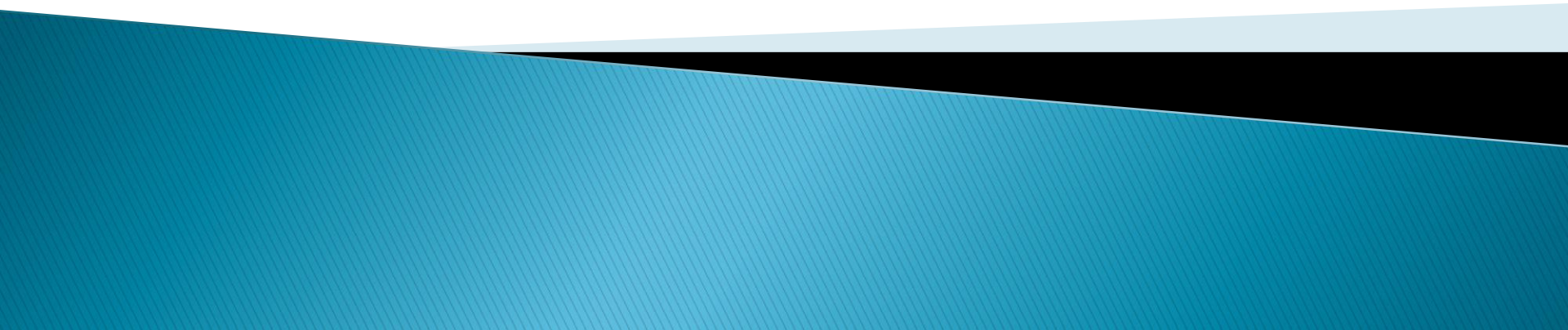


HIV and the Adipose Tissue Immune Environment

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University of California San Diego



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Slides adapted from John Koethe, MD, MSCI
Vanderbilt University Medical Center



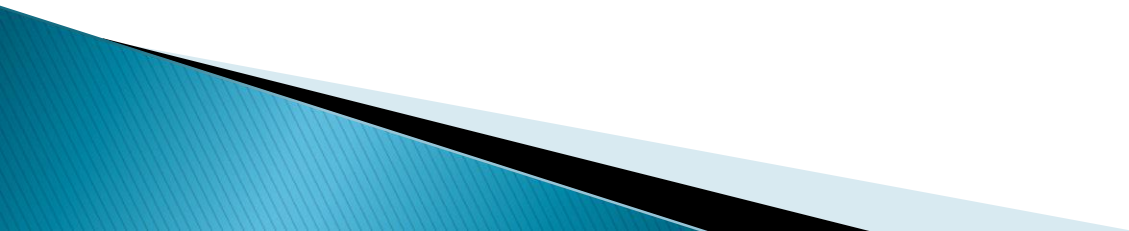


“We just felt it was time that people saw the truth about AIDS”
(Kay Kirby)

Photography by Therese Frare, 1990, no copyright infringement is intended

The Changing Face of the HIV Epidemics

The development of antiretroviral therapy (ART) for the treatment of HIV is one of the greatest achievements of modern medicine.



HIV Medicines Help People with HIV Live Longer

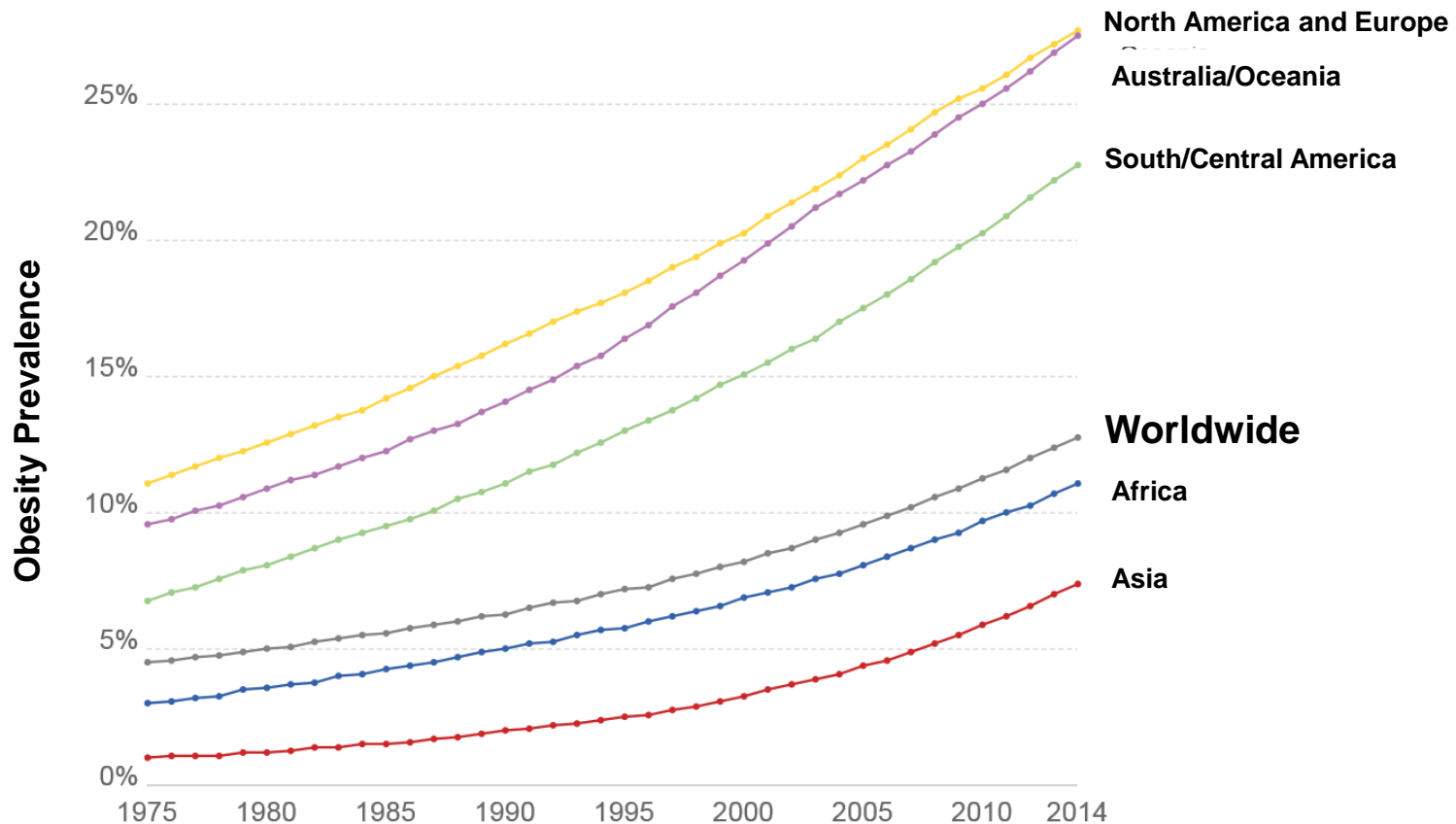
(AVERAGE YEARS OF LIFE)



SOURCES: National Vital Statistics Reports, 2012; PLoS One, 2013; and Journal of the American Medical Association, 1993.

<http://www.cdc.gov/vitalsigns/hiv-aids-medical-care/infographic.html#infographic>

