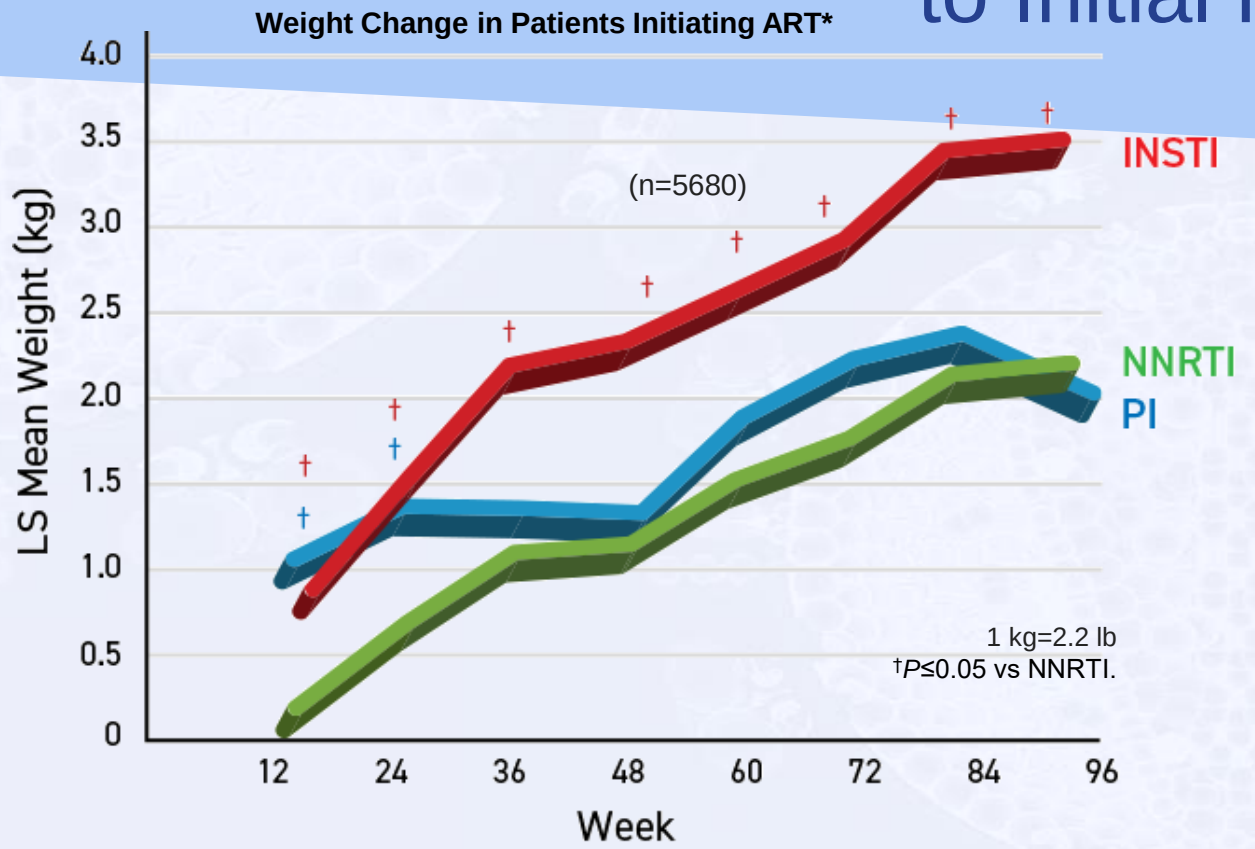
- Over 5 years, weight gain was greater in treatment-naïve patients who started therapy with an INSTI vs those who started with a PI or NNRTI[1]
  - Statistical significance was not described between classes of ART[2]

- NA-ACCORD was an observational study that evaluated ART-naïve patients with HIV (n=22,972) from 13 cohorts who initiated a sustained 3-drug ART regimen with an INSTI, PI, or NNRTI over the period of 2007 to 2016[1]
- Outcomes included predicted weight change by ART class (INSTI, PI, NNRTI) within 5 years of ART initiation[1]

ART=antiretroviral therapy; ARV=antiretroviral; INSTI=integrase strand transfer inhibitor; NA-ACCORD=North American AIDS Cohort Collaboration on Research and Design; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

References: 1. Bourgi K, et al. *J Int AIDS Soc.* 2020;23(4):e25484. **2.** Supplementary to: Bourgi K, et al. *J Int AIDS Soc.* 2020;23(4):e25484.

