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Lipids, Lipodystrophy, and Obesity: Metabolic Issues in HIV

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Workshop Series 2019

This activity is jointly provided by the Annenberg Center for Health Sciences at Eisenhower, the American Academy of HIV Medicine, in collaboration with Postgraduate Institute for Medicine.

This activity is supported by an independent educational grant from Gilead Sciences.

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Target Audience/Program Overview

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

Co-morbidities such as diabetes mellitus, insulin resistance, cardiovascular disease, and metabolic syndrome are on the rise among people living with HIV. While it has not been discerned what is causing the increased risk for co-morbid disease conditions, it is most likely a combination of multiple factors. The first is the presence of the virus itself. HIV infection is associated with persistent inflammation. Among patients who are diagnosed with HIV late and have advanced disease, there are increased rates of complications, particularly AIDS-associated cancers. In the absence of antiretroviral therapy, ongoing inflammation predisposes individuals with adverse health outcomes. Similarly, treatment for HIV may also be a factor. Some antiretroviral medications are associated with toxicities that may contribute to increased risk of adverse events. Similarly, patients who have been on treatment for a long period of time also may experience toxicity due to years on treatment. Lastly, there are patient-specific and social factors. Some studies have demonstrated a higher rate of traditional risk factors such as cardiovascular disease risk associated with smoking, dyslipidemia, hypertension or diabetes among patients living with HIV.

Continuing Medical Education

Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Annenberg Center for Health Sciences at Eisenhower and American Academy of HIV Medicine. The Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Annenberg Center for Health Sciences at Eisenhower 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.

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Pharmacists Continuing Medical Education

Accreditation Statement

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation

This program has been developed according to the ACPE Criteria for Quality and is assigned ACPE Universal Activity #0797-9999-19-115-L02-P. This program is designated for up to **2.5 contact hours (0.25CEUs) of continuing pharmacy education credit.**

Type of Activity: Application

For Pharmacists: Upon receipt of the completed activity evaluation form, transcript information will be sent to the NABP CPE Monitor Service within 4 weeks.

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Disclosure Information

The Annenberg Center for Health Sciences at Eisenhower staff involved in this activity have no relevant commercial relationships to disclose.

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Faculty, Planner and Managers Disclosures

Daniel Lee, MD

- Industry funded research/investigator: None
- Consultant: Thera technologies, ViiV Healthcare
- Speakers Bureau: Theratechnologies, EMD Serono, ViiV Healthcare, Merck
- Independent Contractor: ViiV Healthcare
- Advisory Committee/Board: None
- Stock/Ownership: Gilead Sciences

American Academy of HIV Medicine (AAHIVM)

The AAHIVM planners and managers have nothing to disclose

Postgraduate Institute of Medicine (PIM)

The PIM planners and managers have nothing to disclose

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Disclosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications.

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.

In this activity the faculty do discuss the use of investigational antiretroviral agents and treatment regimens that are not approved by treatment guidelines.

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/Receiving CE Credit

There is no fee for this educational activity.

Method of Participation/Receiving CE Credit

If you wish to receive acknowledgment for completing this activity, please complete the evaluation on www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluation by Course" and search by course ID 14818. Upon registering and successfully completing activity evaluation, your certificate will be made available immediately.

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Learning Objectives

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

- Identify and evaluate dyslipidemia, lipodystrophy, and weight gain, as well as the presence of HIV-associated lipodystrophy in people living with HIV infection (PLWH).
- Recognize the connected relationship of lipids, fat, and glucose and how this impacts weight gain.
- Review the differences in management and treatment of dyslipidemia in people living with and without HIV infection.
- Illustrate how to diagnose, manage and provide individualized treatment for patients with lipodystrophy.

Overview

- Dyslipidemia
  - Contributing factors
  - Relationship of lipids, fat, and glucose
  - Clinical management
- Lipodystrophy
  - Contributing factors to lipoatrophy vs. lipohypertrophy
  - Clinical evaluation (including live demonstration of body composition measurements)
  - Clinical management
- Weight Gain and Obesity
  - Contributing factors – INSTIs and TAF?
  - Unanswered questions

BLACK BOX WARNING/DISCLAIMER

This talk represents my opinion based upon my interpretation of the data and my clinical observations from seeing patients in the Owen Lipid/Lipodystrophy Clinic for the past 20+ years