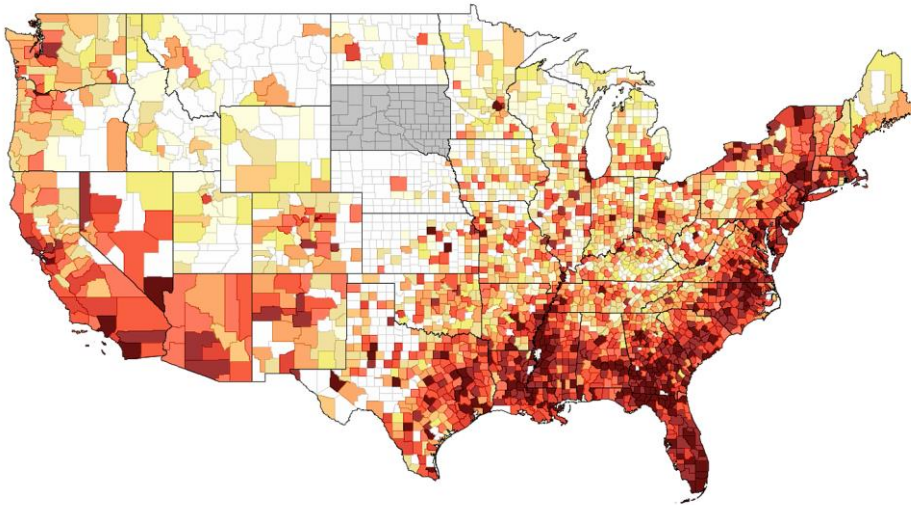
Obesity Prevalence is Rising Worldwide



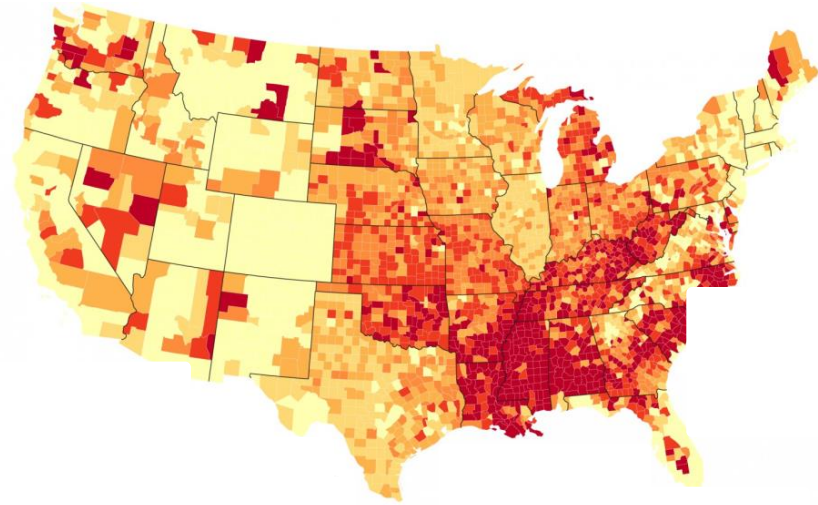
Source: WHO Fact Sheets 2018 & UN Food and Agricultural Organization

Overlapping Epidemics: HIV and Obesity in the US

HIV prevalence



Obesity prevalence



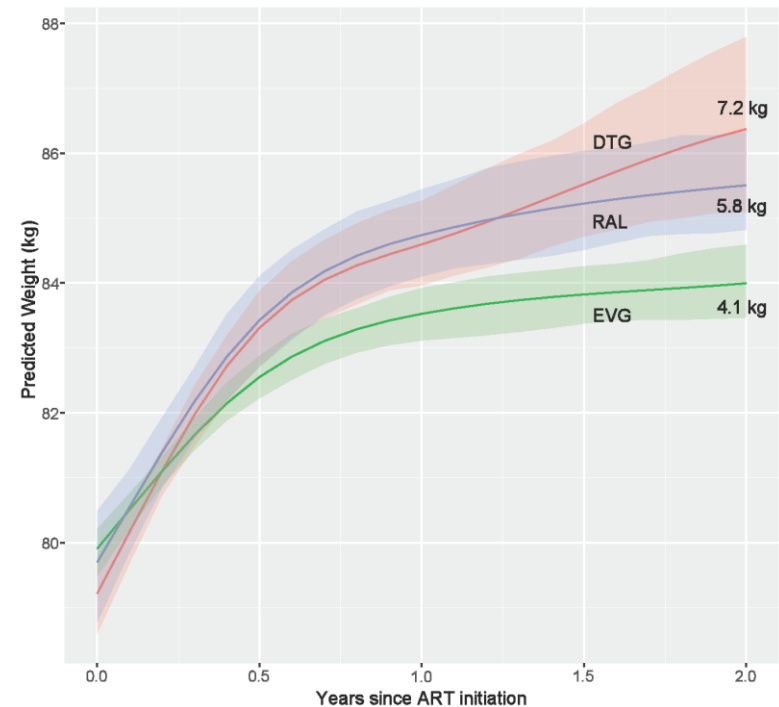
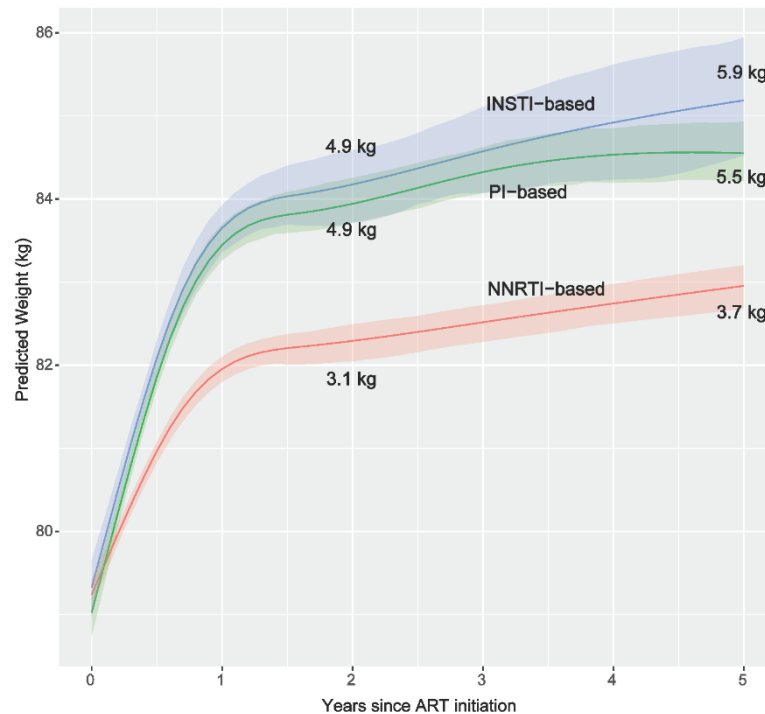
Source: *AIDSVu.com* and *CDC Overweight and Obesity* (<https://www.cdc.gov/obesity/>)

Obesity and HIV-infection

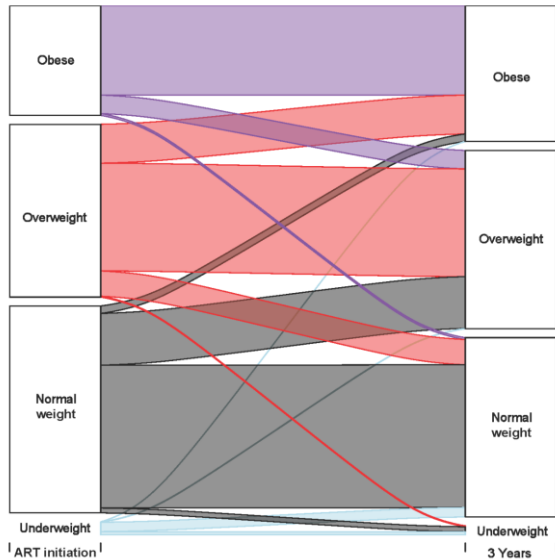
- ▶ Over half of PWH are overweight or obese
- ▶ Excessive increase of weight post ART initiation
- ▶ Increased incidence of abdominal obesity

Weight Gain in Treatment-Naïve Persons Starting ART in the US and Canada

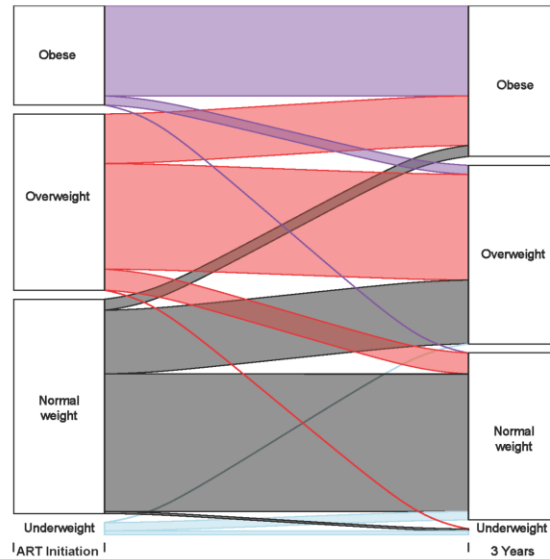
22,972 patients starting ART from 2007–2016 in the US and Canada