Weight Gain in Treatment-naïve Patients Varies According to Initial Regimen



- Weight gain was greater in treatment-naïve patients who started therapy with an INSTI (3.24 kg) vs those who started with a PI (1.72 kg) or NNRTI (1.93 kg)
- Black women gained approximately twice as much weight as women of other races

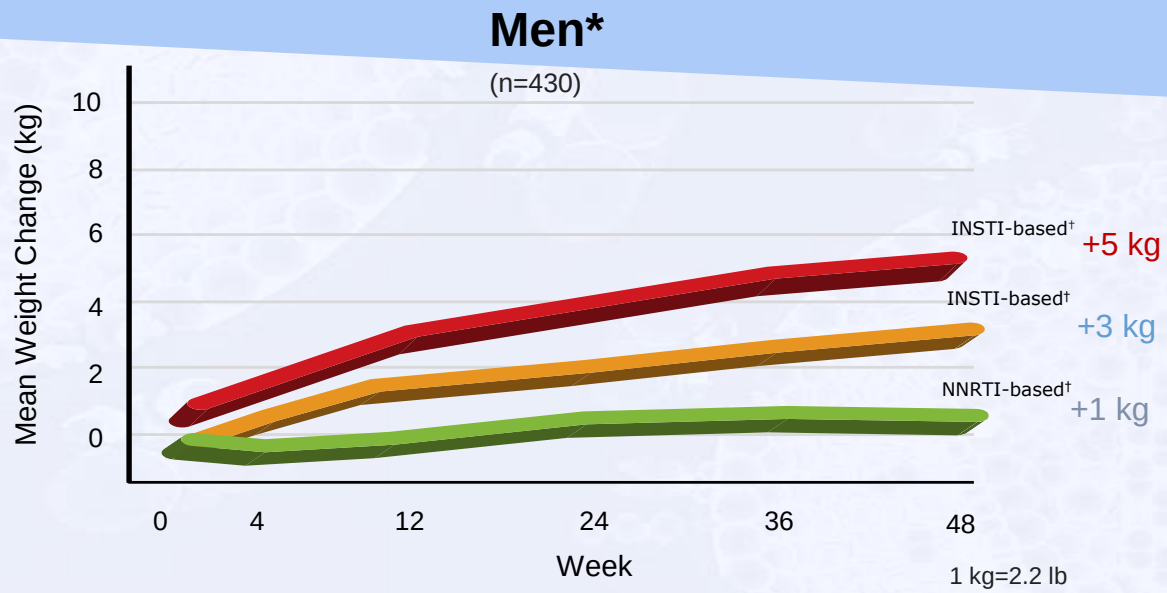
Meta-analysis of pooled data from 8 Phase 3, randomized clinical trials (n=5680) to identify demographic, HIV disease–, and ART-related risk factors for weight gain after the initiation of ART, highlighting the multifactorial nature of ART-associated weight gain. Limitations: Evaluating the effect of ART drugs on weight gain is confounded by HIV disease factors (eg, return to health). The mechanism and long-term consequences of this weight gain are unknown. Body composition data were not available, so the anatomical distribution of observed weight gain could not be determined.

