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Impact of HIV and Its Treatment on Weight and Body Habitus

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This activity is jointly provided by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine.

This activity is supported by independent educational grants from EMDSerono and Theratecholoigies.

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Target Audience

This activity has been designed to meet the educational needs of physicians, physician assistants, nurse practitioners, and pharmacists; other healthcare providers, such as nurses, nutritionists, social workers, and case managers are also encouraged to attend.

Statement of Need/Program Overview

HIV-associated weight and body composition change has been associated with the treatment of the disease since the introduction of antiretroviral therapy in the mid-1990s. Metabolic syndromes such as insulin resistance, diabetes mellitus and dyslipidemia have been a significant concern in people with HIV. This webinar and workshop series will address the unique challenges of unintended weight and body composition changes in people with HIV and how health care professionals can address these new and emerging health issues.

Joint Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine. Postgraduate institute for Medicine is accredited by the American Council for Continuing Medical Education (ACCME), Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Physician Continuing Medical Education

CREDIT DESIGNATION

- PACE designates this live activity for a maximum of 2.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Pharmacist Continuing Education

CREDIT DESIGNATION

- PACE designates this continuing education activity for 2.5 contact hour(s) (0.25 CEUs) of the Accrediting Council for Pharmacy Education.
  (Universal Activity Number JA4008073-9999-24-224-L02-P)

- Type of Activity: Application

Upon completion of the online evaluation, your credit will be submitted to CPE Monitor. Pharmacists have up to thirty (30) days to complete the evaluation and claim credit. Please check your NABP account within thirty (30) days to make sure the credit has posted.

Nursing Continuing Professional Development

CREDIT DESIGNATION

- The maximum number of hours awarded for this Nursing Continuing Professional Development Activity is 2.5 contact hours.
- Designated for 1.0 contact hours of pharmacotherapy credit for Advanced Practice Registered Nurses.

Disclosure Information

Disclosure of Conflicts of Interest

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Faculty Disclosures:

The ***faculty*** reported the following financial relationships or relationships to products or devices they have with ineligible companies:

Dr. Lee receives Consultant/Advisor/Speaker fees from EMDSerono and Theratechnologies. He also owns less than five percent stock in Gilead Sciences.

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The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Fee Information

There is no fee for this educational activity.

Acknowledgments

Dr. Lee would like to thank and acknowledge Dr. John Koethe for allowing for the use of some of his slides in the development of this presentation.

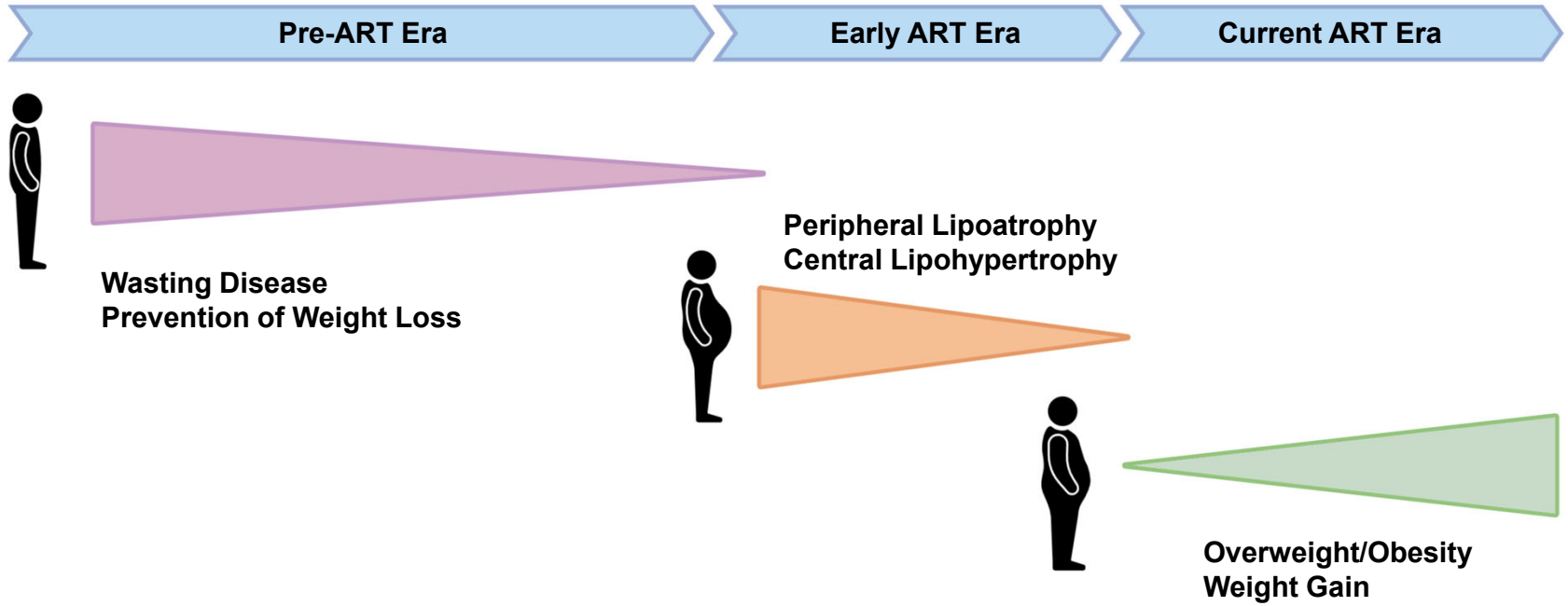
Educational Objectives

Upon completion of this activity, participants should be able to:

- Discuss the evolution of weight and body habitus-related comorbidities, such as HIV-associated wasting, loss of lean muscle mass and weight and adipose tissue gain, over time, including the impact on morbidity and mortality
- Describe the recent studies evaluating the management of HIV-associated weight and body habitus changes.
- Discuss the evolving role of antiretroviral agents when evaluating weight-suppressing, weight-neutral and weight-promoting agents among people with HIV.
- Incorporate into clinical practice both pharmacological and non-pharmacological interventions to manage weight and body habitus changes, taking into consideration the accompanying changes in body composition.

Nutrition, Weight, and Body Habitus Concerns in PWH Over Time

1981 to Today



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Slide courtesy of Dr. John Koethe

HIV-Associated Wasting (HIVAW)

Early Definition of HIV-Associated Wasting (HIVAW)

- Wasting was declared an AIDS defining illness in 1987
- CDC definition of wasting: involuntary loss of at least 10% of ideal body weight (IBW) **with** associated symptoms of chronic fever, weakness, or diarrhea for >30 days[1]
- Prevalence: estimated to be 25%-30%[2-3], but likely underestimated due to those with loss of weight, but lack of associated symptoms

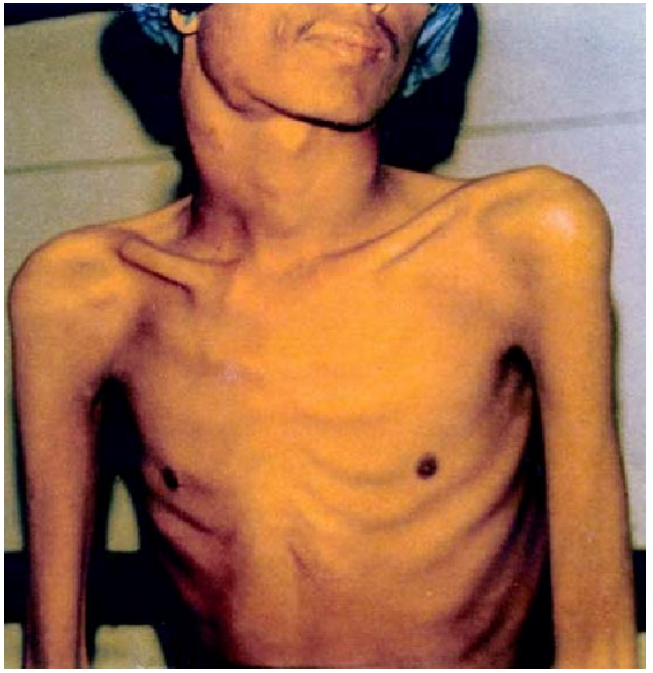

Image from Singh TN and Singh HL. Kathmandu Univ Med J (KUMJ). 2005 Oct-Dec;3(4):425-7

1. Centers for Disease Control and Prevention. *MMWR* 1987; 36: 1-15s.
2. Jones JL, et al. *MMWR CDC Surveill Summ* 1999; 48: 1-22.
3. Smit E, et al. *Am J Epidemiol* 2002; 156: 211-8.

Clinical Impact of HIV-Associated Wasting[1-4]

- Associated with high morbidity and mortality
- Increased physical weakness
- Decreased physical functioning
- Decreased physical endurance
- Increased risk for hospitalization
- Increased risk of developing opportunistic infections
- Decreased quality of life
- Decreased survival

1. Kotler DP, et al. *Am J Clin Nutr* 1989; 50: 444-7.
2. Palenicek JP, et al. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10: 366-73.
3. Grinspoon S, et al. *Clin Infect Dis* 2003; 36 (Suppl 2): S69-78.
4. Gelato M, et al. *Clin Ther* 2007; 29(11): 2269-2288.

HIVAW in the Current Antiretroviral Therapy Era

- HIVAW is an HIV-related condition characterized by abnormalities in protein synthesis, proteolysis, and lipid metabolism
  - Commonly defined as an **unintentional** loss of body weight or lean body mass (LBM), as well as a **reduction** in physical endurance and overall function[1]
  - Clinical presentation is often very different than the classic presentation from prior to the development of highly active antiretroviral therapy (HAART)
    - Rare to see people with advanced AIDS (except in inpatient settings) due to improved screening for HIV and earlier initiation of ART
    - PWH may present more with generalized weakness and deficits in physical endurance rather than overt loss of body weight or lean body mass
  - Thus, it requires a high level of suspicion to look for and diagnose HIVAW

1. Siddiqui, J, et al. *AIDS* 2022; 36(1): 127–135.

HIV-Associated Weight Loss (HAWL)[1]

- HAWL is a newly proposed updated definition of HIVAW that is clinically relevant to what is seen in the current antiretroviral era
  - Expert consensus panel of experienced HIV providers
  - HAWL is defined as sustained, unintentional weight loss in PWH (on ART with suppressed viral load <200 copies/mL) that:
    - Occurs in the absence of a concurrent illness or condition (other than HIV infection) that could readily account for such weight loss
    - Is characterized by >5% loss of premorbid body weight over 6 months or >10% loss of premorbid body weight over 12 months (in the absence of objective weight loss, low BMI [<20 kg/m^2] is sufficient)
    - May, in some cases, be accompanying reductions in physical functioning, including difficulty with completing activities of daily living, low physical strength, and slow gait speed
  - The former definition of HIVAW still pertains to those PWH who have prolonged, non-suppressed viremia with viral load >200 copies/mL)

1. Bedimo R, Hardy D, Lee D, Palella F, and Wohl DA. *Clin Infect Dis* 2024;79(Supplement_2):S63-S75.

HIV-Associated Weight Loss (HAWL)[1]

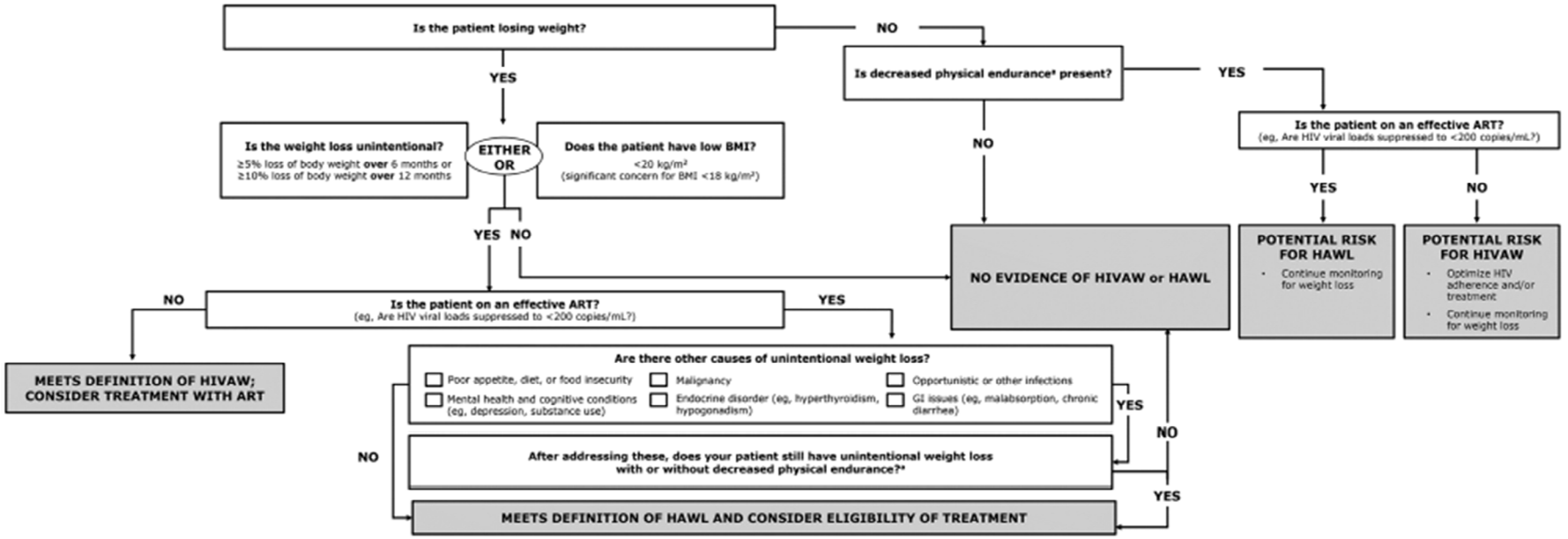

Figure 2. Screening algorithm for HIVAW versus HAWL in PWH in the modern treatment era. [a]Decreased physical endurance defined as difficulty completing activities such as activities of daily living (ADLs) or instrumental ADLs (iADLs). Abbreviations: HAWL, HIV-associated weight loss; HIVAW, HIV-associated wasting; PWH, people with HIV.

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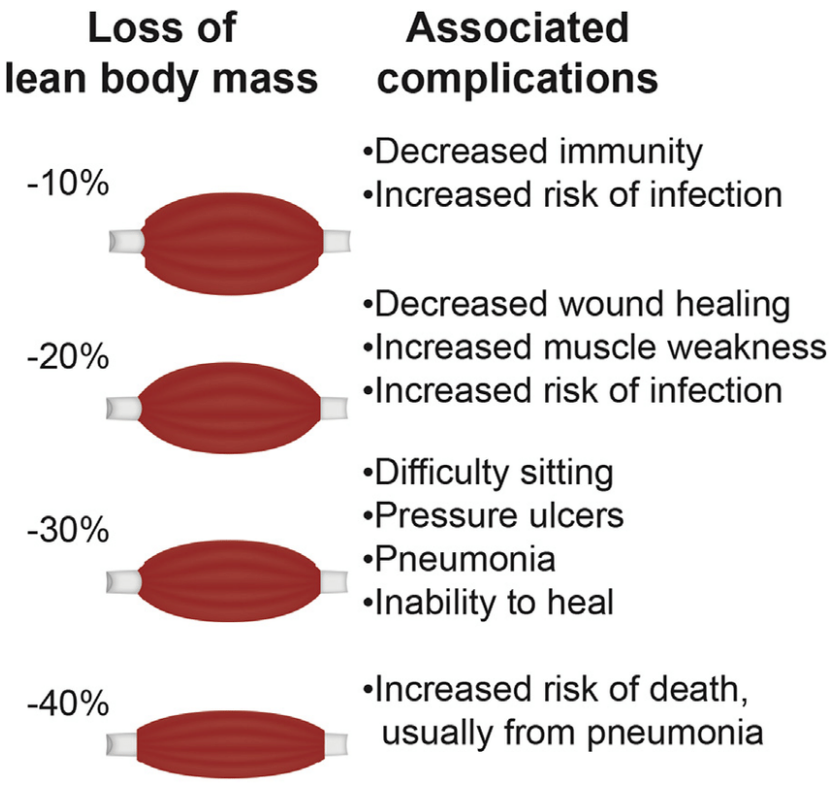
1. Bedimo R, Hardy D, Lee D, Palella F, and Wohl DA. *Clin Infect Dis* 2024;79(Supplement_2):S63-S75.