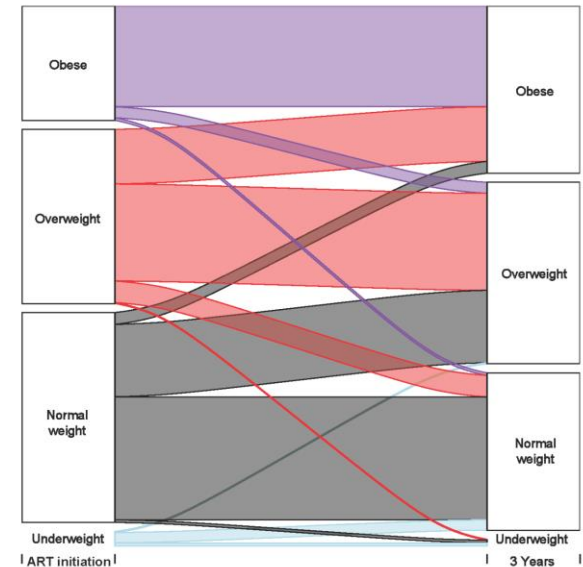
NNRTI-based regimens



PI-based regimens



INSTI-based regimens



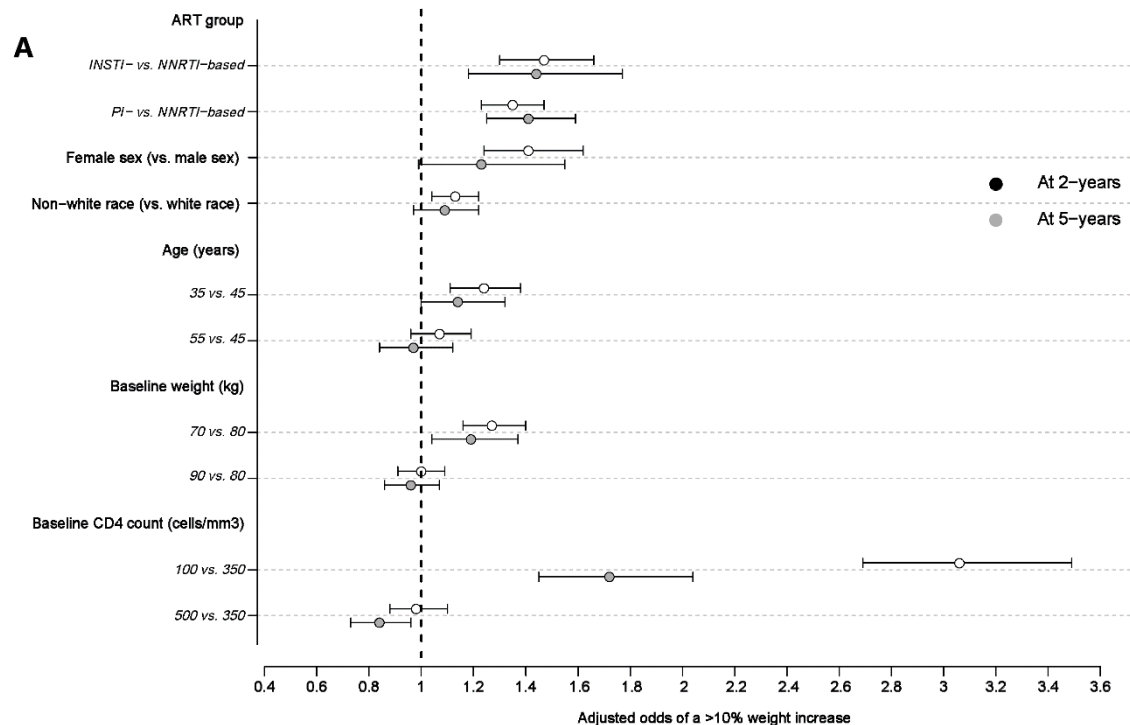
After 3 years of ART:

- NNRTI: 25% normal-BMI became overweight, 22% of overweight became obese
- PI: 29% normal-BMI became overweight, 26% of overweight became obese
- INSTIs: 32% normal-BMI became overweight, 28% of overweight became obese

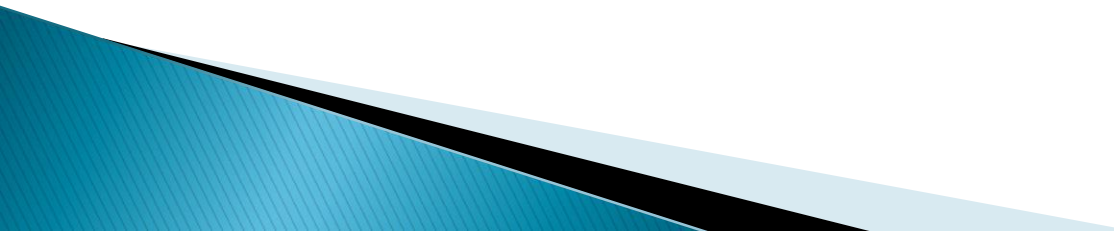
Adjusted odds of a >10% weight increase at 2- and 5-years among NA-ACCORD participants starting ART

Higher odds of weight gain

- INSTI or PI-based ART (vs. NNRTI)
- Women
- Non-whites
- Younger
- Lower baseline weight and CD4 count

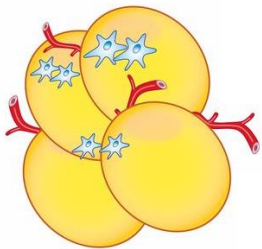


Adipose Tissue Quality

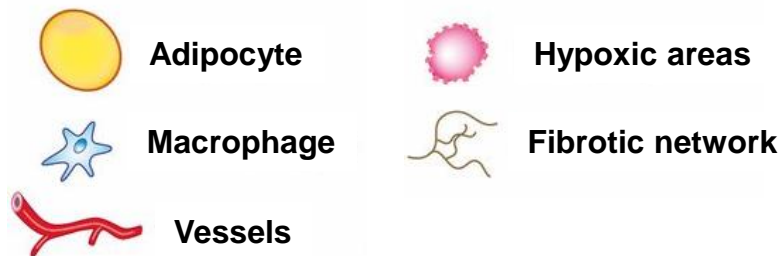
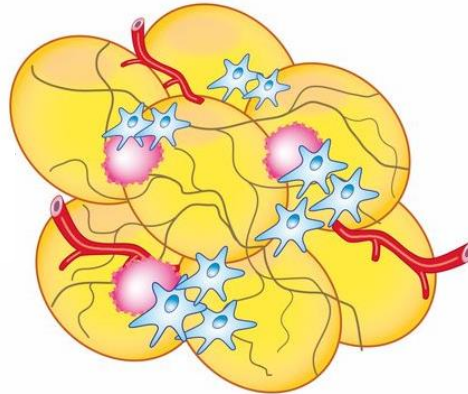
- ▶ One of the largest organs in the body
 - ▶ Performs diverse functions including
 - Energy storage and release
 - Regulation of appetite
 - Neuroendocrine signaling
 - Modulation of immunity
 - (...)
- 

The 'unhealthy' expansion of adipose tissue in obesity

Lean adipose tissue



Obese adipose tissue



- Reduced expression of master regulatory genes: *PPAR-γ*, *C/EBPα*, others
- Altered T cell and macrophage populations
- Blunted insulin effects on lipoprotein lipase (LPL) and hormone sensitive lipase (HSL)

↓ LPL: Reduced lipid storage

↑ HSL: Increased lipid release



- Increased IL-6, TNF- α release
- Increased circulating free fatty acids (FFA)
- Increased muscle FFA uptake and toxicity
- Ectopic liver, epicardial, visceral, and skeletal lipid deposits

Adipocytes and HIV-Infection

ART drugs

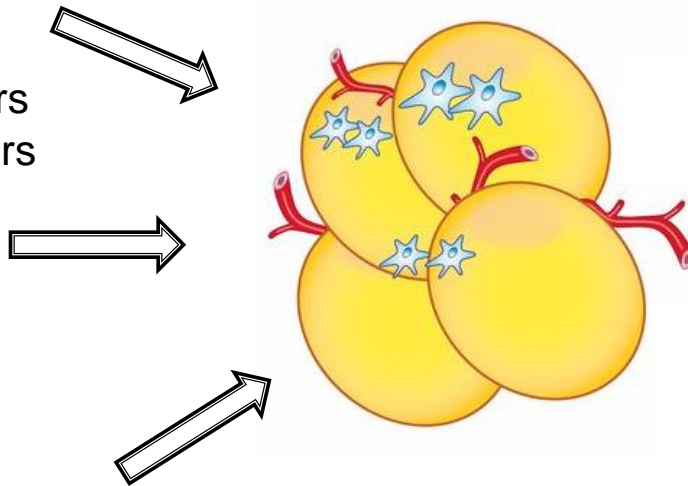
- NRTIs
- NNRTIs
- Protease Inhibitors
- Integrase Inhibitors

Viral proteins

- Vpr
- Nef
- Tat

Altered immune environment

- Increased CD8:CD4 T cell ratio
- Changes in macrophage density and cytokine expression
- Presence of CD4+ cells with latent HIV (viral reservoir ?)