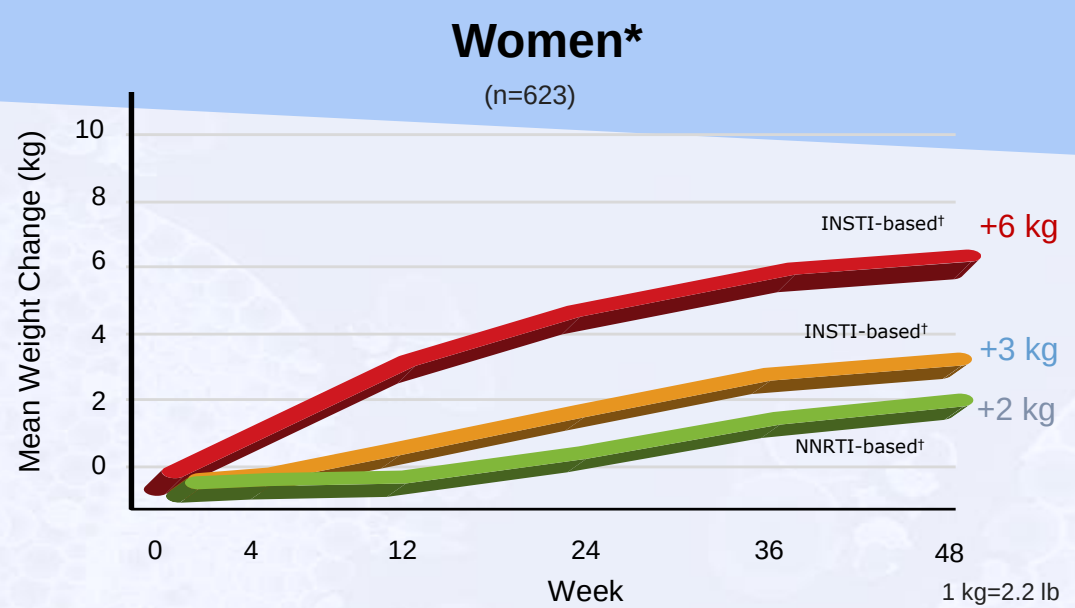
*Adapted from Sax PE, et al, by permission of Oxford University Press for the Infectious Diseases Society of America.

ART=antiretroviral therapy; INSTI=integrase strand transfer inhibitor; LS=least squares; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

Reference: Sax PE, et al. *Clin Infect Dis*. 2019; doi:10.1093/cid/ciz999

Patients in the ADVANCE Trial Experienced Progressive Weight Gain on Specific ARV Regimens





- Greater weight gain is seen with INSTI-based ART vs NNRTI-based ART[1]
- There is no plateau from Week 48 to Week 96 for women (data not shown)[2]

The ADVANCE study was a Phase 3, 48-week, open-label, randomized trial in South Africa that compared 2 INSTI-based triple-therapy regimens† vs the local standard-of-care NNRTI-based triple-therapy regimen† in patients >12 years of age (n=1053) with an extension out to 96 weeks.[1] Limitations: Open-label design and lack of standardized pill quantity per group. The mechanism and long-term consequences of this weight gain are unclear.[1,2]

*Adapted from Venter WDF, et al, by permission of the Massachusetts Medical Society.[1]

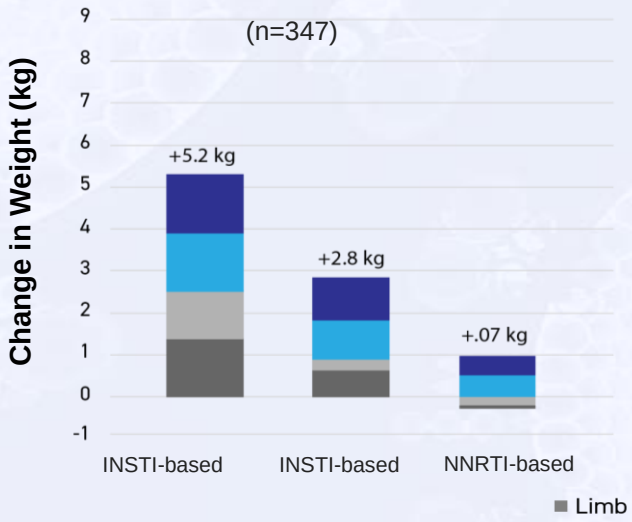
†In combination with NRTI/NtRTI.

ART=antiretroviral therapy; ARV=antiretroviral; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NtRTI=nucleotide reverse transcriptase inhibitor.