Importance of Lean Body Mass (LBM)[1]

- Lean body mass (LBM)
  - Equals body weight minus fat mass
  - Includes
    - Organ tissue
    - Blood and blood constituents
    - Skin and bones
    - Intracellular and extracellular water
    - Skeletal muscles
- Skeletal muscle has multiple functions
  - Physical movement
  - Site of glucose uptake/storage
  - Reservoir of amino acids to support protein synthesis or energy production



1. Argiles JM, et al. *J Am Med Dir Assoc* 2016; 17: 789-96.

Why is HAWL being underdiagnosed?

- Common misperceptions can lead to HAWL being overlooked and underdiagnosed
  - Reversal of HAWL occurs simply with initiation and continuation of ART
  - HAWL is no longer prevalent among well-controlled PWH receiving ART
  - Screening for HAWL is unnecessary
- Body composition changes may cloud our perception that a PWH may have decreased muscle mass or LBM
  - Weight gain attributed to Integrase Strand Transfer Inhibitors (INSTIs) and tenofovir alafenamide (TAF)
  - Lipodystrophy
- Increased telemedicine visits – less weight measurements performed
- Heavy reliance on loss of body weight/LBM to make diagnosis of HAWL with less emphasis on evaluation of physical function and/or physical endurance

Prevalence of HIVAW in the Current Antiretroviral Therapy Era

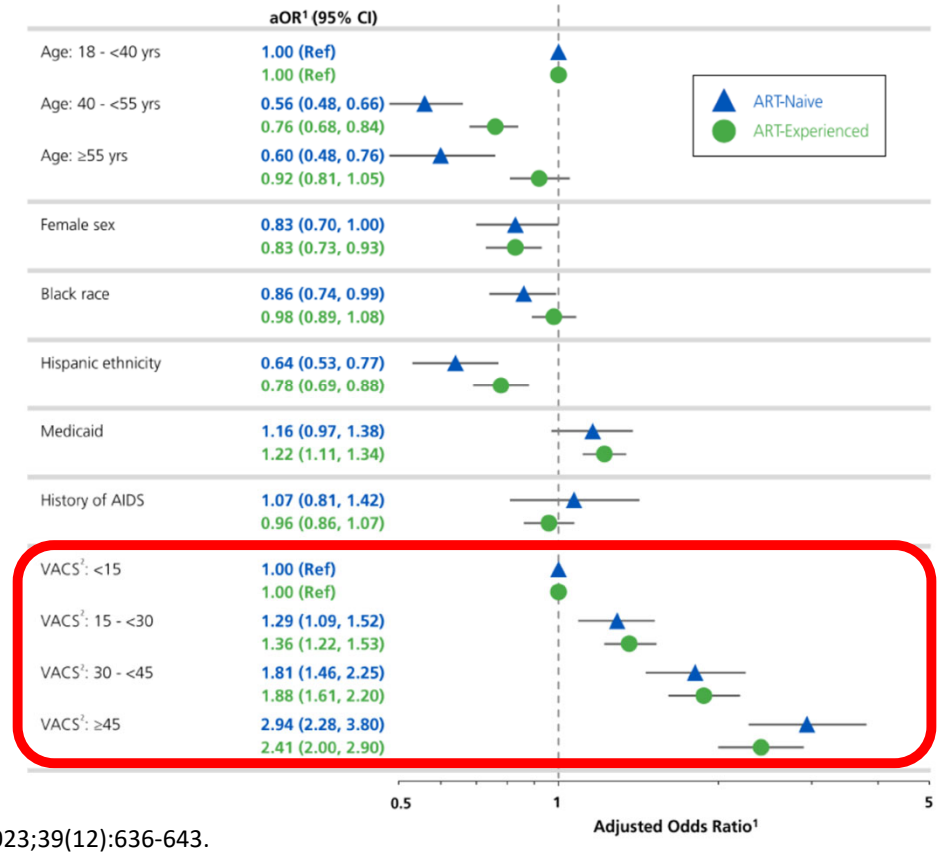
- Siddiqui, *et al*. conducted a database analysis of healthcare claims data for commercial health plan enrollees with evidence of HIV infection to estimate the prevalence of HIVAW between January 2005 and July 2007[1]
  - 8.3% had evidence of HIVAW
  - Those with HIVAW were more likely to be older and male
- Siddiqui, *et al*. conducted another database analysis of medical and pharmacy claims data using IBM MarketScan Commercial, Medicare Supplemental, and Medicaid Databases to estimate the prevalence of HIVAW between July 2012 and September 2018[2]
  - Cumulative HIVAW prevalence was 18.3% (or 3.1% per year)
  - Strongest associations with the likelihood of meeting the definition of HIVAW were for those individuals with Medicaid and hospitalization(s)

1. Siddiqui, J, et al. *Curr Med Res Opin* 2009; 25: 1307-17.
2. Siddiqui, J, et al. *AIDS* 2022: 36(1): 127–35.

Incidence of HIVAW in the Current Antiretroviral Therapy Era

- Wohlfeiler, *et al*. conducted a database analysis of the OPERA observational cohort to estimate the incidence of HIVAW between January 2016 and December 2020[1,2]
  - Incident HIVAW/low weight was identified in 7% of the population of PWH over 4 years
  - Increasing VACS Mortality Index Score, resulting from increased severity of HIV and/or comorbidities, were associated with higher odds of incident HIVAW/low weight

Figure 1. Predictors of Incident HIV-Associated Wasting/Low Weight Among 11,525 ART-Naïve and 39,166 ART-Experienced People with HIV in OPERA®

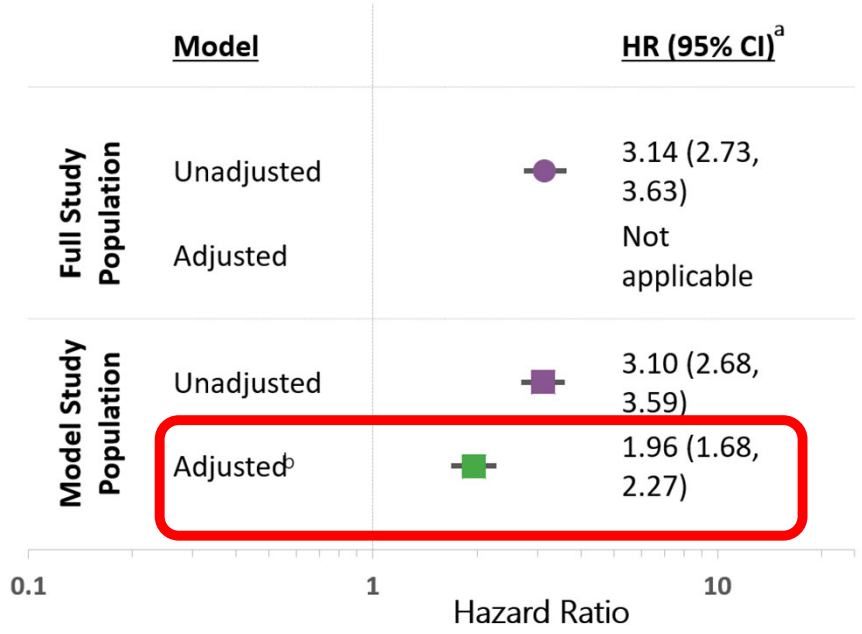


1. Wohlfeiler MB, et al. ACTHIV, May 5-7, 2022.
2. Wohlfeiler MB, et al. *AIDS Res Hum Retroviruses*. 2023;39(12):636-643.

Association Between Incidence of HIVAW and All-Cause Mortality

- Wohlfeiler, *et al*. conducted a database analysis of the OPERA observational cohort to evaluate the association between incidence of HIVAW and all-cause mortality between January 2016 and December 2020[1,2]
  - Incident HIVAW/low weight was associated with **twice** the risk of all-cause mortality, despite adjustment for changes in viral load and VACS Mortality Index Scores

Figure 2. Association between incident HIVAW/low weight and all-cause mortality over follow-up



1. Wohlfeiler MB, et al. ID Week 2022, October 19-23, 2022.
2. Wohlfeiler MB, et al. *AIDS Res Hum Retroviruses*. 2024;40(7):428-434.

Potential Causes of HIVAW[1]

- Inadequate nutrient intake
  - Oral, esophageal, and intestinal disorders
  - Anorexia
  - Psychological disorders
  - Economic/financial issues
  - Malabsorption
- Untreated HIV infection
  - Opportunistic infections
  - Malignancies
- Altered metabolism
  - Increased resting energy expenditure
  - Hormonal abnormalities
    - Hypogonadism
    - Hyperthyroidism
  - Cytokine dysregulation

1. Mangili A, et al. *Clin Infect Dis* 2006; 42: 836-42.

Assessment of HIVAW and HAWL

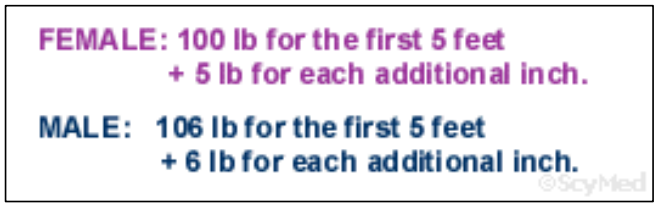
- History
  - Weight loss?
  - Anorexia?
  - Nausea?
  - Dietary intake?
  - Diarrhea?
  - Fatigue?
  - Weakness?
  - Problems with activities of daily living (ADLs)?
  - Difficulty with instrumental activities of daily living (IADLs)?
  - Body image issues?
  - Depression?
  - Food access?
  - Financial situation?

Assessment of HIVAW and HAWL (2)

- Physical examination
  - Perform physical with the patient completely undressed or in a gown
  - Examine for signs of muscle atrophy in the extremities, abdomen, and buttock
  - Rule out infections, malignancies, and other medical problems which may contribute to wasting
  - Consider performing anthropometric or circumference measurements
- Laboratory tests
  - CD4 count
  - HIV RNA PCR (viral load)
  - Serum testosterone level
  - Serum albumin or prealbumin
  - Thyroid function tests

Assessment of HIVAW and HAWL (3)

- Objective measures
  - Vital signs
    - Height (cm) and Weight (kg)
    - Body mass index (BMI) = height/(weight)^2 [kg/m^2]
  - Ideal body weight (IBW) measurement[1]:



  - Body composition measurements
    - Mid-arm (bicep) measurements
    - Mid-leg (thigh) measurements
    - Waist circumference
  - Bioelectrical Impedance Analysis – track body cell mass

1. http://www.scymed.com/en/smnxpn/pndfc237.htm

Treatment of HIVAW and HAWL

- Should be individualized
- Aimed at the cause(s) of wasting
  - Correct anorexia
  - Increase or improve nutritional intake
  - Maximize immune status
  - Treat immediate causes of wasting
  - Address psychosocial issues
- Institute a supervised exercise program
- Consider referral to a registered dietician to evaluate diet
- Consider use of testosterone, anabolic agents, and/or recombinant human growth hormone*

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* rHGH is the only FDA-approved treatment for HIV-Associated Wasting

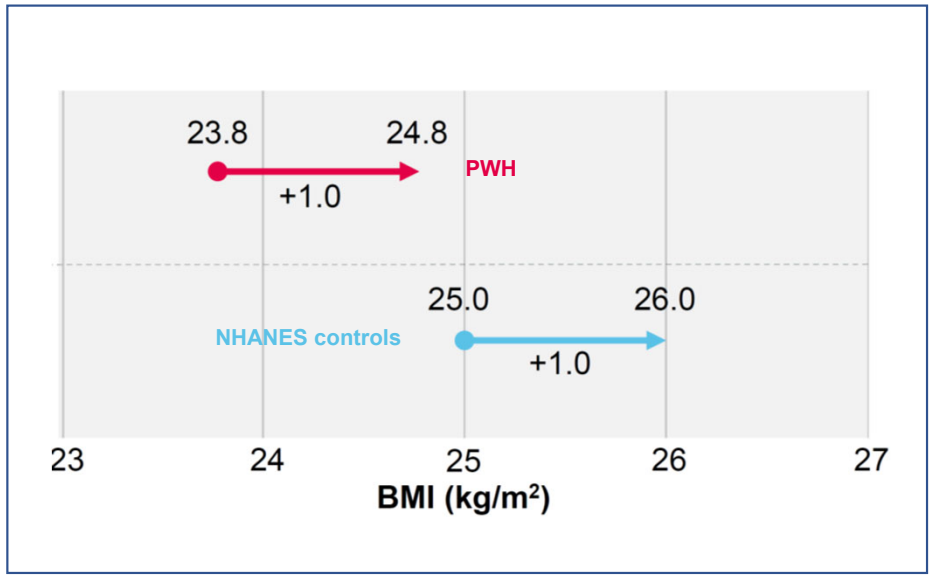
Summary Points

- HIV-associated weight loss remains a continued issue in the HAART era
  - Associated with high morbidity and mortality
  - Etiology is often multifactorial
  - Characterized by the loss of lean body mass, but may manifest more subtly with symptoms of generalized weakness, fatigue, decrease in endurance
  - Treatment should be directed towards addressing the underlying etiologies
  - Pharmacologic medications may be needed including, antianorexic agents, androgens and anabolic steroids, and recombinant human growth hormone
  - A detailed and thorough evaluation, along with a high level of suspicion, may be needed to make this important diagnosis

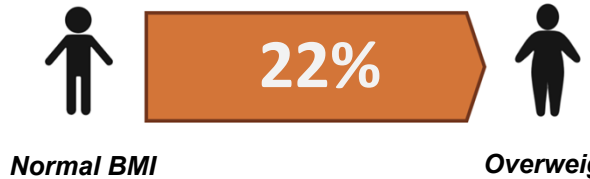
Weight Gain Associated with HIV

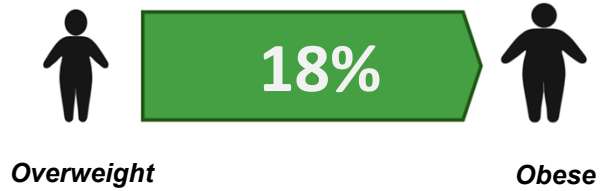
Body Mass Index at HIV Treatment Initiation Has Increased and PWH Gain Weight on ART

BMI at ART initiation in the United States from 1998 to 2010 among PWH and age/sex/race matched controls