Adipocytes:

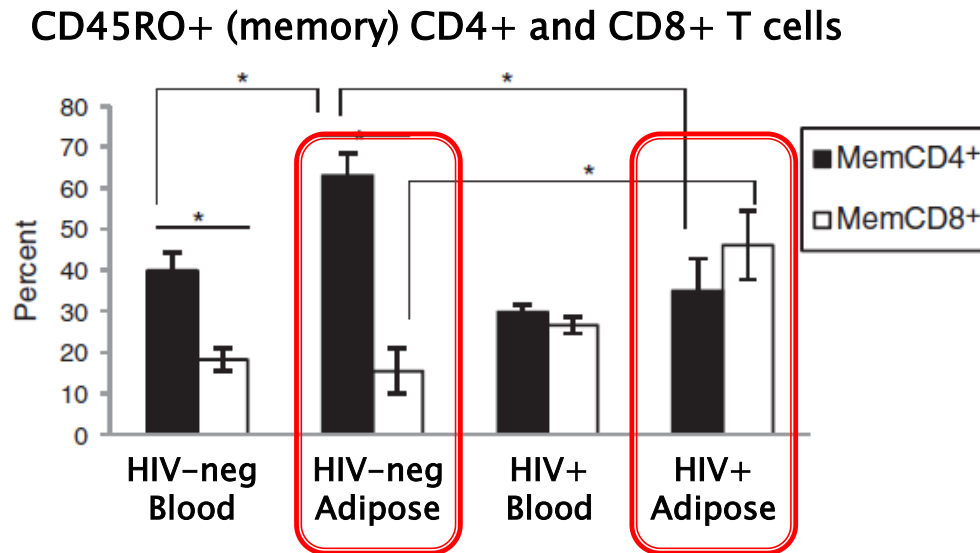
- Reduced mitochondrial DNA content & respiratory chain proteins
- Reduced PPAR- γ , C/EBP α , adiponectin, GLUT4, & LPL expression
- Reduced (FFA) to TG conversion / storage
- Increased constitutive IL-6, TNF- α expression
- Reduced adipogenesis
- Increased fibrosis / impaired cell-cell signaling

Summary of ART effects on adipocytes

	NRTIs	NNRTIs	Protease Inhibitors	Integrase Inhibitors	CCR5 Inhibitors
↓ Mitochondrial DNA (mtDNA)					
↓ Non-mtDNA dependent functions (krebs cycle, increased β -oxidation products)					
↓ Mitochondrial Complex I and IV					
↓ Adipogenesis / maturation					
↓ Regulatory gene expression					
↓ Lipoprotein lipase & adiponectin expression					
↓ Insulin signaling & GLUT4 expression					
↑ Inflammatory mediator expression					
↑ Reactive oxygen species					
↑ Apoptosis					
Possible <i>reduced</i> inflammation					?

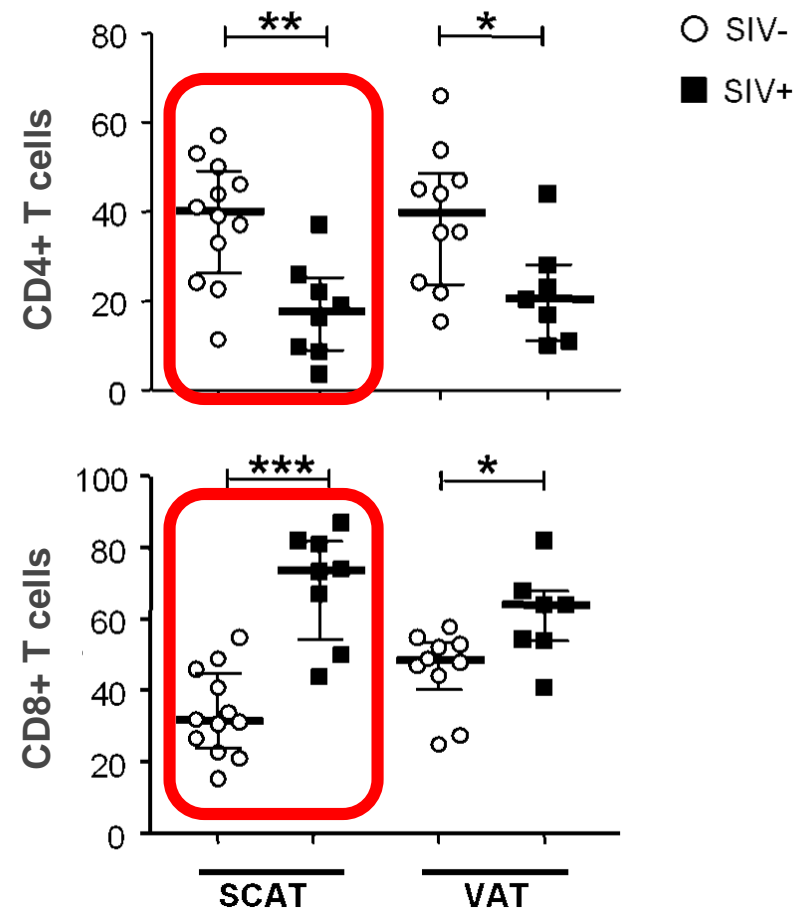
Adipose tissue CD4+ and CD8+ T cell profiles change with HIV and SIV infection

Adipose tissue from PWH has a far higher memory CD8:CD4 ratio compared to persons without HIV...



Adipose tissue CD4+ and CD8+ T cell profiles change with HIV and SIV infection

...And adipose tissue from SIV+ macaques shows a similar enrichment for CD8+ T cells and reduced CD4 cells



CD8+ T cells likely have a role in adipose tissue inflammation and insulin resistance

- ▶ CD8 T cell infiltration into adipose tissue is posited to promote 'inflammatory' obesity as opposed to 'healthy' obesity
- ▶ CD8 T cell infiltration precedes macrophage infiltration
- ▶ T cell receptor (TCR) β ^{-/-} mice have reduced adipose tissue inflammation, improved glucose tolerance, and improved insulin sensitivity.
- ▶ Immunotherapy with anti-CD8 antibody depletes adipose tissue CD8+ T cells, reduces adipose tissue macrophage density, and improves glucose tolerance in diet-induced obese mice.
- ▶ In obese mice the adipose tissue CD8+ T cells are effector memory (CD44⁺ CD62L⁻), possibly reflecting antigen-driven selection