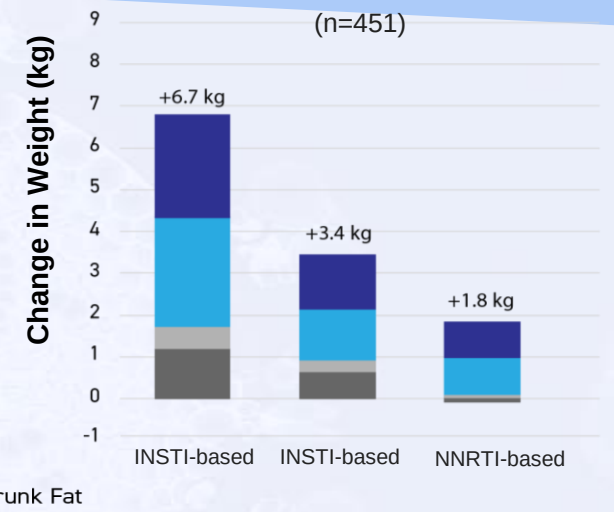
References: 1. Venter WDF, et al. *N Engl J Med*. 2019;381(9):803-815. **2.** McCann K, et al. Presented at 17th European AIDS Conference; 2019.

Weight Gain Was Largely Due to Accumulation of Trunk Fat in Patients in the ADVANCE Trial

Changes in Body Composition as Measured by DXA: Men (Week 48)[1]*



Changes in Body Composition as Measured by DXA: Women (Week 48)[1]*



- Distribution of the weight gain is predominately due to accumulation of trunk (and limb) fat vs lean mass[1,2]
- Trunk fat is composed of VAT and abdominal SAT[3]

The Phase 3 ADVANCE study was a 48-week, open-label, randomized trial in South Africa that compared 2 INSTI-based triple-therapy regimens† in combination with NRTI/NtRTI vs the local standard-of-care NNRTI-based triple-therapy regimen† in combination with NRTI/NtRTI in patients >12 years of age (n=1053) with an extension out to 96 weeks.[2] Limitations: Open-label design and lack of standardized pill quantity per group.[2]

*Adapted from Venter WDF, et al, by permission of the Massachusetts Medical Society.[1]

†In combination with NRTI/NtRTI.

ARV=antiretroviral; DXA=dual-energy x-ray absorptiometry; INSTI=integrase strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NtRTI=nucleotide reverse transcriptase inhibitor; SAT=subcutaneous adipose tissue; VAT=visceral adipose tissue.

References: 1. Supplementary to: Venter WDF, et al. *N Engl J Med*. 2019;281(9):803-815. **2.** Venter WDF, et al. *N Engl J Med.* 2019;381(9):803-815. **3.** Ibrahim MM. *Obes Rev*. 2010;11:11-18.

Switch from TAF to TDF

- **<u>CHARACTERISE</u>**: open label study follow up to ADVANCE after participants were switched to TDF/3TC/DTG (TLD)