Shifts in BMI categories in the 3 years after ART initiation



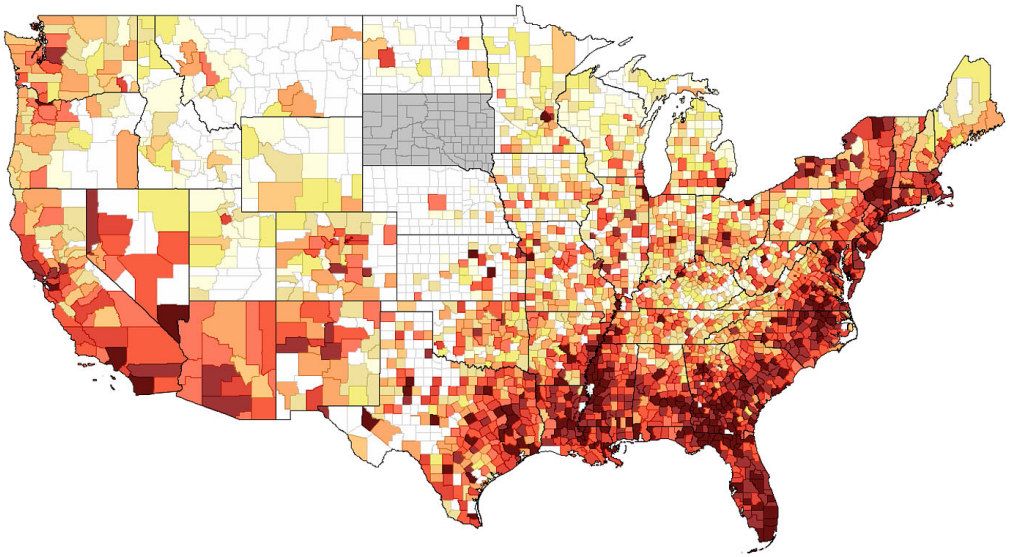


Approximately 80% of weight gain occurs in the first year of ART

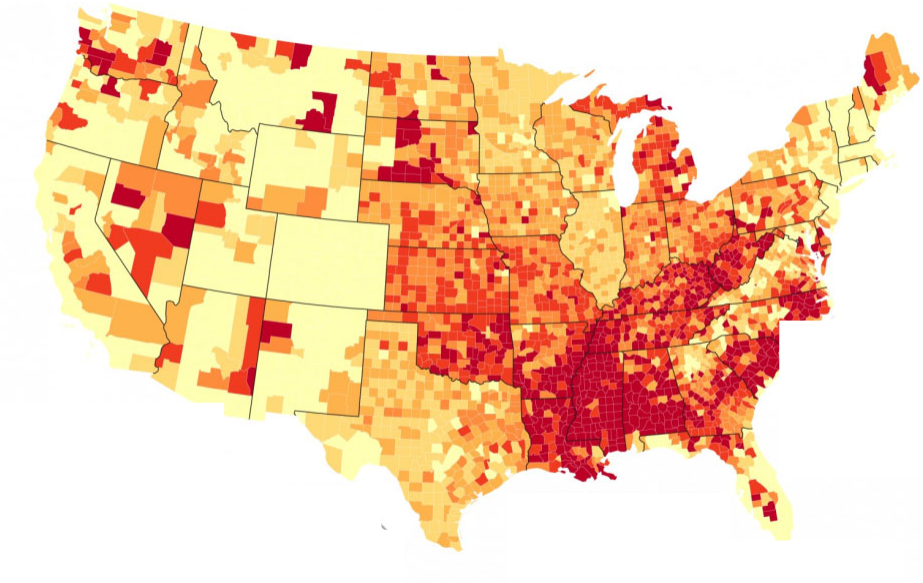
Overlapping Epidemics

HIV and Obesity in the United States

HIV prevalence



Obesity prevalence



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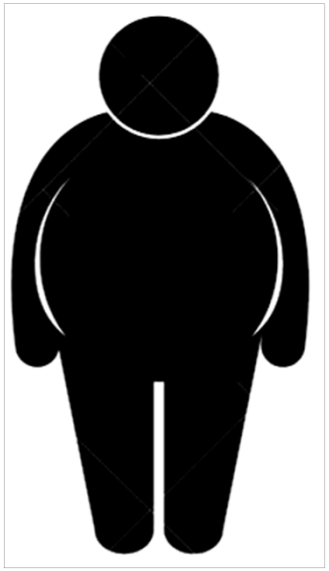
Sources: AIDSVu.com, National Center for Health Statistics (https://www.cdc.gov/dhdsp/maps)

Slide courtesy of Dr. John Koethe

Contributors to Metabolic Health: HIV, ART, and Environment

HIV and ART
- Altered lipid trafficking
- Energy absorption
- Basal energy expenditure
- Adipose tissue distribution
- Inflammation



Diet
- Food preferences
- Food insecurity
- Access to healthy foods (food deserts)

Activity
- Regular exercise
- Opportunities for physical activity
- Safety, walkability

Environment
Sociocultural knowledge, Economic resources
Attitudes, beliefs, & practices regarding diet, nutrition, exercise
Conceptions of 'health'

Host
- Race/ethnicity
- Gender
- Family history
- Other medications

Habits
- Smoking
- Alcohol
- Illicit Drug Use

Mental Health
- Depression
- Stress
- Stigma

Slide courtesy of Dr. John Koethe

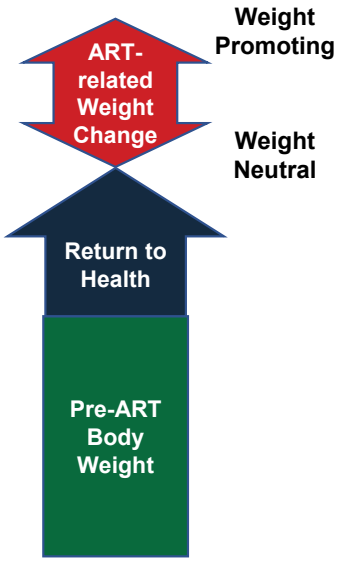
Rising Obesity Prevalence in PWH Reflects Broader Trends

- General trends:
  - An 'obesogenic' environment in many countries: changing dietary and lifestyle patterns
  - Overlapping HIV and obesity epidemics in key populations: African Americans/Hispanics, lower socioeconomic status, specific geographies
- HIV-specific factors:
  - Earlier diagnosis, linkage to care and treatment
  - Entry into HIV care accompanied by access to other resources: food assistance/benefits, smoking cessation, mental health treatment
  - Potential role of ART agents in weight gain

Impact of Weight Gain on Overall Health

- Higher blood pressure → Hypertension
- Higher cholesterol → Hyperlipidemia
- Higher blood sugar → Hyperglycemia → Prediabetes → Diabetes
- Increased risk of cardiovascular disease (CVD) and myocardial infarction
- Increased risk of cerebrovascular disease and stroke
- Increased risk of some cancers (e.g., endometrial, breast, colon)
- Increased risk of gallbladder disease (e.g., gallstones, cholecystitis)
- Increased risk of gout
- Increased risk of osteoarthritis and body pain
- Increased risk of breathing difficulties (e.g., asthma, sleep apnea)
- Increased risk of mental illness (e.g., depression, anxiety)

Our Understanding of Weight Gain and ART Has Changed Over Time



Model #1
Early INSTI and TAF Weight Studies

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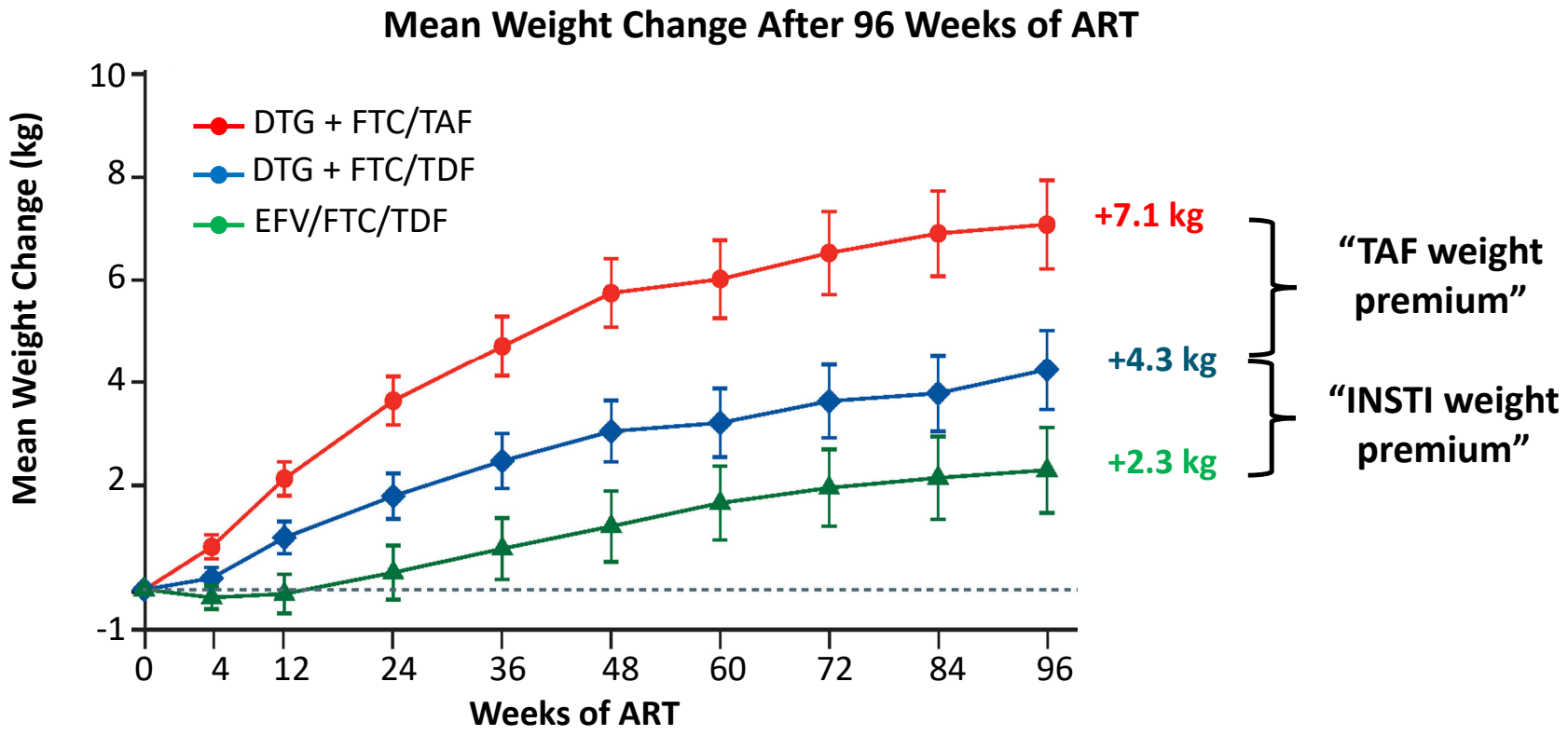
Slide courtesy of Dr. John Koethe

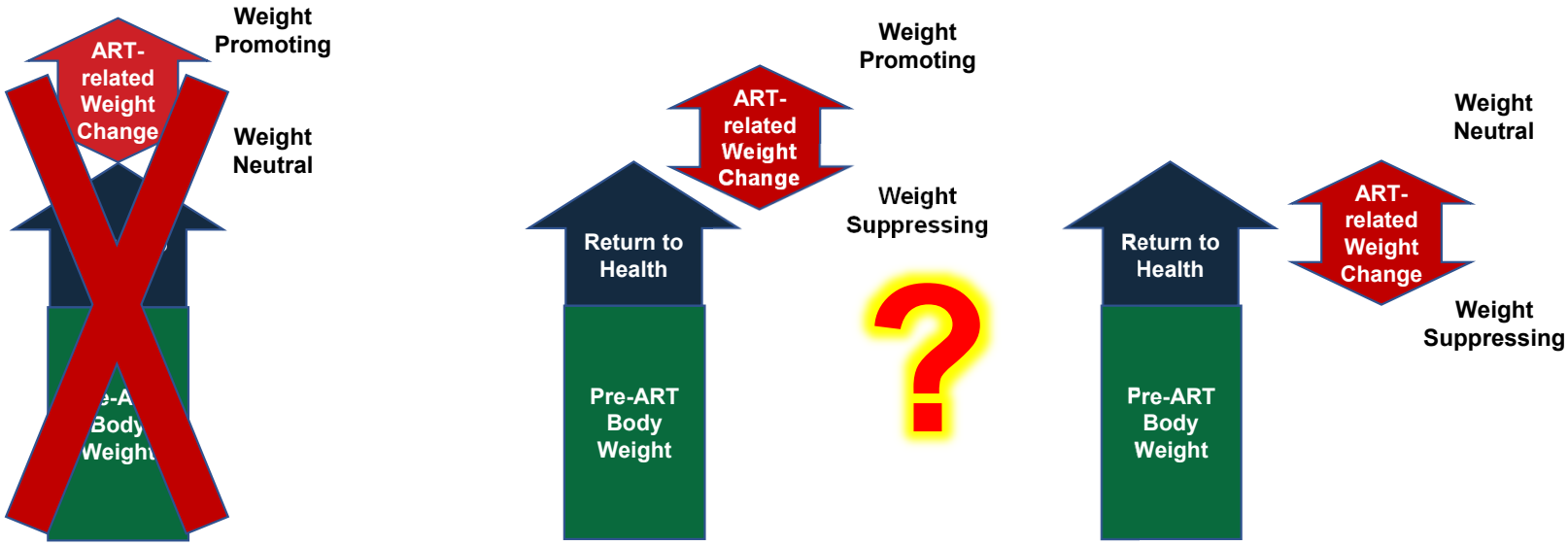
ADVANCE South Africa: ART Starting DTG + FTC/TAF, DTG + FTC/TDF, or EFV/FTC/TDF



1) Venter W, et al. *N Engl J Med*. 2019;381:803-815. 2) Venter W, et al. *Lancet HIV*. 2020;7:e666-e676.

Slide courtesy of Dr. John Koethe

Our Understanding of Weight Gain and ART Has Changed Over Time



Model #1
Early INSTI and TAF Weight Studies

Model #2

Model #3

More Recent Interpretation of ART and Pre-Exposure Prophylaxis Trials

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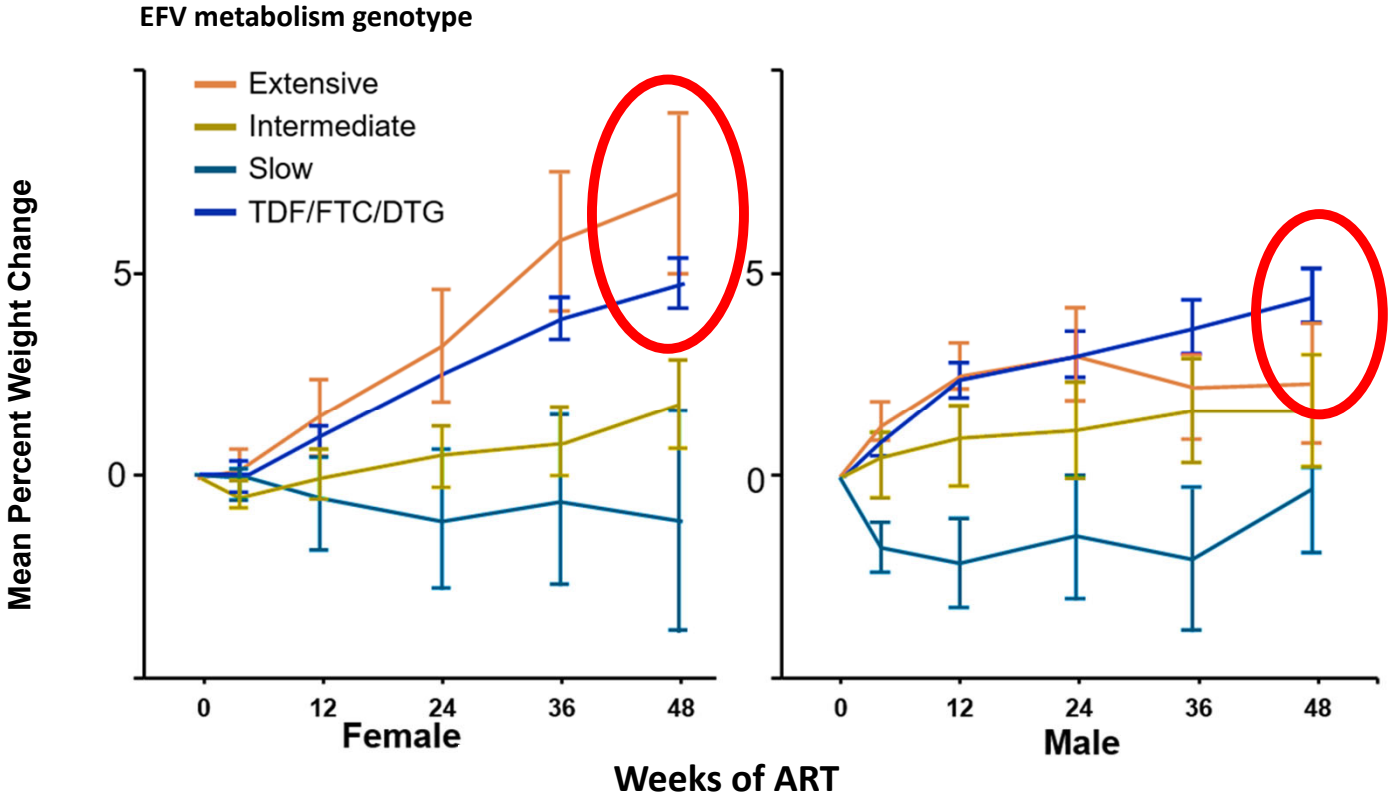
Slide courtesy of Dr. John Koethe

Drug Metabolism Genotypes Explain Much of the ADVANCE DTG vs. EFV Weight Difference

- In ADVANCE, weight gain was similar between "extensive" (fast) EFV metabolizers, based on CYP2B6 liver enzyme genotype, and participants on DTG (both with TDF/FTC)
- Among women, extensive EFV metabolizers <u>gained more weight</u> than DTG recipients