S. Winer, Y. Chan, G. Paltser et al., *Nature Medicine*, 15:921–929, 2009.

S. Nishimura, I. Manabe, M. Nagasaki et al. *Nature Medicine*, 15:914–920, 2009.

I. M. Khan, X.-Y. Dai Perrard, J. L. Perrard et al., *Atherosclerosis*, 233:419–428, 2014.

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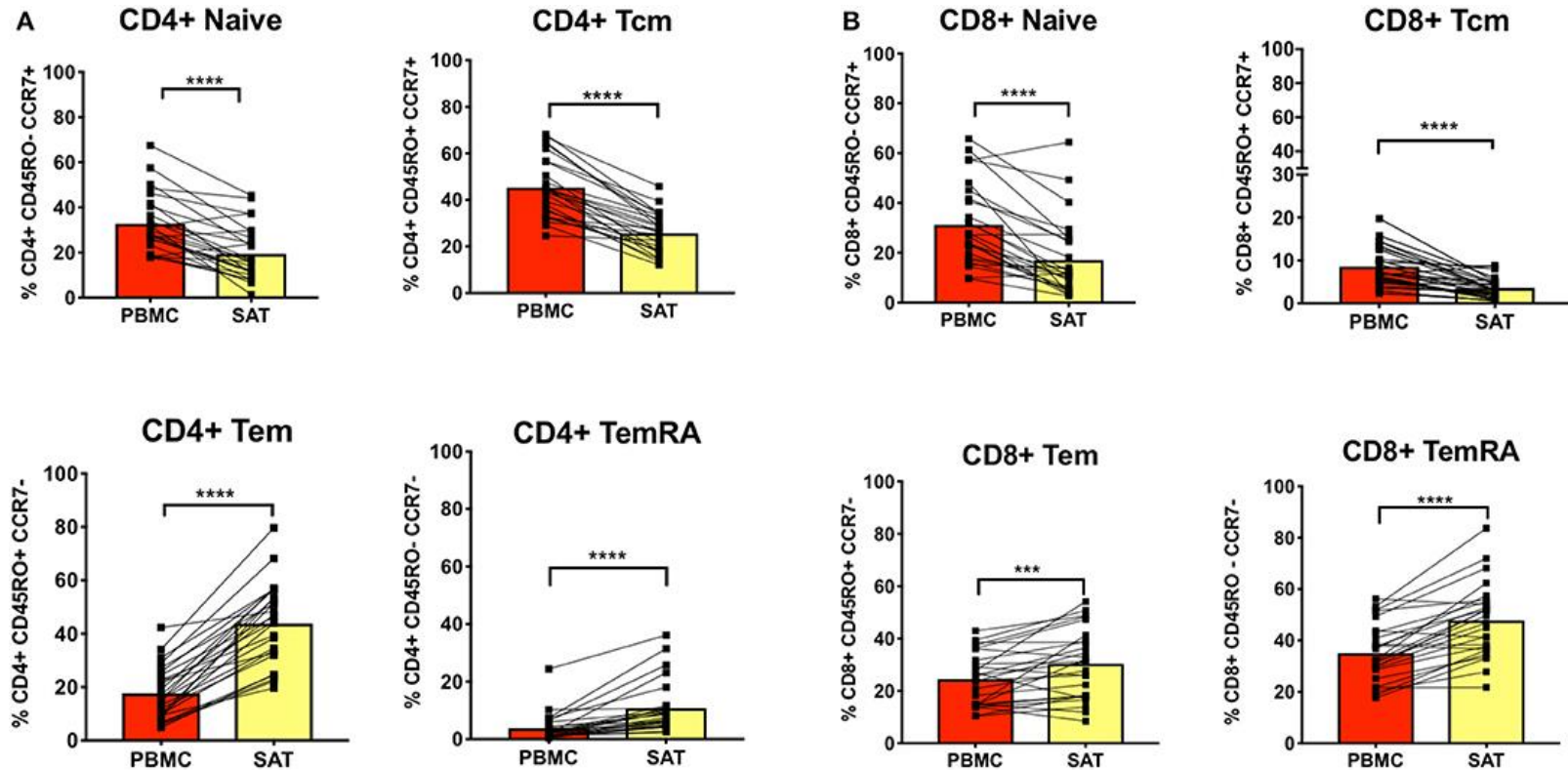
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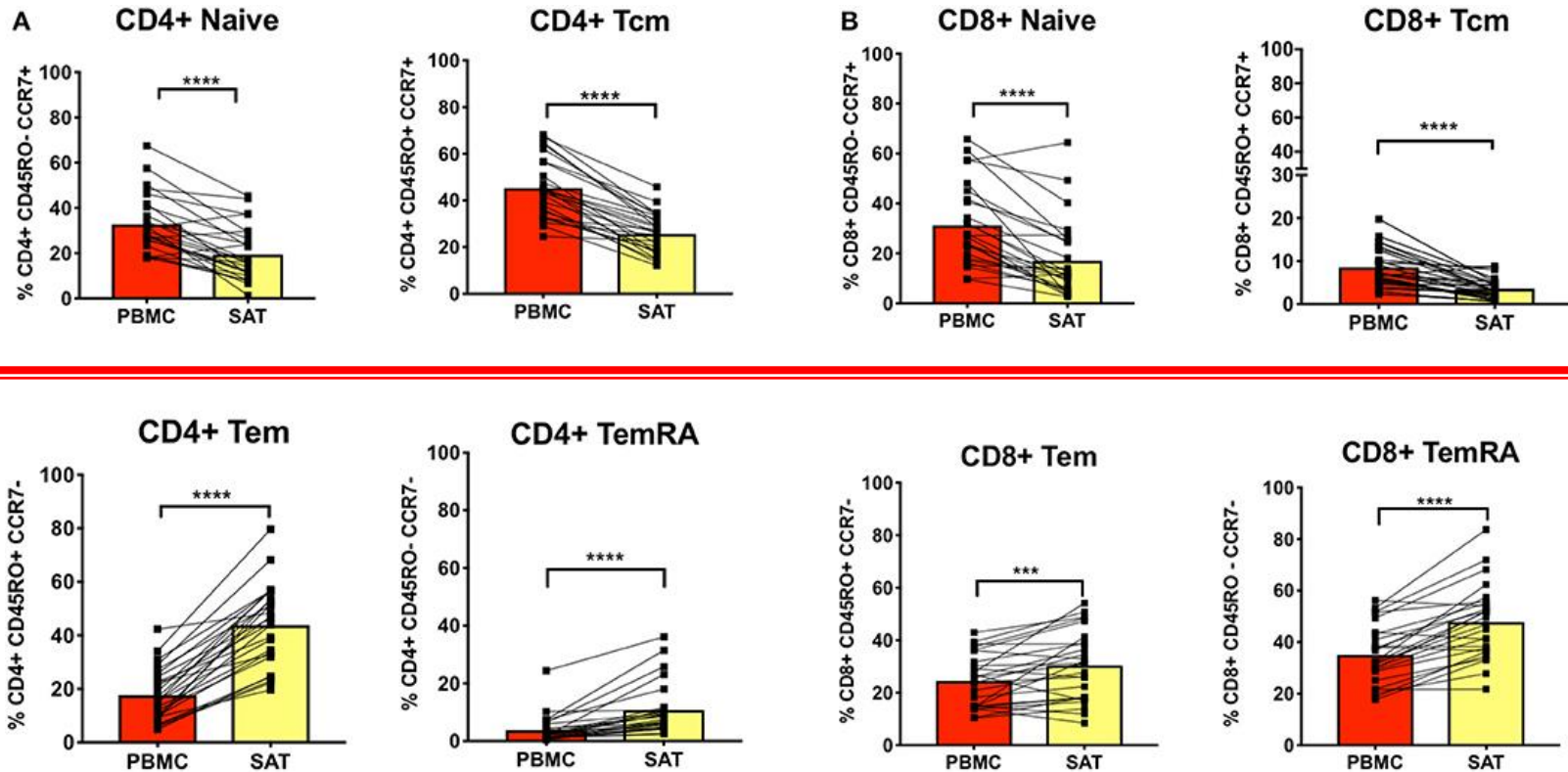
Adipose Tissue in Persons With HIV Is Enriched for CD4⁺ T Effector Memory and T Effector Memory RA⁺ Cells, Which Show Higher CD69 Expression and CD57, CX3CR1, GPR56 Co-expression With Increasing Glucose Intolerance

Celestine N. Wanjalla^{1,2†}, Wyatt J. McDonnell^{1,2,3,4*†}, Louise Barnett⁵, Joshua D. Simmons⁵, Briana D. Furch^{1,5}, Morgan C. Lima^{1,5}, Beverly O. Woodward^{1,5}, Run Fan⁶, Ye Fei⁶, Paxton G. Baker⁷, Ramesh Ram⁸, Mark A. Pilkinton^{1,2}, Mona Mashayekhi^{9,10}, Nancy J. Brown⁹, Simon A. Mallal^{1,2,5,7,8}, Spyros A. Kalams^{1,2,5} and John R. Koethe^{1,2*}*