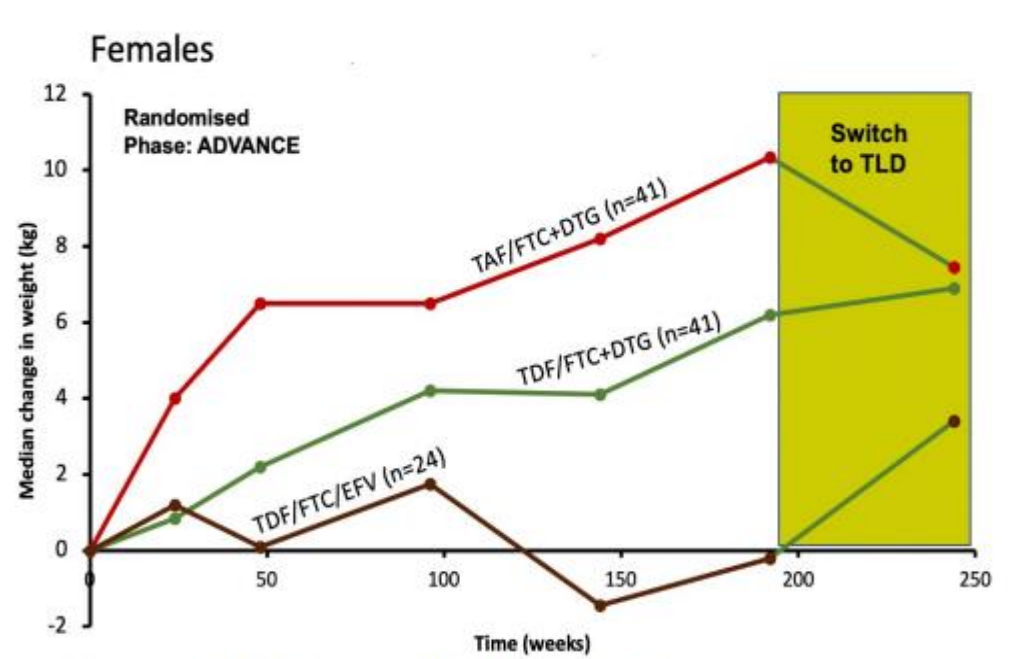


Figure 1: Median weight change for females