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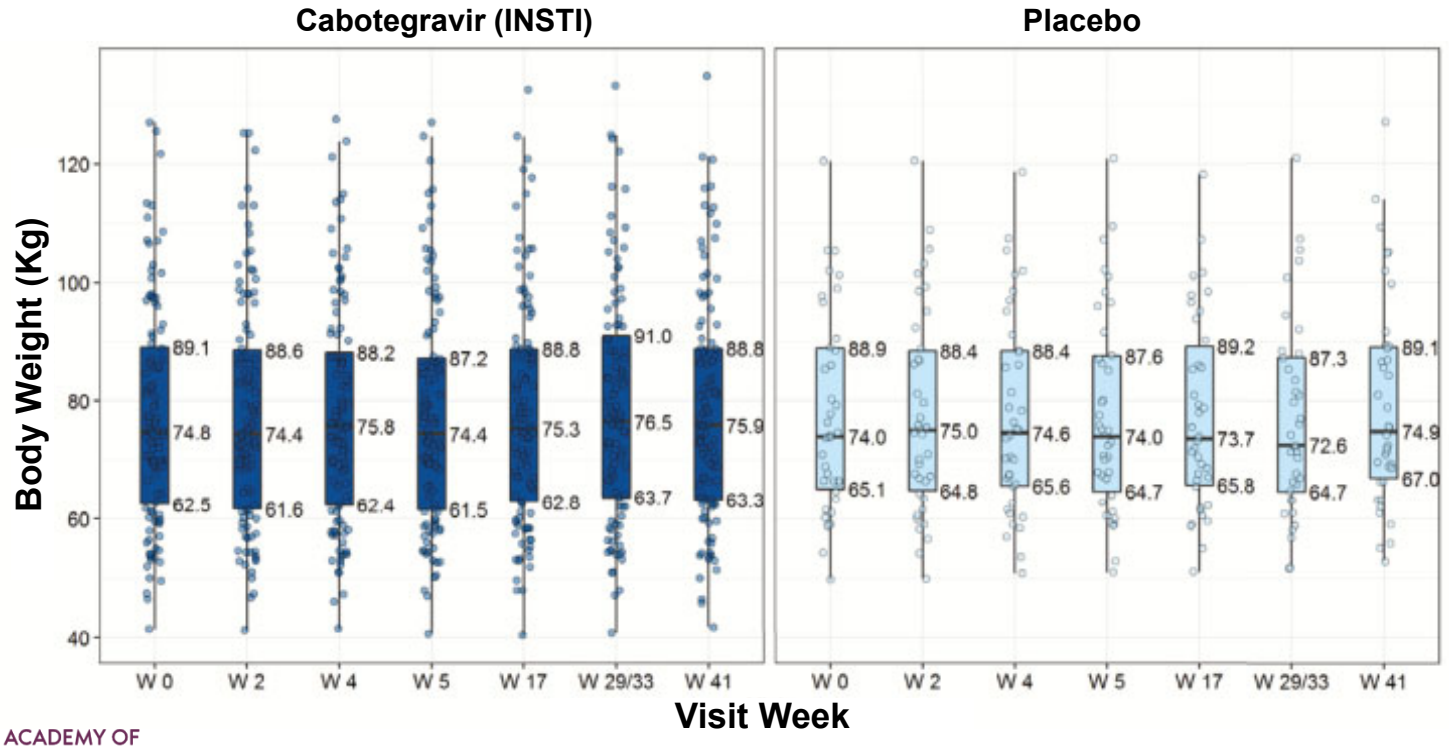
Griesel R, et al. *Clin. Infect. Diseases.* 2021;73:e3902-e3909.

Slide courtesy of Dr. John Koethe

Pre-Exposure Prophylaxis (PrEP) Trials: ART Drugs Without the HIV

Stable Body Weight with Cabotegravir Versus Placebo Over 41 Weeks in the HPTN 077 PrEP Trial



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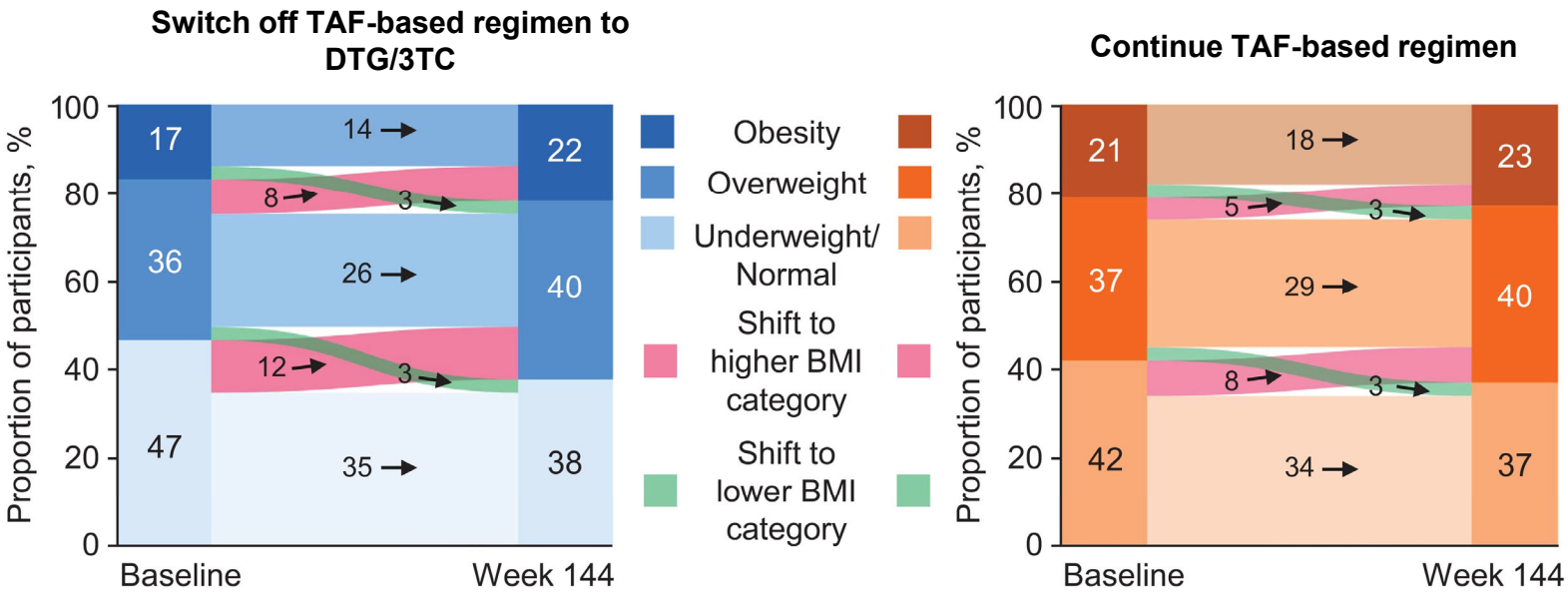
Landovitz RJ, et al. *Clin Infect Dis*. 2020;70(2):319-322.

Slide courtesy of Dr. John Koethe

TDF Appears Weight Suppressive and Stopping TAF Does Not Induce Weight Loss

No Substantial Weight Loss with TAF-Sparing Regimen Change in TANGO Study

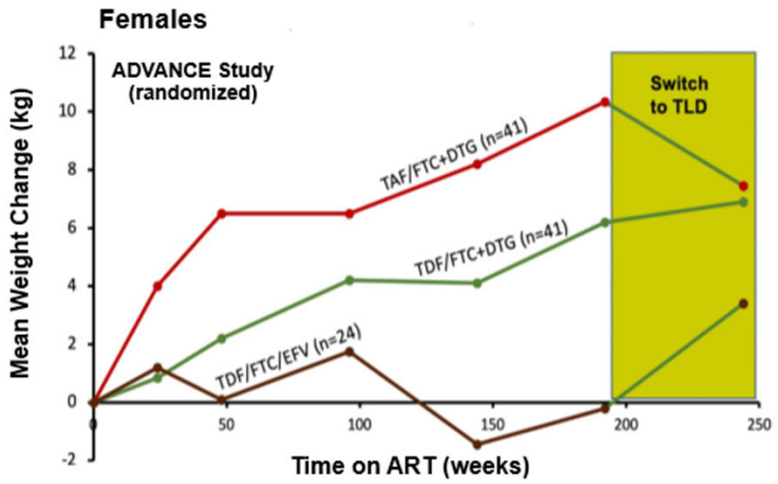


Batterham RL, et al. *Open Forum Infect Dis.* 2023;10:ofad359.

Slide courtesy of Dr. John Koethe

Switching Multiple ART Regimens to a Single Regimen Promotes Weight Convergence

The CHARACTERIZE Study: ADVANCE Participants on 3 Different Regimens Switched to TDF/3TC/DTG



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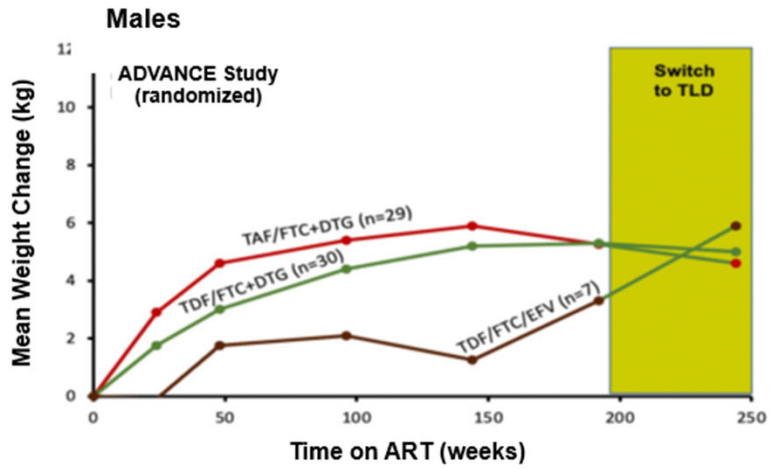

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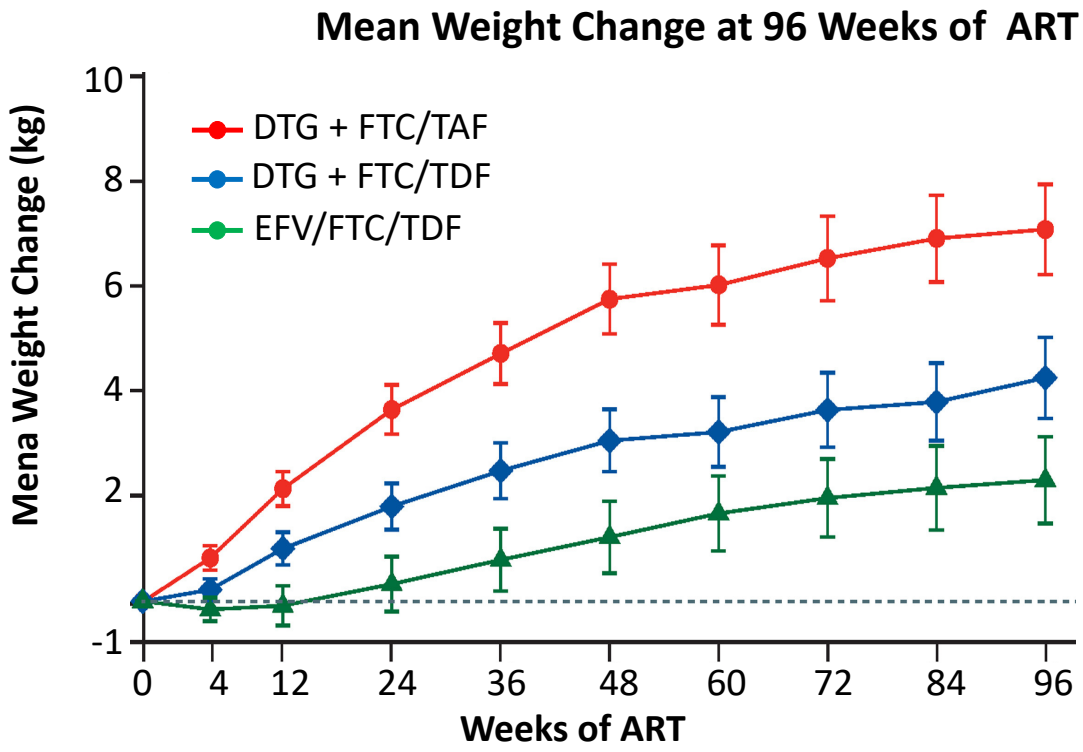
1) Bosch B, et al. CROI 2023 Abstract 671. 2) Bosch B, et al. *Clin Infect Dis.* 2023;76:1492-1495.

Slide courtesy of Dr. John Koethe

Irrespective of Regimen, Weight Gain on ART Remains Highly Variable



+7.1 kg: Standard Deviation 7.4 kg

+4.3 kg: Standard Deviation 6.7kg

+2.3 kg: Standard Deviation 7.0kg

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1) Venter W, et al. *N Engl J Med.* 2019;381:803-815. 2) Venter W, et al. *Lancet HIV.* 2020;7:e666-e676.

Slide courtesy of Dr. John Koethe

Risk Factors for a >10% Weight Gain in Pooled Randomized Clinical Trials

Odds of a >10% Weight Gain After 48 Weeks of ART in 8 Pooled RCTs

Variable	Odds Ratio	95% CI	p-value
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	<0.01
EVG/c vs EFV	1.36	(1.04–1.78)	0.03
CD4 count (<200 vs ≥200)	4.36	(3.6–5.27)	<0.001
HIV RNA (>100K vs ≤100K)	1.98	(1.65–2.37)	<0.001
BMI			
Normal vs overweight	1.54	(1.27–1.87)	<0.001
Normal vs obese	1.66	(1.29–2.15)	<0.001
Sex (female vs male)	1.54	(1.21–1.96)	<0.001
Race (black vs non-black)	1.32	(1.10–1.59)	<0.01

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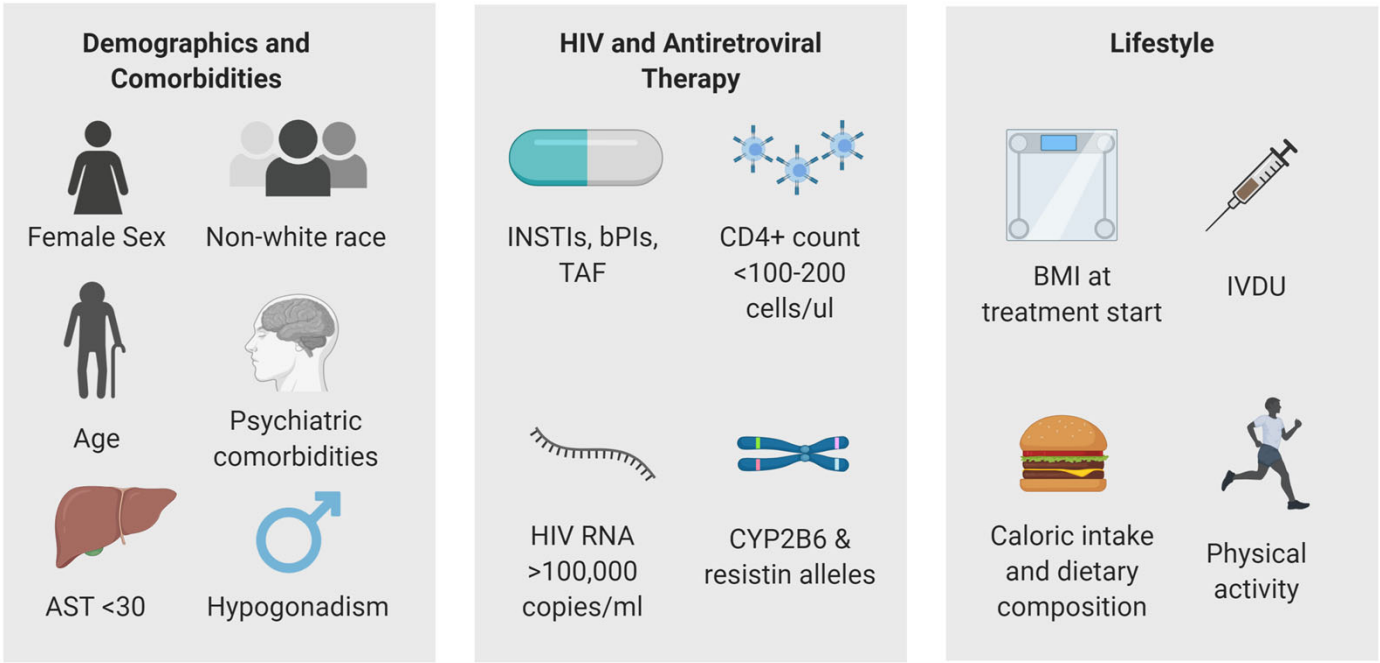
Sax. *Clin Infect Dis*. 2020;71:1379.