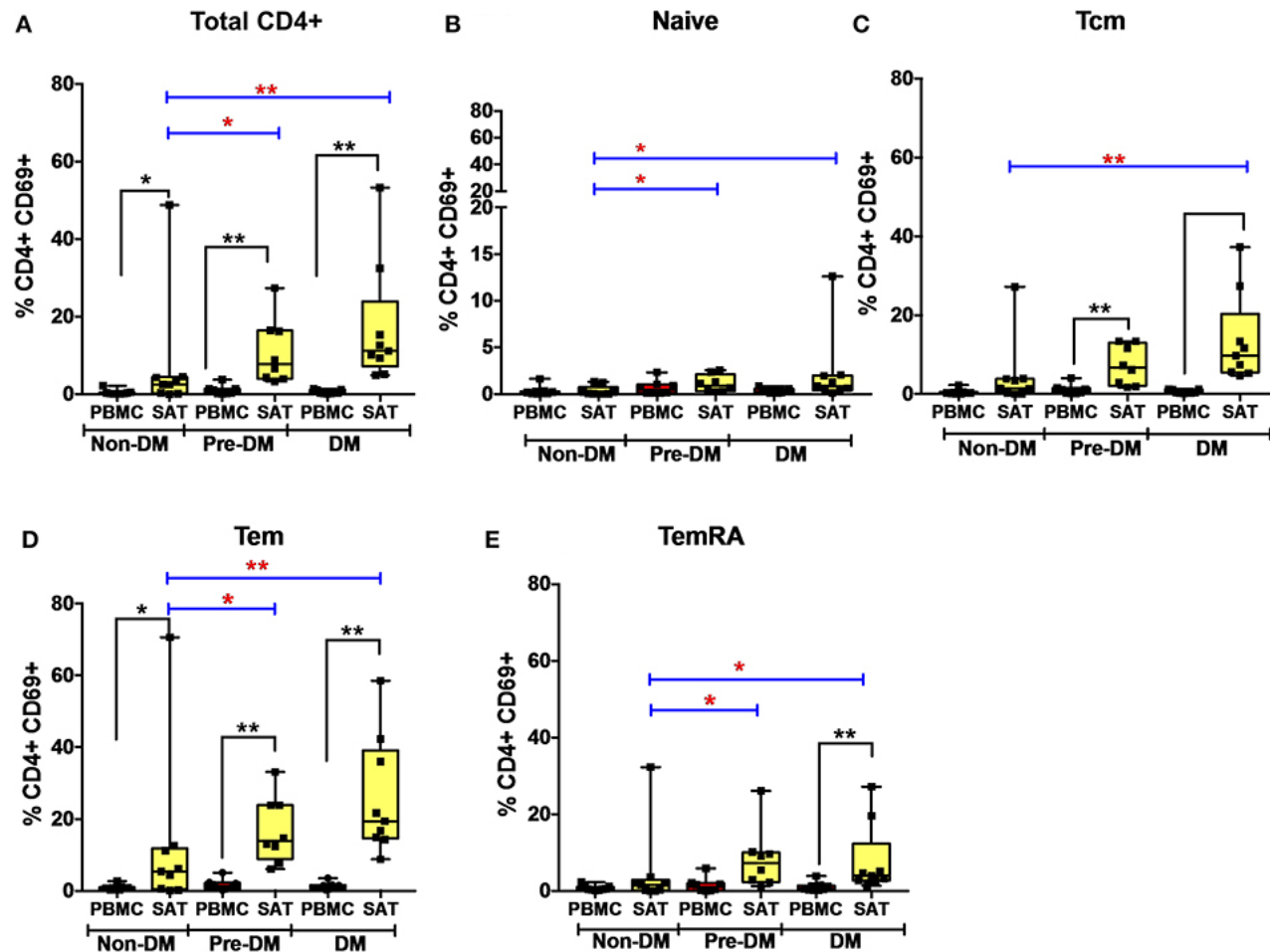
Subcutaneous adipose tissue has a higher percentage of TEM and TEMRA cells compared to blood in PWH



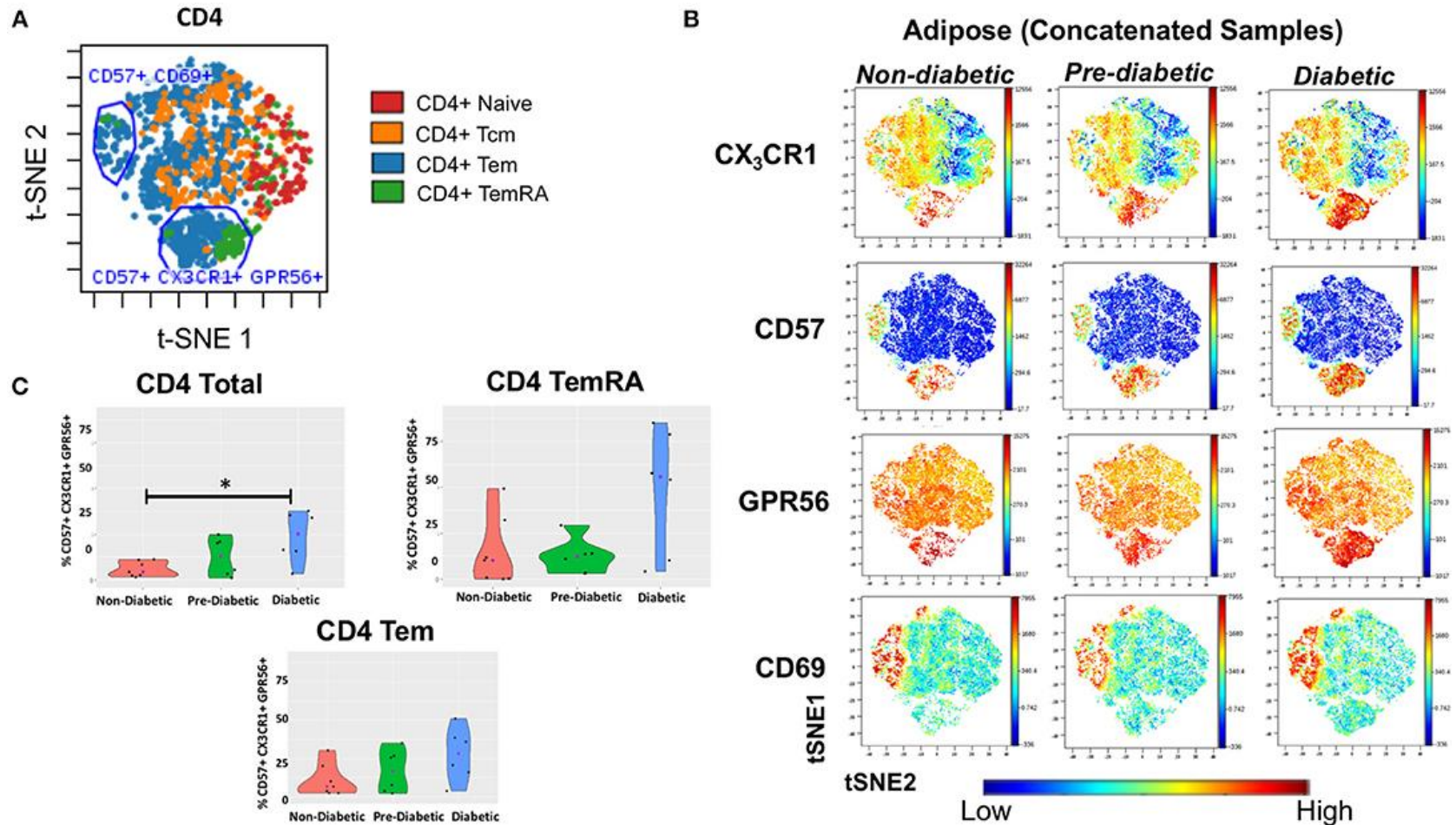
Subcutaneous adipose tissue has a higher percentage of TEM and TEMRA cells compared to blood in PWH



CD69 expression on subcutaneous adipose tissue CD4⁺ T cells increases with progressive glucose intolerance




CD4⁺ T cells co-expressing CD57, CX3CR1, GPR56 in subcutaneous adipose tissue increase with progressive glucose intolerance



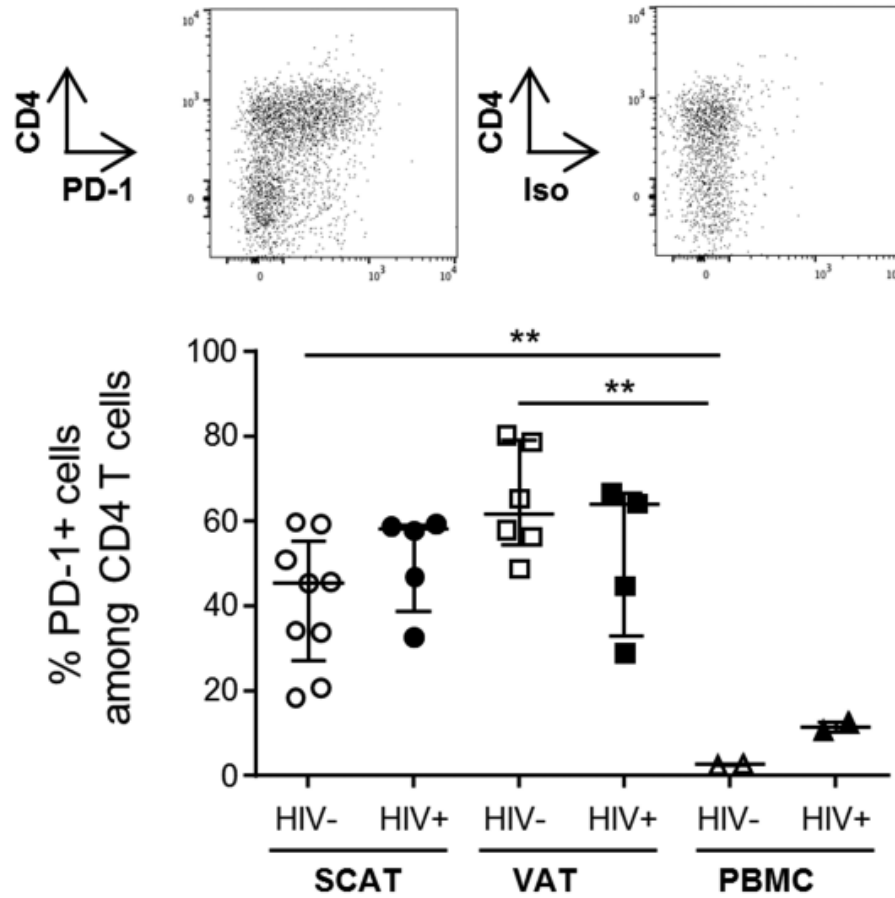
Research Article

High proportion of PD-1-expressing CD4⁺ T cells in adipose tissue constitutes an immunomodulatory microenvironment that may support HIV persistence