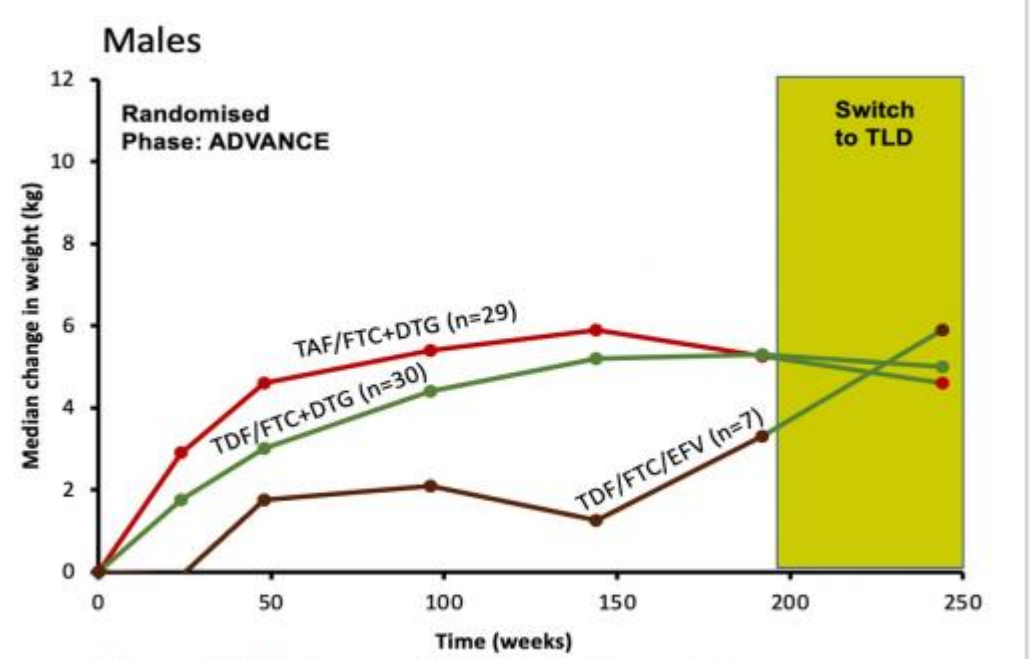
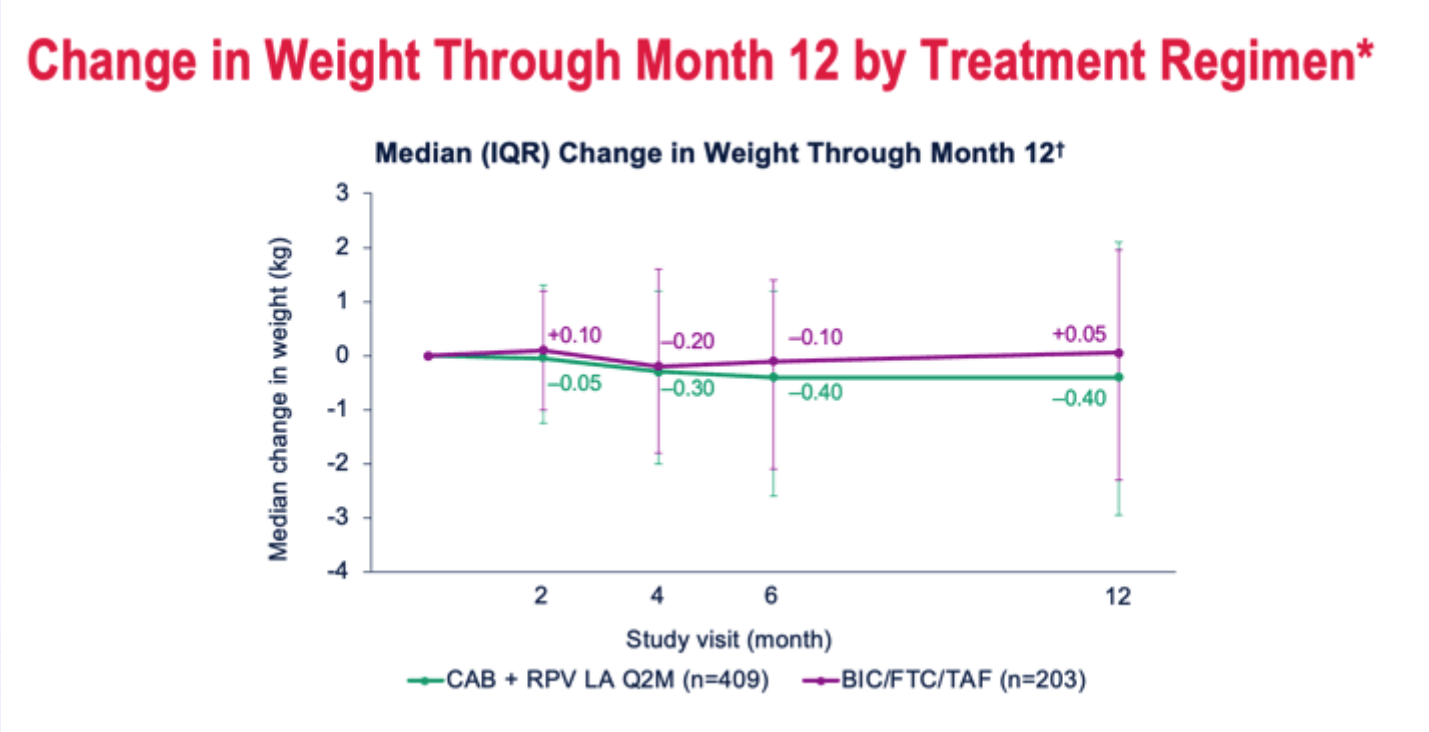