Slide courtesy of Dr. John Koethe

Summary of Factors Associated with Weight Gain on ART and Higher Body Mass Index in PWH

Factors Associated with Greater Weight Gain or a Higher BMI Among PWH on ART Across Multiple Studies



Antiretrovirals and Weight Change: Weighing the Evidence

- Expert panel was convened to review weight changes in the general population and PWH
  - Included weight data from select major randomized trials that enrolled people without HIV (PrEP) and antiretroviral trials in PWH (including initial therapy and switch studies in those with virologic suppression)
  - Conclusions:
    - Dolutegravir (DTG), Bictegravir (BIC), and Tenofovir Alefenamide (TAF) were found to be weight neutral
    - Tenofovir disoproxil fumarate (TDF) and Efavirenz (EFV) were found to be weight attenuating
    - Switching of antiretrovirals for weight gain is not currently recommended

Wohl DA, et al. *Clin Infect Dis*. Published online April 12, 2024. doi:10.1093/cid/ciae191

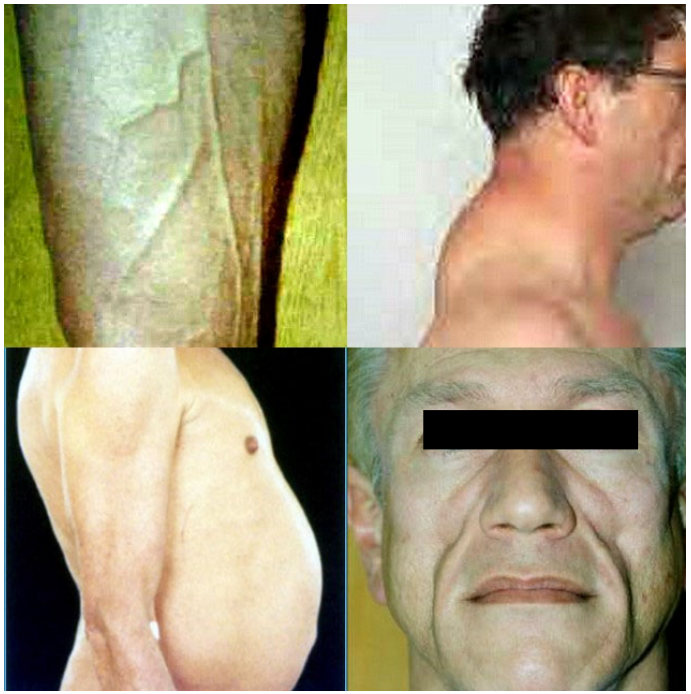
Summary Points

- We currently live in an “obesogenic” environment in which weight gain is common worldwide
- Weight gain can dramatically impact the development of other comorbidities, which may increase the risk of cardiovascular disease, cerebrovascular disease, and even cancers
- Initial observational cohort and pooled trial data suggested that weight gain is greater for PWH starting INSTI and TAF-containing regimens, and that weight gain can also occur when switching to these agents
- Weight gain is common after starting ART, and women, persons of African heritage, and those with advanced disease appear more susceptible
- Recent expert panel concluded that INSTIs and TAF were weight-neutral while TDF and Efavirenz were weight-attenuating

Body Habitus Changes Associated with HIV and Its Consequences

Less Overt Lipodystrophy but Visceral Fat Accumulation is Still Present in the Modern ART Era

The Past…



- Over 50% prevalence of clinically apparent lipodystrophy in the early combination ART era
- Most commonly observed with thymidine analogue and early protease inhibitor combination regimens
- Characterized by subcutaneous limb and facial fat wasting, with enlargement of visceral and dorsocervical fat compartments
- Accompanied by increased circulating triglyceride levels, insulin resistance, and elevated risk of cardiovascular events

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Slide courtesy of Dr. John Koethe

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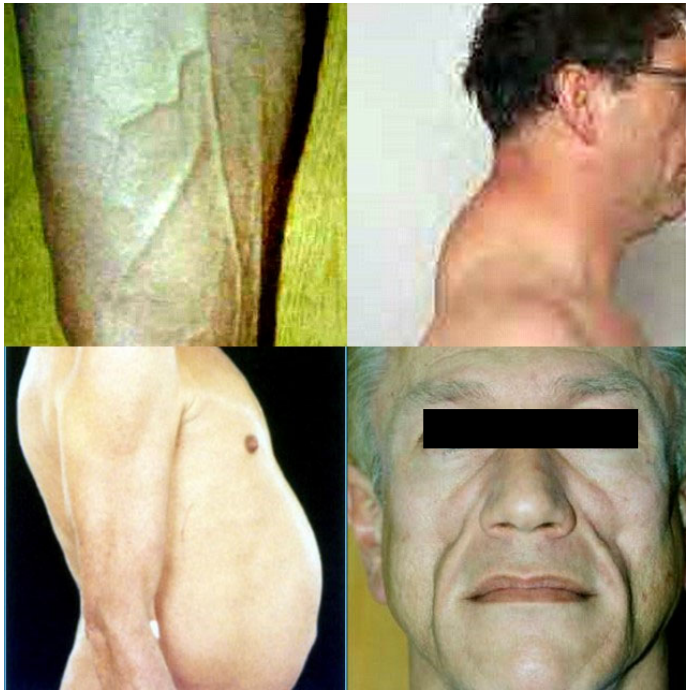

…and the Present

Comparison of Visceral Fat in HIV+ and HIV-negative Men in the Multi-center AIDS Cohort Study (MACS)

BMI Category	HIV+	HIV-negative	*p-value*
	Median visceral fat area, cm^2 (IQR)	Median visceral fat area, cm^2 (IQR)	
Normal BMI	**115** (76–158)	88 (57–132)	**<.001**
Overweight	**170** (124–220)	155 (112–210)	**.002**
Obese	233 (184–291)	244 (175–285)	.88

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Palella FJ, et al. *Open Forum Infect Dis.* 2016;3:ofw098.

Slide courtesy of Dr. John Koethe

Where Weight is Regained on ART Affects Cardiovascular and Metabolic Disease Risk

HIV infection

Weight Loss

- Increased resting energy expenditure
- Loss of appetite
- Accelerated skeletal muscle catabolism & reduced protein deposition
- Accelerated lipolysis (fat loss)
- Reduced nutrient absorption
- More rapid bowel transit time
- Inflammation

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Slide courtesy of Dr. John Koethe

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ART initiation

"Return to Health"

- Reduced resting energy requirements
- Improved appetite and nutrient absorption
- Impaired energy storage in subcutaneous fat & altered lipid kinetics
- Variable microbiome and microbial translocation improvement
- Access to nutrition and smoking cessation services
- Treatment of psychiatric comorbidities
- Specific ART regimen

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Slide courtesy of Dr. John Koethe

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Stable ART

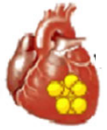
Response spectrum

Subcutaneous fat loss / impairment

Visceral fat deposition

Hepatic steatosis

Peri/epicardial fat



Muscle fat / sarcopenia

<u>Comorbid conditions:</u>

- **Insulin resistance / diabetes**
- **Hypertriglyceremia and mixed hyperlipidemia**
- **Liver fibrosis**
- **Hypertension**
- **Coronary and peripheral artery atherosclerosis**
- **Frailty (including sarcopenic obesity)**
- **Neurocognitive decline**
- **Increased inflammation**

<u>Other consequences:</u>

- **Impaired mobility**
- **Body shape changes: peripheral lipoatrophy & central lipohypertrophy**
- **Reduced quality of life**
- **Depression & anxiety**

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Slide courtesy of Dr. John Koethe

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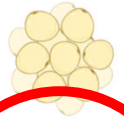
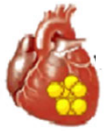


Visceral fat deposition

Hepatic steatosis

Peri/epicardial fat



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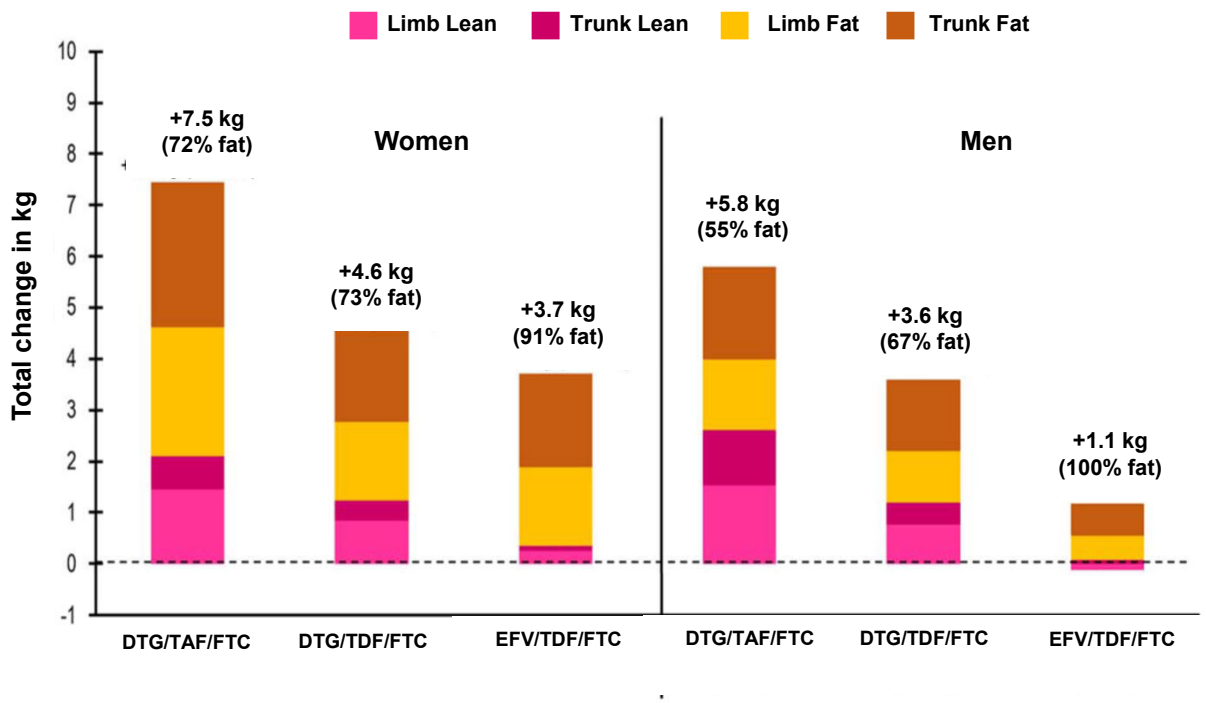
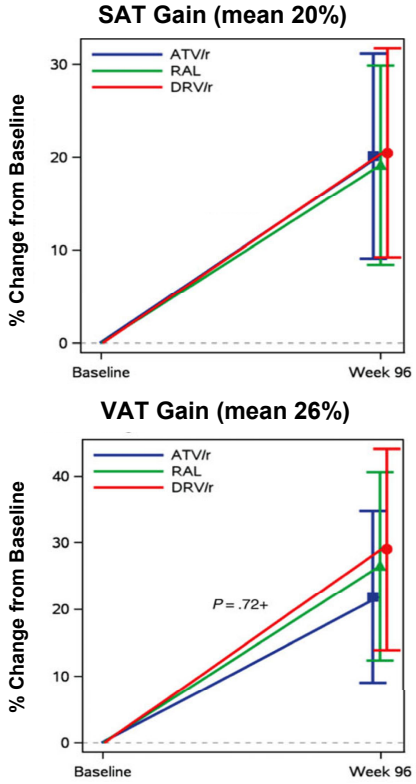
Slide courtesy of Dr. John Koethe

Weight Gain on ART Differs by Anatomic Depot

Change in fat and lean mass over 96 weeks of ART in ADVANCE



Change in abdominal SAT and VAT over 96 weeks in ACTG 5260s



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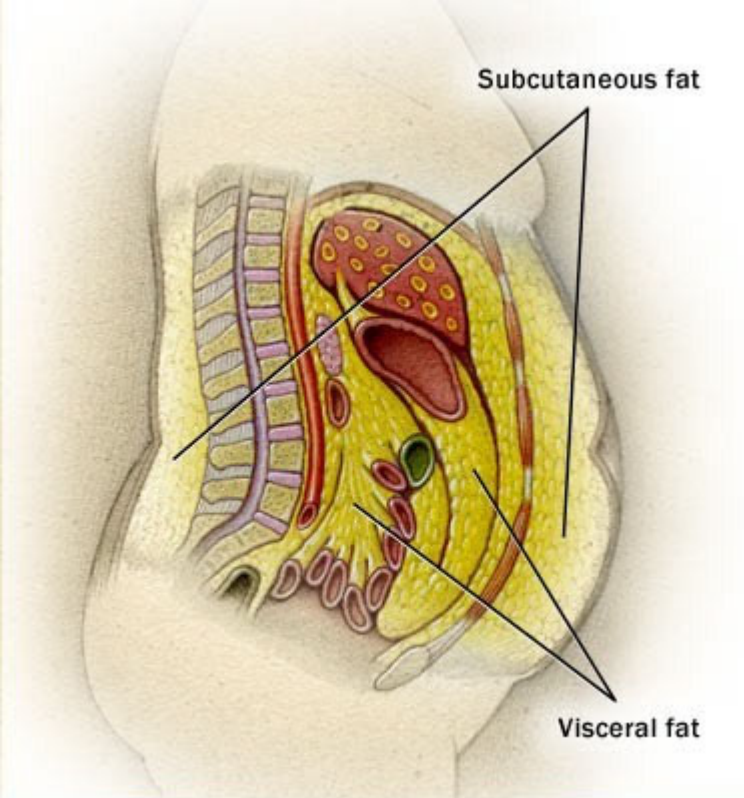
1) Venter W, et al. *Lancet HIV*. 2020;7:e666-e676. 2) McComsey GA, et al. *Clin Infect Dis*. 2016;62:853-62.

Slide courtesy of Dr. John Koethe

What is Visceral Adipose Tissue (VAT)?