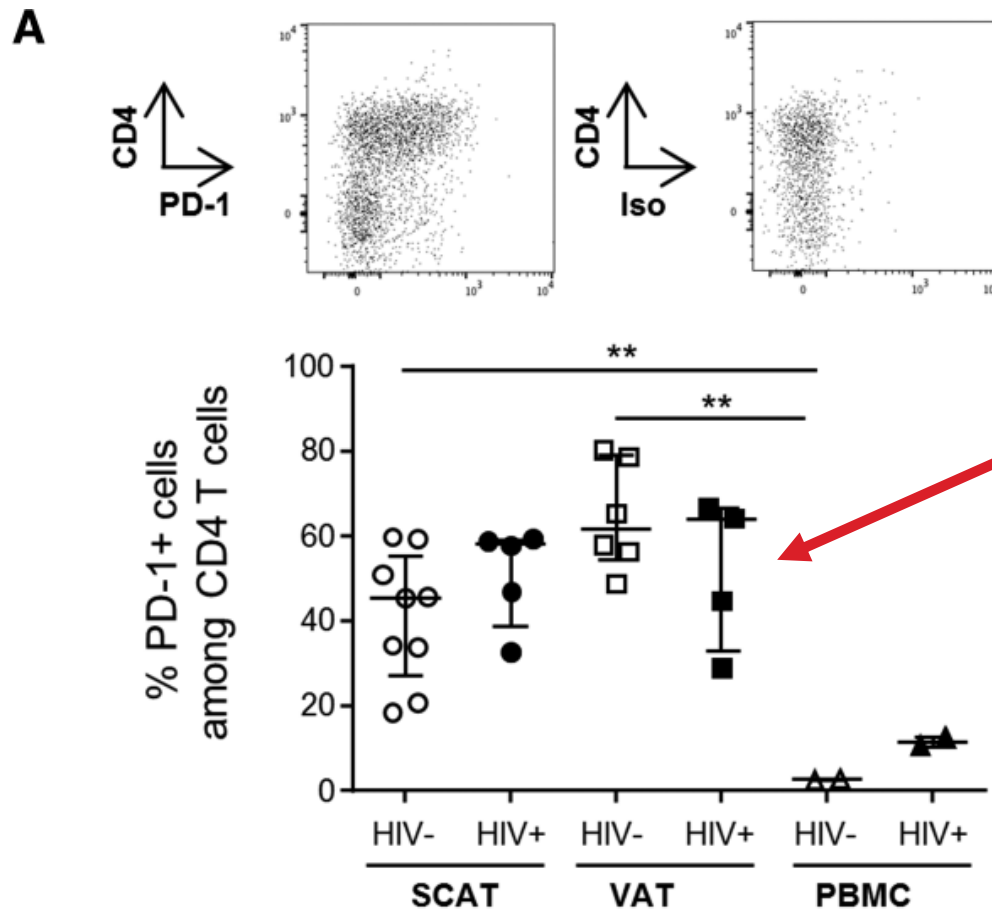
*Abderaouf Damouche^{1,2}, Guillaume Pourcher³, Valérie Pourcher⁴,
Stéphane Benoist⁵, Elodie Busson⁶, Jean-Jacques Lataillade⁶, Mélanie Le
Van^{1,2}, Thierry Lazure⁷, Julien Adam⁸, Benoît Favier^{1,2}, Bruno Vaslin^{1,2},
Michaela Müller-Trutwin⁹, Olivier Lambotte^{*1,2,10}
and Christine Bourgeois^{*1,2}* 

PD-1 was expressed by a high proportion of tissue-resident memory CD4⁺ T cells

A



PD-1 was expressed by a high proportion of tissue-resident memory CD4⁺ T cells



PD-1 expressing cells are enriched with HIV DNA

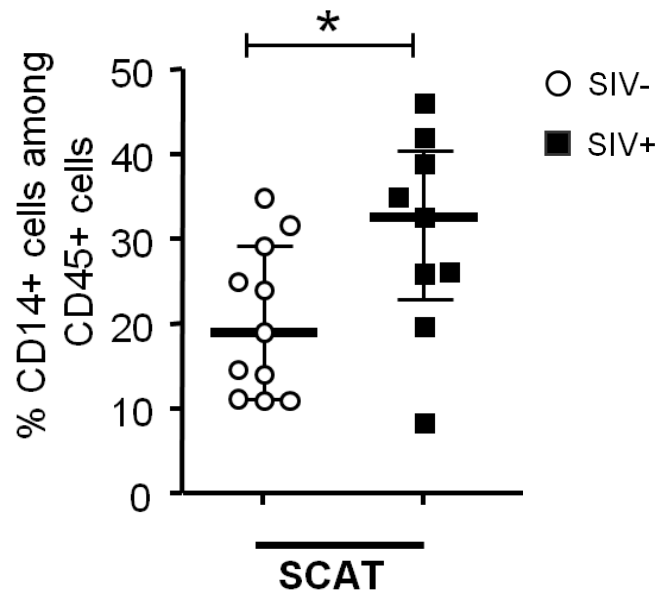
Inhibit inflammatory activity

More data is needed on adipose tissue macrophages in HIV....

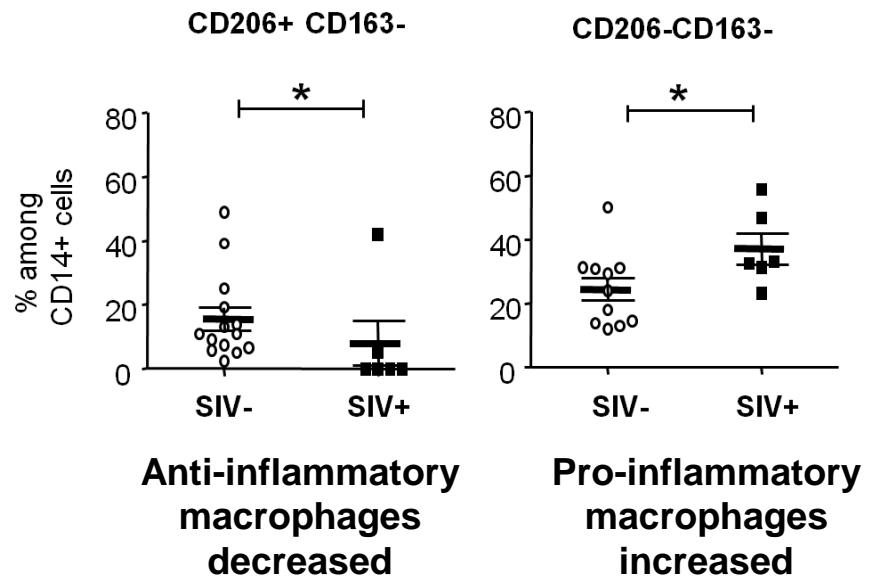
- Circulating HIV DNA higher in CD14⁺CD16⁺ monocyte from HIV+ lipoatrophic persons compared to non-lipoatrophic (Shikuma 2014)
- Adipose tissue macrophage density slightly higher or similar between PWH and HIV-negative controls in two studies
- However, PWH had higher IL-12p40, IL-6, IL-8, and MIP-1 α suggesting greater activity or M1 polarization