Figure 2: Median weight change for males

Besch B, et al. CID. 2023: 76 (15 April)

Switch from INSTI + TAF to CAB/RPV

- **SOLAR**: multi-center, randomized study, open-label, noninferiority study
- Virally suppressed participants were randomized to either BIC/FTC/TAF daily or LA CAB + RPV IM every 2 months (with or without oral lead in)

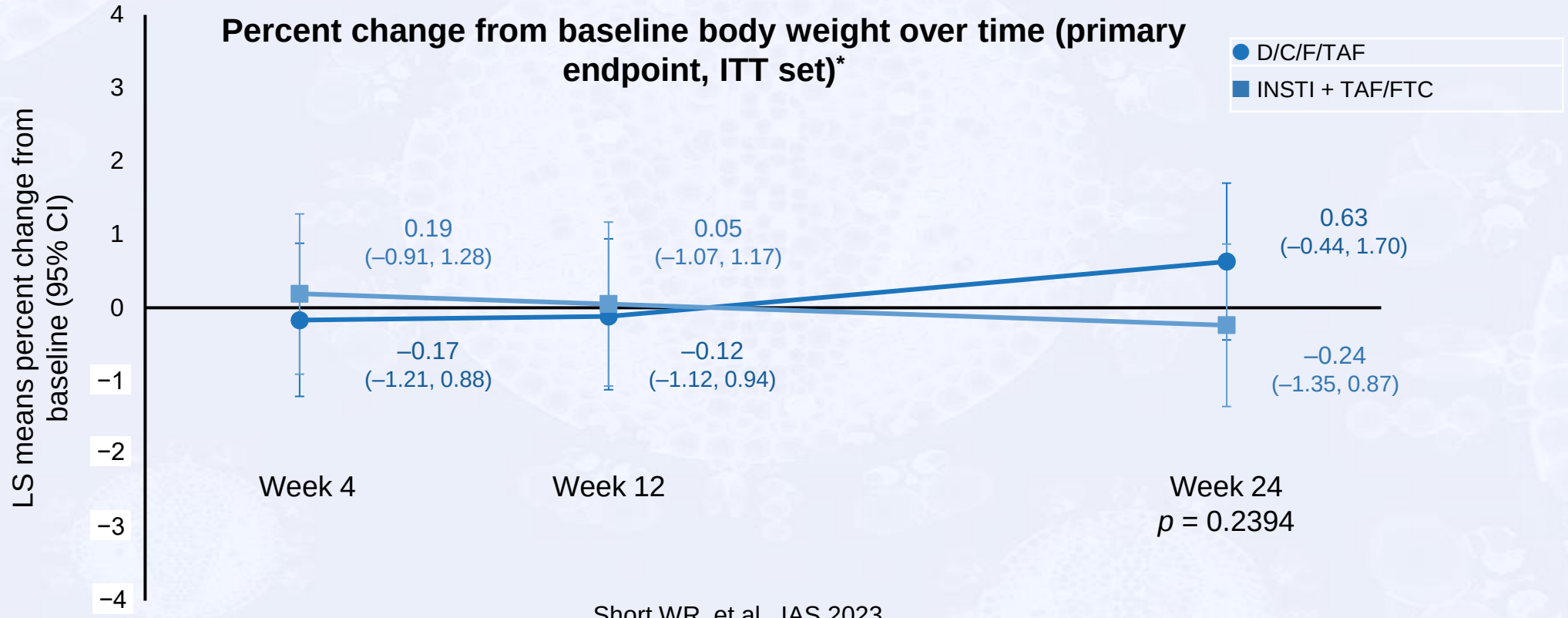


Tan DHS, et al. CROI 2023.

DEFINE: No Significant Difference in Percent Change in Body Weight From Baseline to Week 24 Between Arms

IAS 2023

*LS means percent changes in body weight were calculated in the ITT set of randomized participants who had received ≥1 dose of the study drug using a MMRM, in which visits were repeated measures. Participants in the ITT set with baseline records and ≥1 postbaseline record were included.
CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat; LS, least squares; MMRM, mixed model for repeated measures; TAF/FTC, tenofovir alafenamide/emtricitabine.



Short WR, et al. IAS 2023.