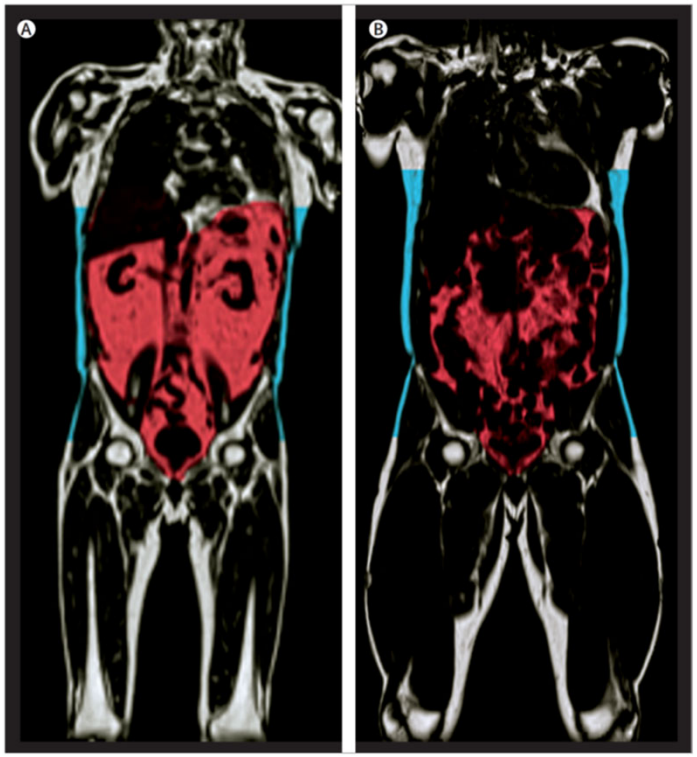
- Visceral adipose tissue (**VAT**) is the most clinically apparent site of ectopic fat accumulation
- VAT refers to fat below the rectus sheath and encircling the internal organs
- Clinically, increased VAT is evident as abdominal distension disproportional to other fat depots, such as the buttocks or limbs
- VAT is the main contributor to an increased waist-to-hip ratio
- VAT may be apparent to patients as a 'firm' abdomen or an inability to 'pinch' skin and fat tissue proportional to waist size



Slide courtesy of Dr. John Koethe

Visceral Adipose Tissue Expansion is Exaggerated in PWH and Major Contributor to Metabolic Disease

- Health outcomes in persons with obesity as defined by BMI ≥30 kg/m^2 are highly heterogeneous
- Concept of Metabolically Healthy vs. Unhealthy Obesity largely defined by extent of **VAT**
- 30 years of MRI and CT imaging studies demonstrate VAT is a marker of mortality and cardiometabolic disease risk independent of abdominal SAT



67 y/o male
BMI 25 kg/m^2 and VAT 2.6 L/m^2

53 y/o male
BMI 30 kg/m^2 and VAT 0.9 L/m^2

Slide courtesy of Dr. John Koethe

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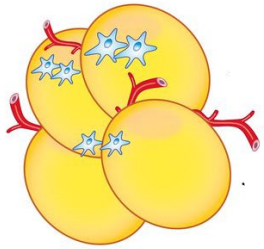
Subcutaneous Adipocytes and HIV: A Hostile Environment

Antiretroviral medications
(esp. thymidine analogues)

HIV viral proteins

HIV-infected macrophages and T cells

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



Subcutaneous adipose tissue

Impaired lipid storage

'Energy excess' state

Effects on Subcutaneous Adipocytes:

- Reduced mitochondrial DNA content & respiratory chain proteins
- Reduced regulatory gene expression (PPAR-γ, C/EBPs)
- Reduced insulin signaling
- Reduced free fatty acid to triglyceride conversion / storage
- Increased lipolysis
- Increased inflammatory mediators (IL-6, TNF-α)
- Increased apoptosis

Visceral adipose tissue and other ectopic fat deposits

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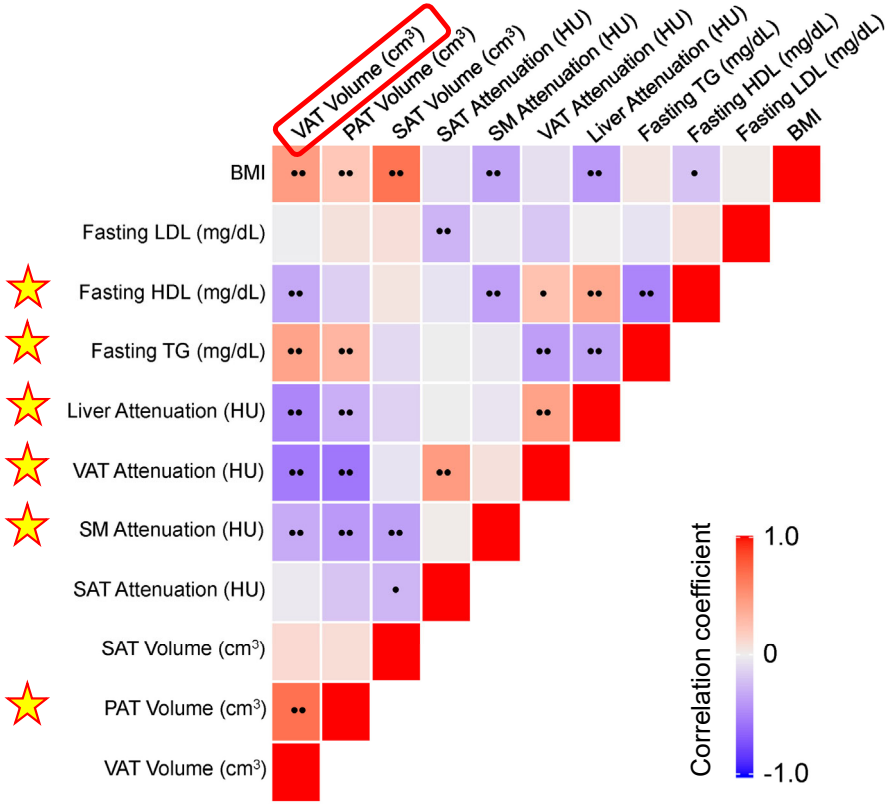
Slide courtesy of Dr. John Koethe

Increased Visceral Adipose Tissue is Accompanied by Other Ectopic Fat Deposits



Among 92 PWH on long-term ART, higher VAT was correlated with:

- Lower fasting HDL and higher triglycerides
- Greater liver fat
- Greater skeletal muscle (SM) fat
- Greater pericardial (heart) fat (PAT)

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Gabriel, C et al. Hepatology Comm. 2021

Slide courtesy of Dr. John Koethe

Summary Points

- Body habitus changes still occur in association with HIV infection and antiretroviral therapy
- While lipodystrophy is less common, visceral fat accumulation remains common in the current antiretroviral era
- The distribution of weight gain on ART is highly variable, and many patients gain increased visceral adipose tissue (**VAT**; below the rectus sheath and encircling the internal organs)
- While VAT is clinically evident as an increased abdominal girth out of proportion to the rest of the body, it is also a marker of fat deposition in the liver, heart, skeletal muscle, and other tissues
- The accumulation of VAT over time increases cardiometabolic risk

Options for Managing Weight Gain Associated with HIV

2022 IAS-USA Guidelines - Weight Gain and Metabolic Complications with ART

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2022 Recommendations of the International Antiviral Society-USA Panel

Rajesh T. Gandhi, MD; Roger Bedimo, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Davey M. Smith, MD; Ellen F. Eaton, MD; Clara Lehmann, MD; Sandra A. Springer, MD; Paul E. Sax, MD; Melanie A. Thompson, MD; Constance A. Benson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Michael S. Saag, MD

Box 3. Weight Gain and Metabolic Complications While Receiving Antiretroviral Therapy (ART)

- Documentation of weight and BMI at baseline and every 6 months is recommended for people with HIV initiating or switching regimens to identify those with excessive weight gain (evidence rating: AIIa)
- Counseling regarding possibility of weight gain and potential cardiometabolic complications is recommended for people with HIV initiating or switching ART (evidence rating: AIII)
- Yearly diabetes screening and assessment of cardiovascular risk score of patients receiving InSTI-based ART is recommended (evidence rating: BIII)
- Lifestyle changes (exercise and diet) are recommended to support people with HIV who gain greater than 5% body weight (evidence rating: AIII)

Abbreviations: BMI, body mass index; InSTI, integrase strand transfer inhibitor.

- Treatment with INSTI- and TAF-based regimens is associated with greater weight gain
- Weight gain can occur with initiation or switch of ART, but also for PrEP
- Data suggest that diabetes risk with weight gain at ART initiation is significant
- Whether weight gain is reversible or not is unclear and under investigation
- Until there are data proving benefit, switching regimens because of weight gain is not recommended (BIIa)
- Exercise and diet intervention are recommended (AIII)
- Semaglutide and other GLP-1 analogues that decrease weight are being studied

Gandhi RT, et al. *JAMA.* Published online December 01, 2022. doi:10.1001/jama.2022.22246

Approaches to Estimating Visceral Adipose Tissue (VAT) in Clinical Practice

Waist circumference

- Readily available in a clinical setting
- Provides a rough estimate of VAT accumulation; may perform better in men
- Conflicting data on whether waist-to-hip ratio is more sensitive for VAT

Computed Tomography

- Can be obtained from routine non-contrast abdominal CT scans
- May require specific request to radiology or use of body composition image analysis software
- Volumetric analysis and surface area (usually at L4/L5 as in MESA) available; surface area more common in studies of PWH

Magnetic Resonance Imaging

- Higher cost but can be derived from clinical images; requires specialized interpretation or software

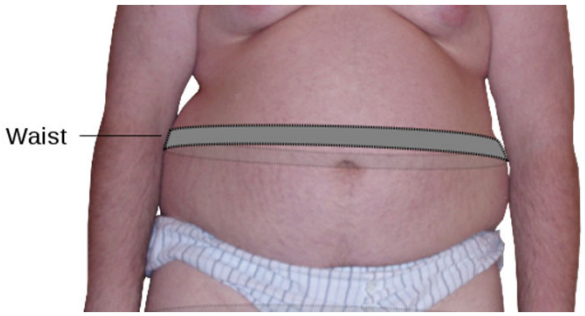
Dual-energy x-ray absorptiometry (DEXA)

- Low radiation exposure and widely available
- Provides estimate of total trunk fat or surface area, but VAT quantitation often relies on image analysis software developed using estimates from the general population

Waist Circumference to Estimate VAT

Waist Circumference

- Measurement of waist circumference feasible in clinic settings
- HIV-specific thresholds not well validated, but extensive general population data
- Most studies use circumference at level of umbilicus or midpoint of iliac crest and lowest rib



Ethnicity-Specific Metabolic Syndrome Threshold Waist Circumference Values (cm) – General Population		
Ethnic origin	**Men**	**Women**
Europe / North Africa	≥94	≥80
Sub-Saharan Africa	≥94	≥80
South Asian, China and Japan	≥90	≥80
South and Central America	≥90	≥80
Middle East and Eastern Mediterranean	≥94	≥80

International Diabetes Federation Consensus Worldwide Definition of Metabolic Syndrome (published 2006, updated 2020). https://www.idf.org/e-library/consensus-statements/60

Slide courtesy of Dr. John Koethe

Measuring Waist Circumference

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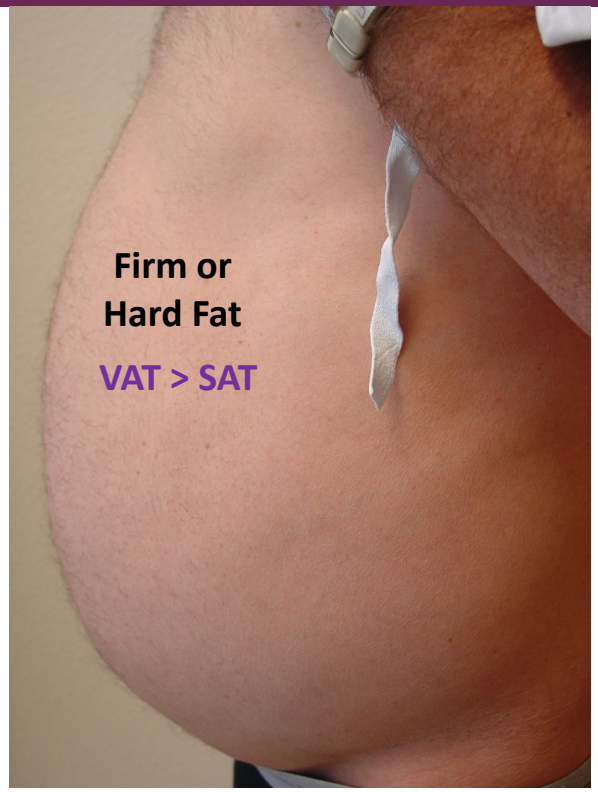
Image from https://intermountainhealthcare.org/blogs/topics/live-well/2019/07/your-waist-circumference-matters-more-than-your-weight/

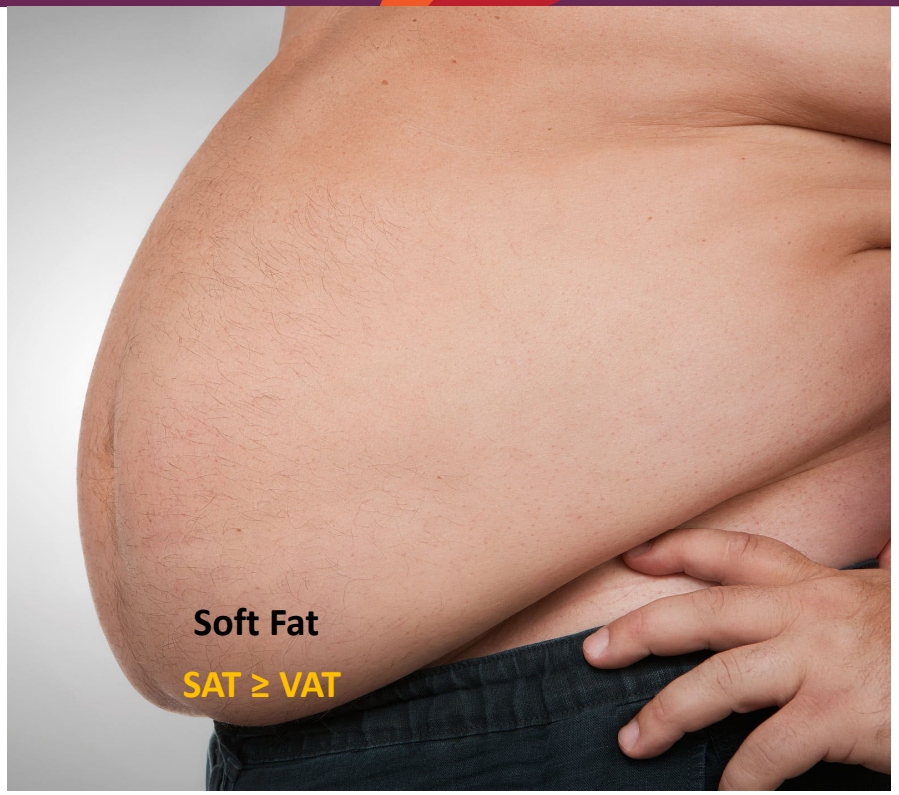
Body Fat “Pinch” Test

Image from https://blog.insidetracker.com/body-fat-measurement-what-options-are-best-for-you

Evaluating VAT on Clinical Exam



Source: Dr. Daniel Lee, University of California at San Diego.



Source: https://www.usatoday.com/story/news/health/2019/01/10/belly-fat-linked-smaller-brain-size-neurology-study-suggests/2534522002/

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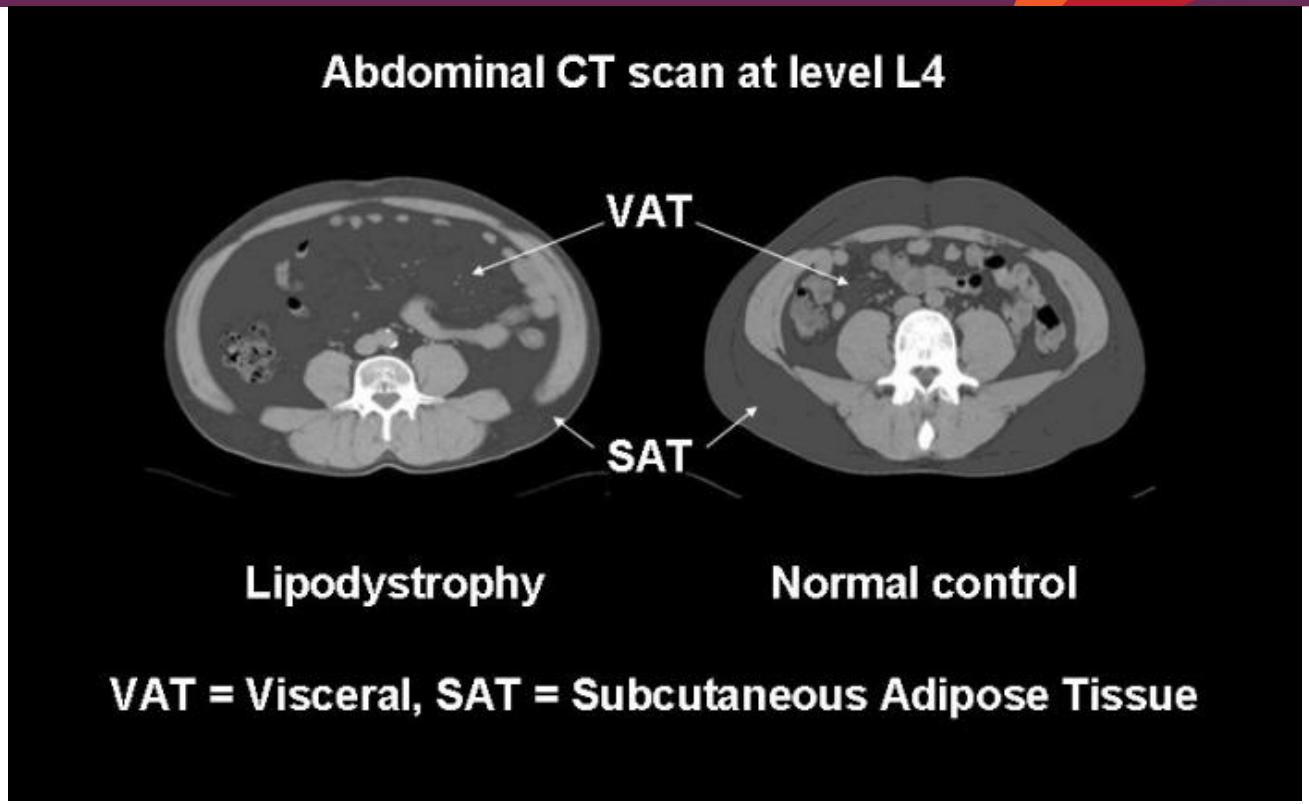
Imaging VAT on Abdominal CT Scan



Source: Dr. Daniel Berger, University of Illinois at Chicago.