...though in SIV infection adipose tissue is enriched for activated macrophages

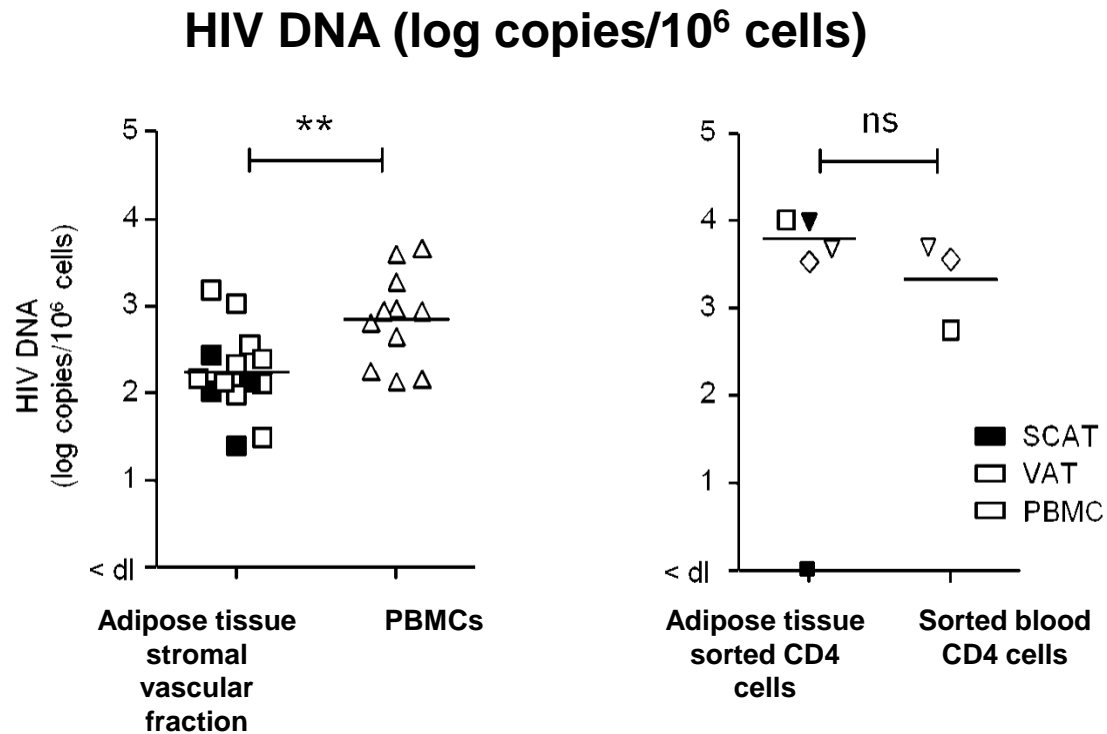
Higher overall proportion of adipose tissue macrophages



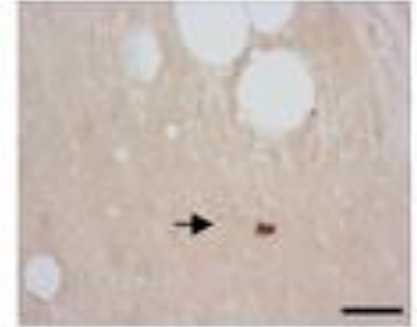
Subcutaneous adipose tissue (SCAT)



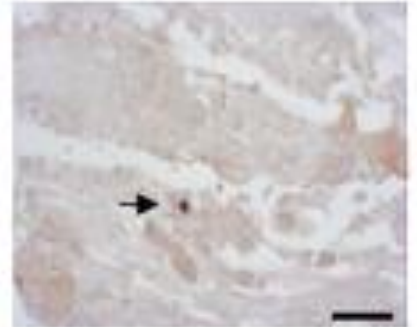
Adipose tissue may serve as a reservoir for latently HIV-infected CD4 cells



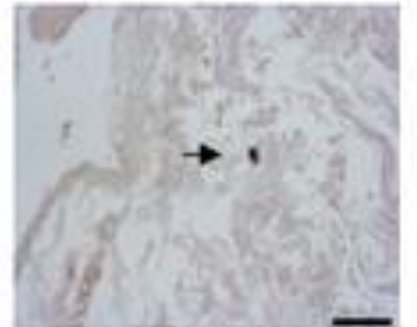
SCAT



SCAT



VAT



HIV *in situ* hybridization

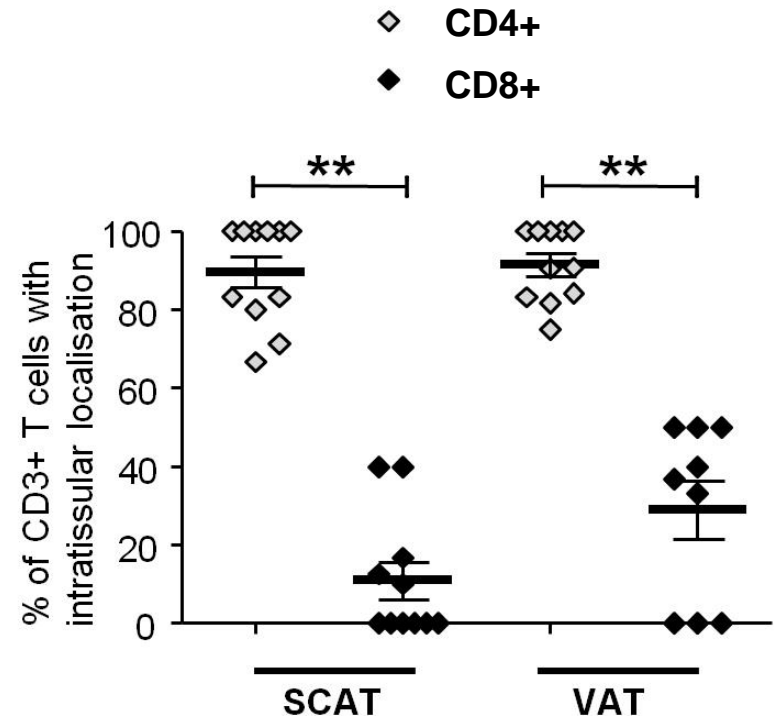
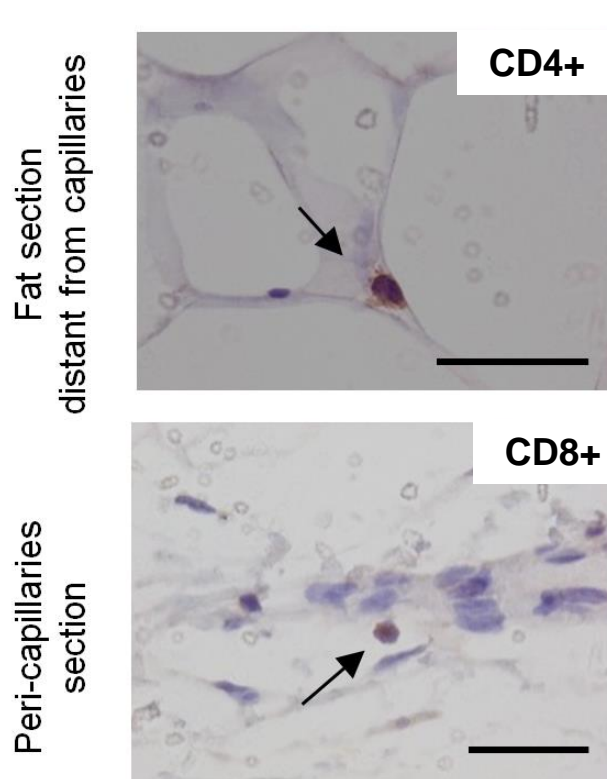
Are HIV-infected CD4 cells really 'resident' in adipose tissue?

- HIV proviral DNA detectable in CD4 T cells of multiple fat depots (Couturier 2015, Damouche 2015, Koethe 2018)
- Viral RNA was less frequently detected
- Viral outgrowth assays show adipose CD4 T cells are infected with replication-competent virus
- HIV DNA copy number similar between adipose tissue CD4 T cells and peripheral CD4 T cells

But is there any evidence these CD4 T cells truly 'reside' in adipose tissue and constitute a viral reservoir?



Are HIV-infected CD4 cells really 'resident' in adipose tissue?



CD4 T cells found 'deeper' in the adipose tissue. May indicate (1) these cells are not simply on 'patrol' and (2) are protected from CD8 T cells limited to the peri-capillary space

Summary (1)

- ▶ Adipose tissue is a complex organ with multiple roles
 - Energy storage
 - Metabolic regulator
 - Endocrine
- ▶ HIV–infection is association with alterations in the adipose tissue
 - Viral protein
 - ART
 - Altered immune milieu

Summary (2)

- ▶ Immune cells are a major component of adipose tissue milieu
 - Enrichment of CD8 T cells (possibly virus specific)
 - Activated resident CD4 T cells
 - Macrophages (pro-inflammatory)
- ▶ Replication competent HIV and SIV proviral reservoir as well as HIV RNA was detected in adipose tissue

Conclusion

Fat depots likely represents a major challenge for cure efforts due to

- ▶ ubiquitous nature of adipose tissue
- ▶ complex inflammatory cellular interactions
- ▶ selective distribution of antiretroviral drugs
- ▶ sequestration of infected immune cells

Thank You