Take Home Points

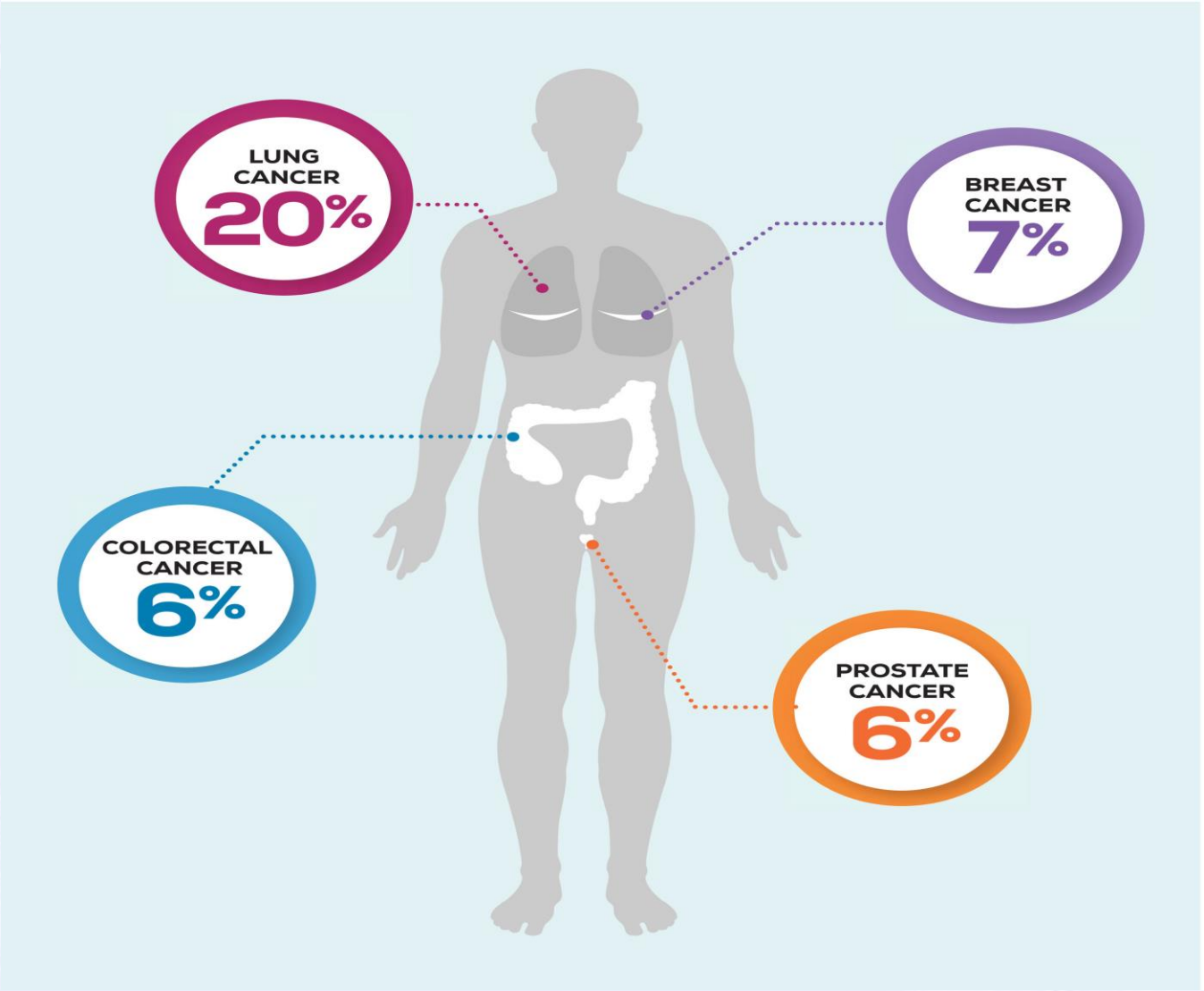
- Switching from TAF to TDF is associated with a modest weight loss
- No weight loss observed when switching from TAF based ART to DTG/3TC, BIC/FTC/TAF to CAB/RPV, or INSTI/TAF to DRV/COB/TAF/FTC
- There is evidence that INSTIs are likely weight neutral and the weight seen with INSTI/TAF is due to inhibitory effects of older drugs
- Management of obesity includes lifestyle modifications + anti-obesity medications

Cancer

Cancer Epidemiology

- Cancer epidemiology has shifted since the introduction of ART
- Rate of AIDS-defining malignancies (Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer) has decreased and the rates of non-AIDS defining malignancies have increased substantially

Cancer Disparities in People with HIV: A Systematic Review of Screening for non-AIDS–Defining Malignancies



Sources: Cancer, Volume: 125, Issue: 6, Pages: 843-853, First published: 15 January 2019, DOI: (10.1002/cncr.31838) and https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.31838.

What to Do in the Clinic:

- This highlights the ongoing potential for reducing mortality through:
  - Targeted cancer screening
  - Prevention of cardiovascular disease (awaiting statin recommendation)
  - Prevention of infectious diseases with vaccination (Influenza, HPV, HBV)
  - Smoking cessation to prevent pulmonary diseases and its complications
  - Hepatitis treatment
  - Screening and management of psychiatric disorders
  - Preventing late HIV diagnosis

Thank You

Perelman School of Medicine
University of Pennsylvania

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