Therapeutic Options to Reduce VAT in HIV: Dietary Intervention

Structured weight loss intervention:

- A 1000 kcal/day energy deficit based on estimated energy requirement of 20 HIV+ women
- Meal replacement used for 2 meals/day, and subjects were instructed to eat a third meal each day containing regular food
- After targeted 6%–8% weight-loss was achieved, dietary intake was adjusted to maintain a stable body weight for 2 weeks

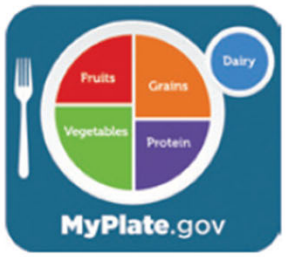
- Total body weight reduction of 7.7% (108 to 100 kg)
- **VAT reduction of 14% (1164 to 997 cm^3)**
- Insulin levels reduced 11%, but no change in triglycerides or LDL

- **Findings suggest dietary intervention can reduce VAT volume in PWH**

Reeds D, et al. Obesity (Silver Spring) 2017

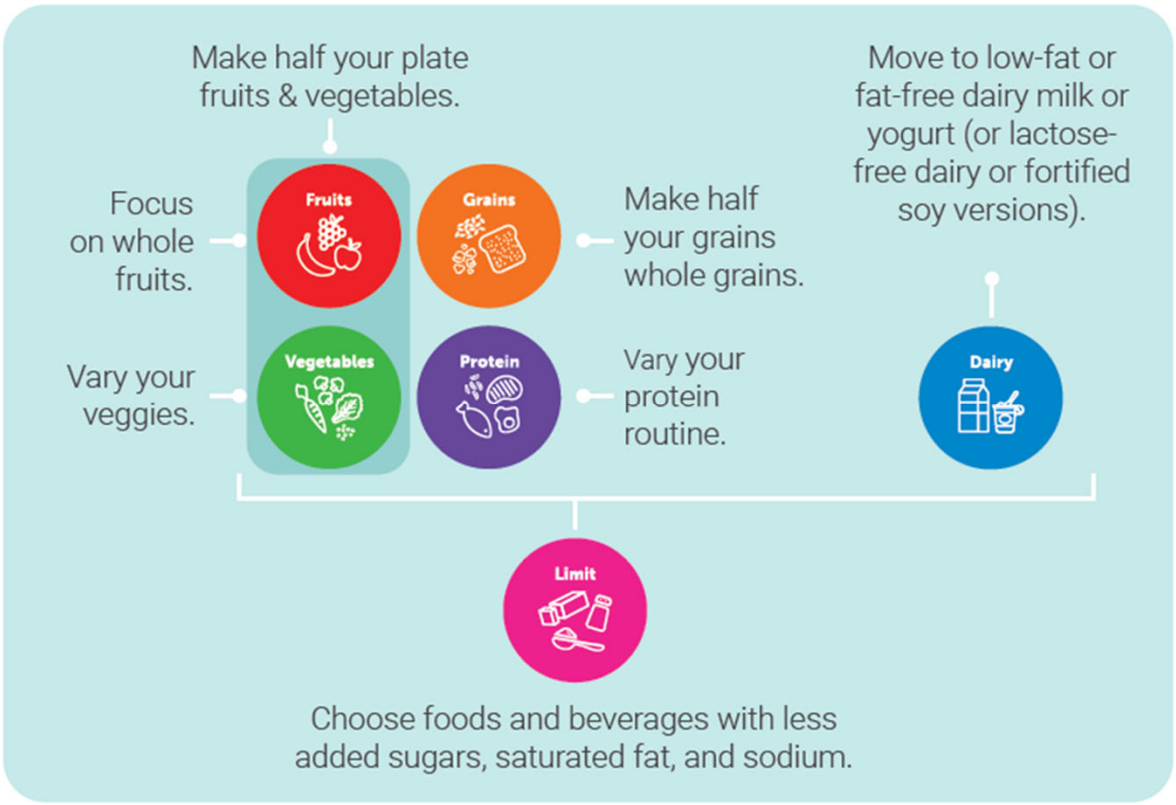
Slide courtesy of Dr. John Koethe

2020 – 2025 USDA Dietary Guidelines



To learn what the right amounts are for you, try the personalized **MyPlate Plan**.[2]

Based on decades of solid science, MyPlate advice can help you day to day and over time.

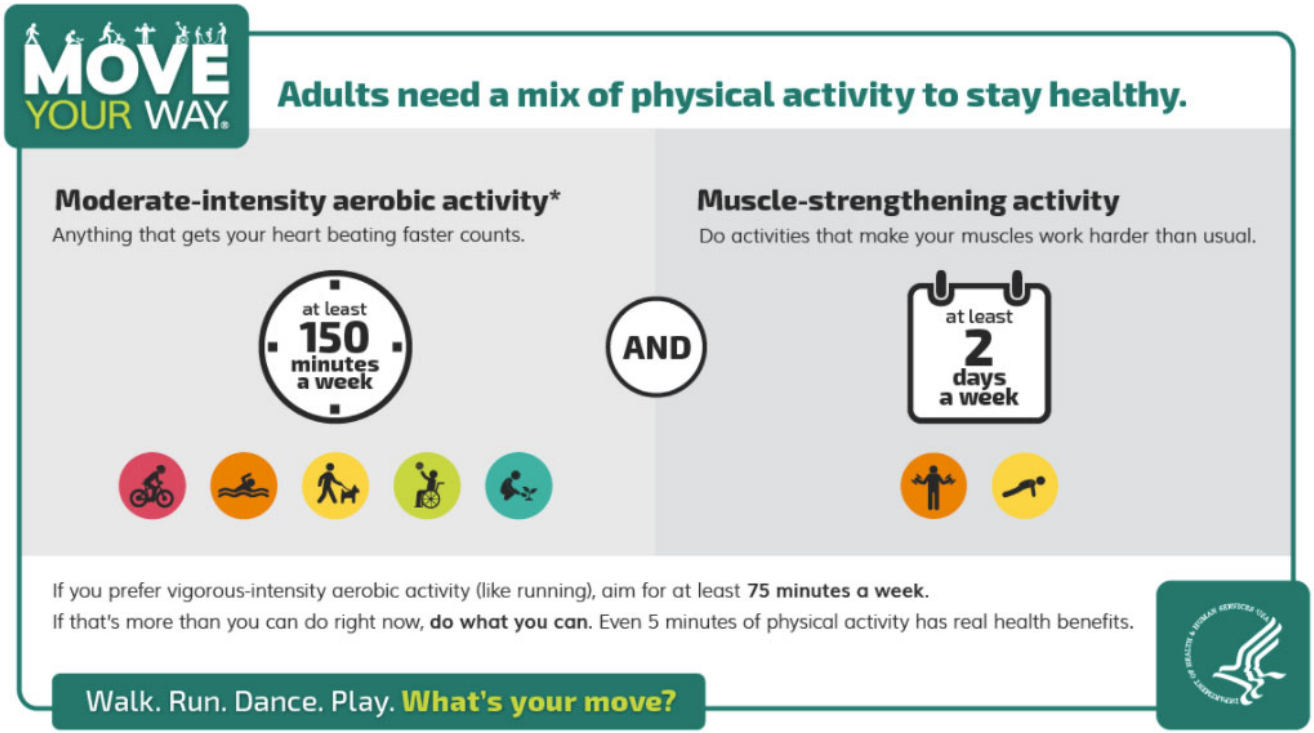


USDA. Dietary Guidelines for Americans 2020-2025. 9th ed.

U.S. DHHS "Move Your Way" Public Message

Practical Tips

- Start low and go slow… BUT GO
- Schedule in activity—make it a priority
- Increase daily activity
- Make it fun
- Vary the exercise routine
- Exercise in a group

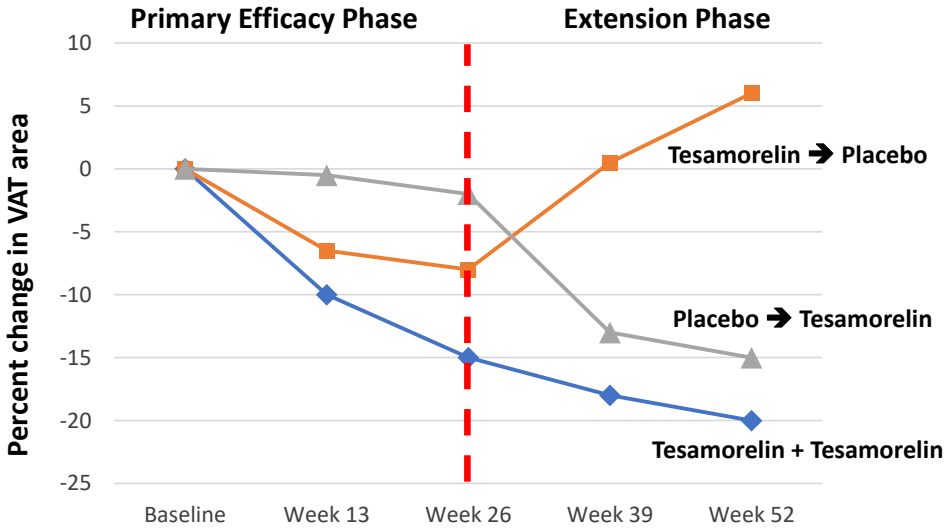


https://health.gov/moveyourway

Therapeutic Options to Reduce VAT in HIV: Pharmacologic

Tesamorelin

- A synthetic form of growth-hormone-releasing hormone (GHRH) which stimulates release of endogenous GH and an increase in level of insulin-like growth factor (IGF-1)
- Currently the only FDA-approved intervention to reduce visceral fat in HIV infection
- Requires daily subcutaneous injection



AMERICAN ACADEMY OF HIV MEDICINE

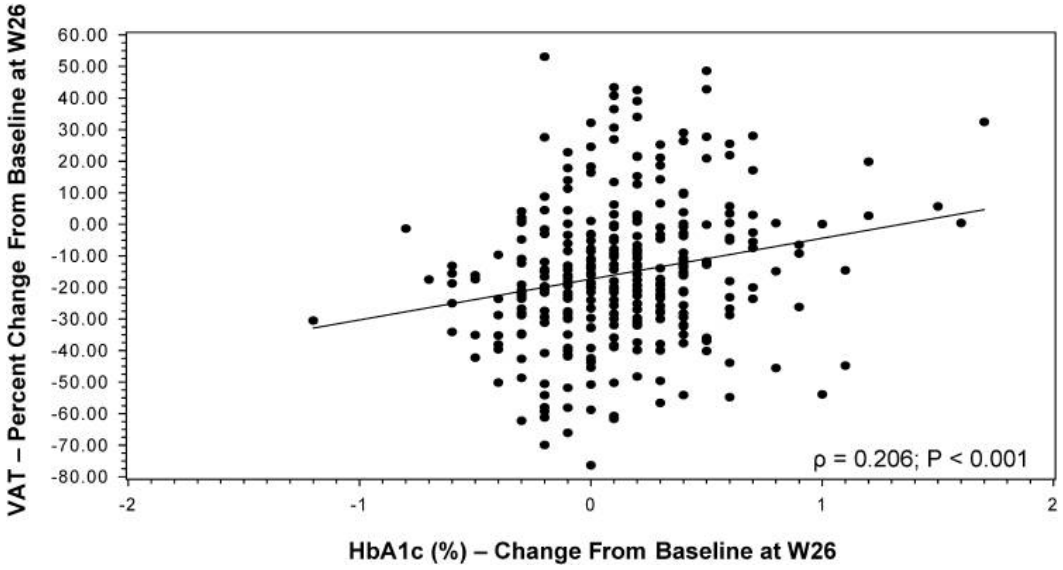
Falutz J, et al. *JAIDS.* 2010

Slide courtesy of Dr. John Koethe

Therapeutic Options to Reduce VAT in HIV: Pharmacologic

Tesamorelin

- 69% of recipients lost ≥8% VAT by week 26, and 72% by week 52 (for those on medication only for 52 weeks)
- Individuals with a ≥8% VAT decline at 52 weeks had significant reductions in triglycerides, but not LDL or fasting glucose
- Overall, a decline in VAT was correlated with a reduction in HbA1c



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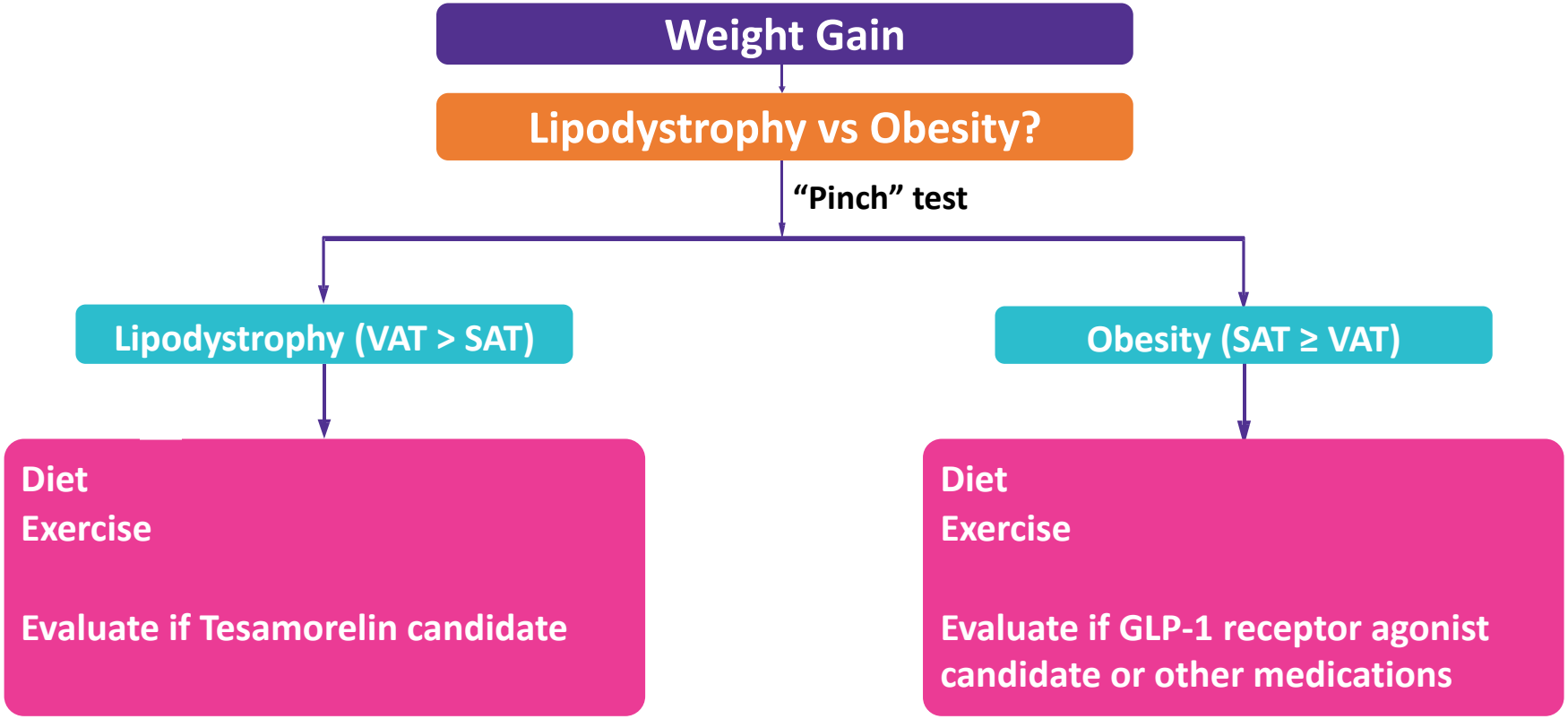
Falutz J, et al. *JAIDS.* 2010

Slide courtesy of Dr. John Koethe

UCSD Owen Metabolic Clinic – Weight Gain Algorithm



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Source: Dr. Daniel Lee, University of California, San Diego - Owen Clinic.

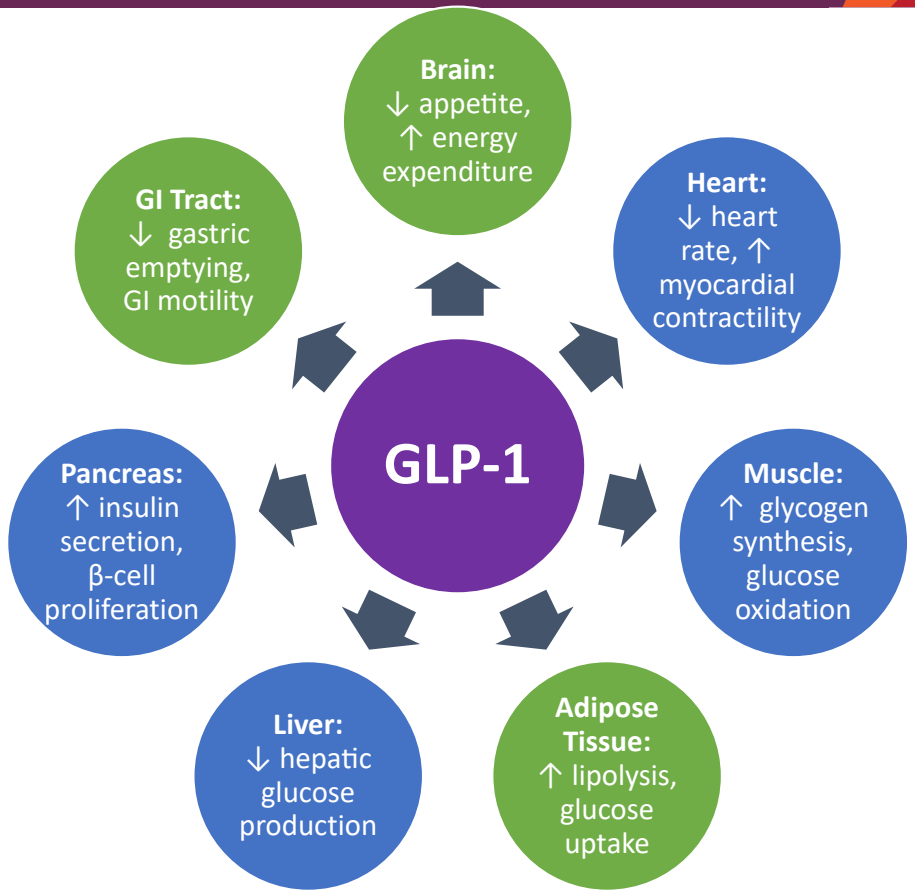
FDA-Approved Medications for Chronic Weight Management

Agents	Mechanism of Action	Effect	Approval Date
Phentermine*	▪ Sympathomimetic	Appetite regulation	1959
Orlistat[+]	▪ Pancreatic lipase inhibition	Reduces fat absorption	1999
Phentermine/topiramate ER[+]	▪ Sympathomimetic ▪ Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	Appetite regulation	2012
Naltrexone/bupropion SR	▪ Opioid receptor antagonist ▪ Dopamine/noradrenaline reuptake inhibitor	Appetite regulation	2014
Liraglutide[+]	▪ GLP-1 receptor agonist	Appetite regulation	2014
Setmelanotide[‡]	▪ Melanocortin 4 receptor agonist (indication: obesity due to POMC, PCSK1, or LEPR deficiency)	Appetite regulation	2020
Semaglutide	▪ GLP-1 receptor agonist	Appetite regulation	2021
Tirzepatide	▪ GLP-1 receptor agonist/GIP receptor agonist	Appetite regulation	2023

[+]Approved for patients aged ≥16 yr. *Approved for patients aged ≥12 yr. [‡]Approved for patients aged ≥6 yr with genetic conditions.

Phentermine PI. Orlistat PI. Phentermine and topiramate ER PI. Naltrexone and bupropion SR PI. Liraglutide PI. Setmelanotide PI. Semaglutide PI.

Pleiotropic Effects of GLP-1 Receptor Agonists



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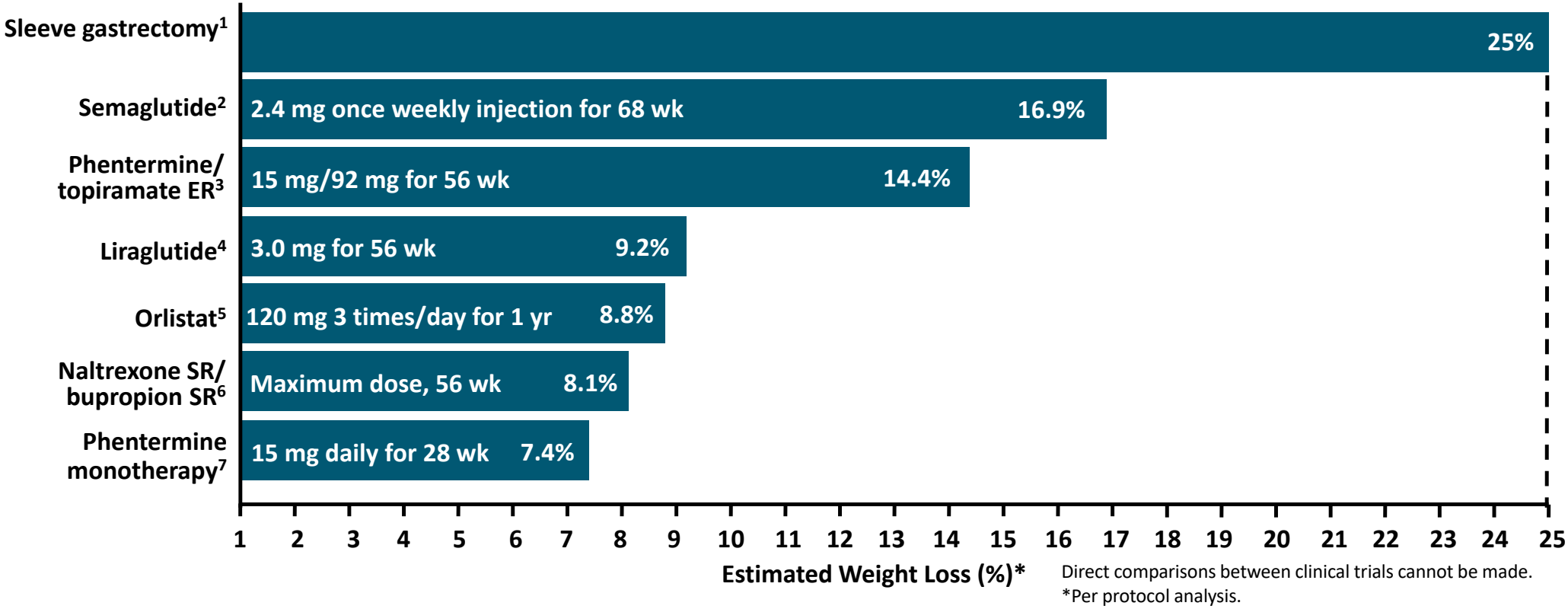
Saraiva. Cardiovasc Diabetol. 2014;13:142.

Efficacy of Current FDA-Approved Obesity Therapies

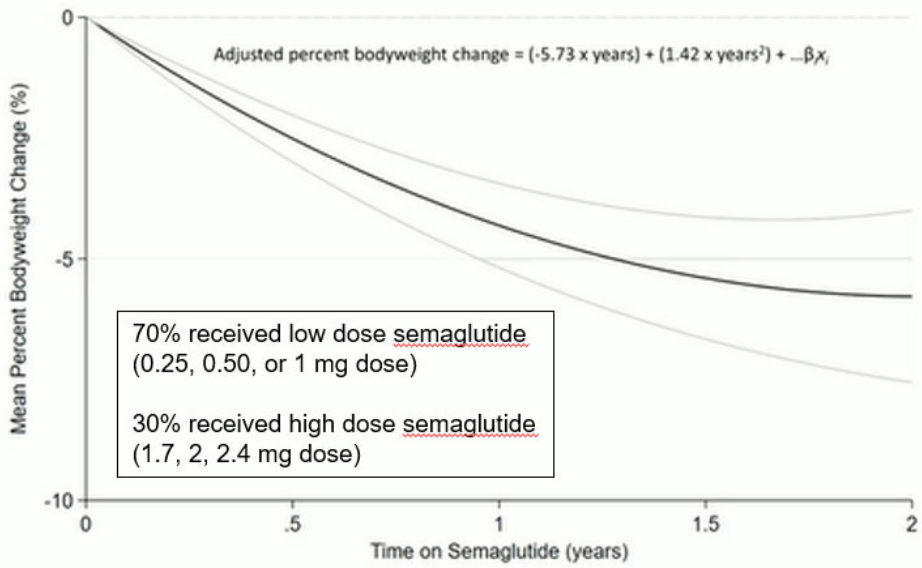


Direct comparisons between clinical trials cannot be made.
*Per protocol analysis.

1. Mechanick. Endocr Pract. 2019;25:1346. 2. Wilding. NEJM. 2021;384:989. 3. Allison. Obesity (Silver Spring). 2012;20:330. 4. Pi-Sunyer. NEJM. 2015;373:11. 5. Finer. Int J Obes Relat Metab Disord. 2000;24:306. 6. Greenway. Lancet. 2010;376:595. 7. Aronne. Obesity (Silver Spring). 2013;21:2163.

Impact of Semaglutide in Weight in PWH

- Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort study (2018-2022; n=222)
  - Initiated injectable or oral semaglutide and had ≥2 weight measurements
  - Baseline characteristics
    - Age (53 years), virologically suppressed (89%), diabetic (77%), female (25%), HbA1c (7.7%)
- Semaglutide results at 1 year
  - Associated with significant weight loss (6.5 kg [5.7% of bodyweight])
  - Amount of weight lost correlated with higher BMI (*P*<0.05)



On average, PWH lost 5.7% of bodyweight (95% CI: -6.9, -4.5)

On average, PWH lost 6.5kg (95% CI: -7.7, -5.2)

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Crane HM, et al. CROI 2024. Abstract 797.

Is the GLP-1 Receptor Agonist, Semaglutide, A Good Option for Weight Loss in PWH?

- The presentation of weight gain and fat distribution in PWH varies
  - Dependent on multiple factors, including prior exposure to legacy antiretroviral therapies
- Important to distinguish the composition of the fat to determine what proportion of the excess weight is composed of visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT)
  - If VAT > SAT, then this suggests a lipohypertrophy phenotype – treatment with tesamorelin (growth hormone-releasing hormone) may be appropriate
  - If SAT ≥ VAT, then this suggests an obesity phenotype – treatment with GLP-1RAs and other weight loss medications may be appropriate
- The use of GLP-1RAs may result in muscle mass loss, which may lead to higher risk of frailty in older PWH

Lee D and Capeau J. AIDS. 2024; 38(4): 603-5. doi: 10.1097/QAD.0000000000003816

Can Switching ART Reverse Weight Gain?

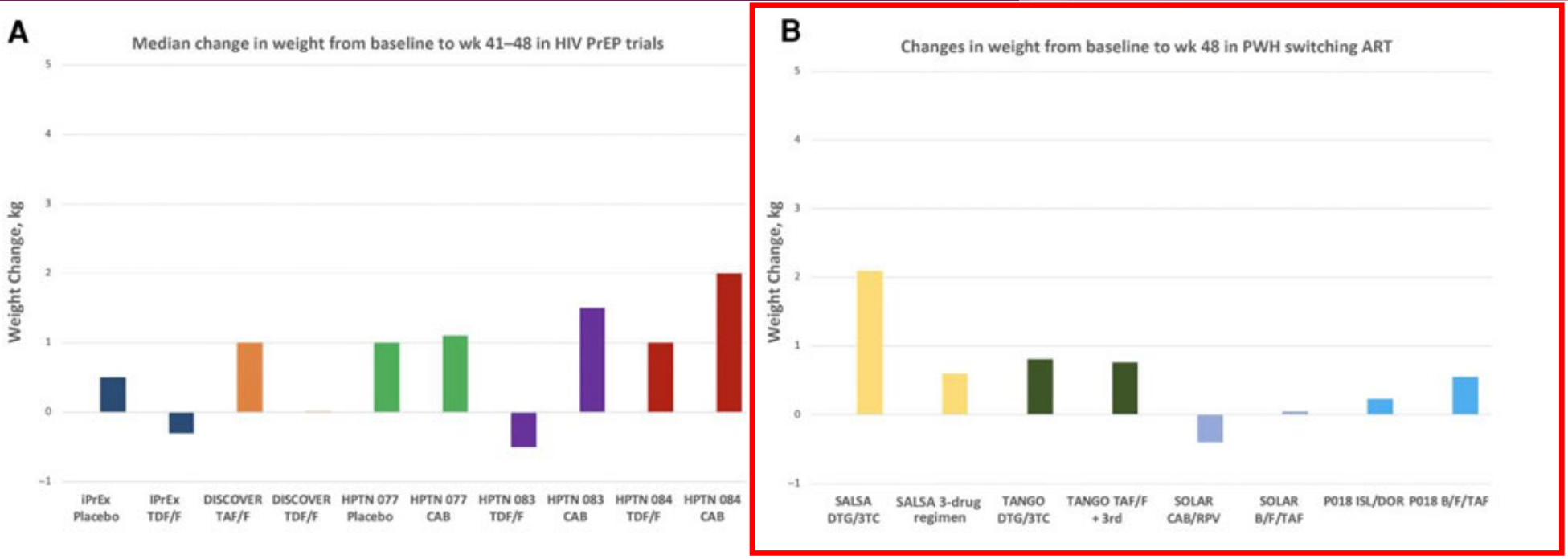

Figure 2. Changes in weight in major trials of preexposure prophylaxis (PrEP) (*A*) and antiretroviral therapy (ART) switch (*B*). All changes represent means, except those for the SOLAR trial, which reported median changes. Abbreviations: 3TC, lamivudine; B, bictegravir; CAB, cabotegravir; DTG, dolutegravir; DOR, doravirine; F, emtricitabine (FTC); HPTN, HIV Prevention Trials Network; ISL, islatravir; PWH, people with HIV; RPV, ; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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Wohl DA, et al. *Clin Infect Dis*. Published online April 12, 2024. doi:10.1093/cid/ciae191

Summary Points

- Recent guidelines (2022 IAS-USA Guidelines) are now including a section on weight changes seen with initiation and switching of antiretroviral therapy including INSTIs and tenofovir alafenamide
- Estimating the presence and severity of VAT can be performed via “pinch” test and/or measuring waist circumference
- Improving diet and increasing physical activity can help with reducing weight and VAT
- Pharmacologic therapy may be an option for those with HIV Lipodystrophy or general obesity
- At this time, switching ART for reducing weight gain is not officially recommended, but continues to be studied

Conclusion

- Both weight loss and weight gain can occur across the clinical spectrum of management of PWH
- Monitoring weight and body habitus changes regularly (including checking waist circumference) can be useful in identifying early weight changes and provide an opportunity for intervention, if needed
- Despite the success of antiretroviral therapy, HIV-associated wasting can still occur and a high degree of vigilance is required at times to make and treat this diagnosis
- Weight gain can occur with the initiation or switching or ART
- Many questions still remain regarding the pathophysiology of weight gain, including the optimal management of these weight changes