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DYSLIPIDEMIA

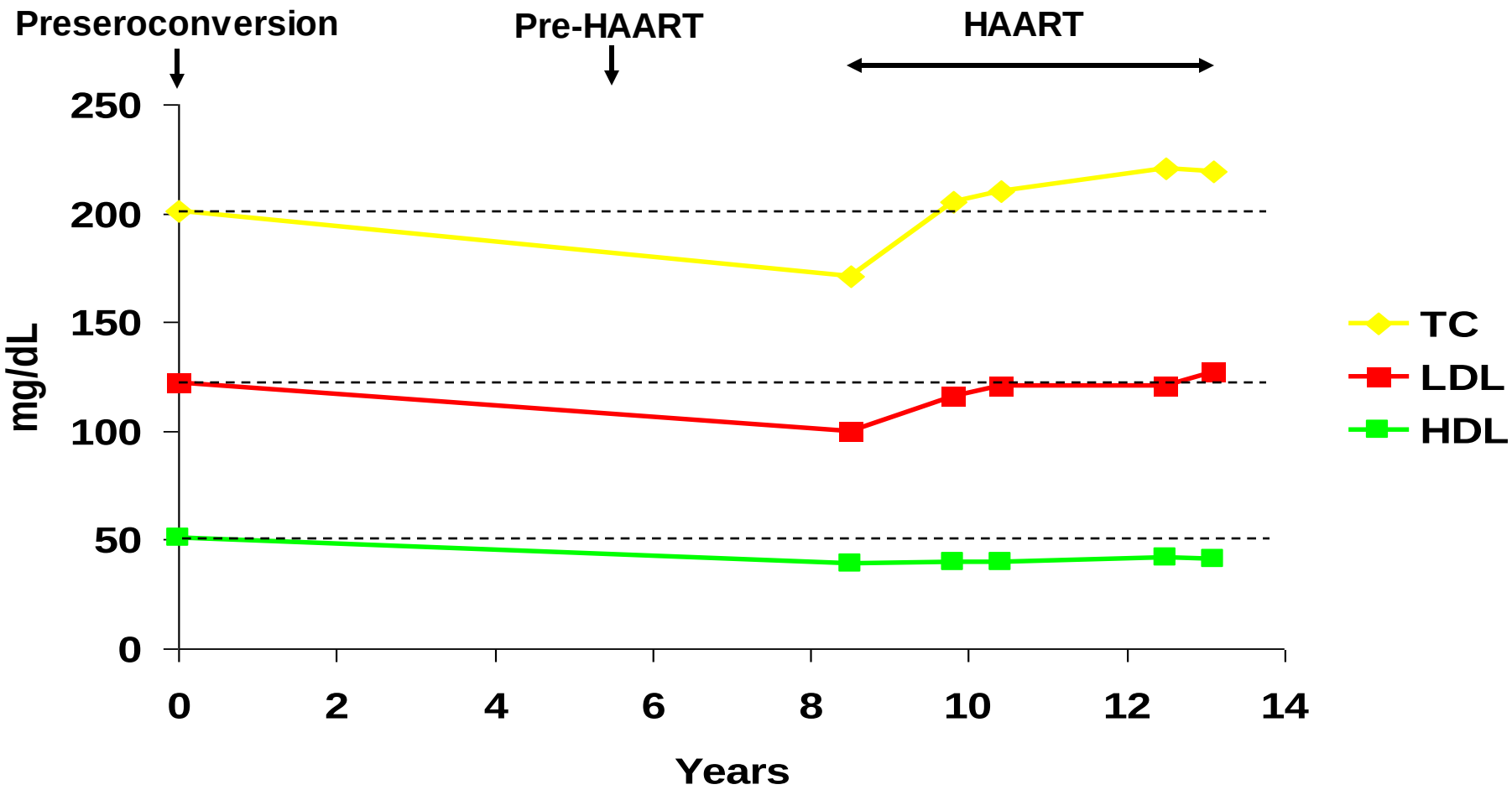
Case Scenario #1

- Patient #1 – 34 year old Caucasian male with HIV for 5 years, CD4 = 280 cells, VL = 145,000 copies/mL
- Patient #2 – 56 year old Latina female with HIV for 1 year, CD4 = 365 cells, VL = 28,000 copies/mL
- Patient #3 – 42 year old African-American male w/PCP pneumonia and recent diagnosis of HIV last week, CD4 = 25 cells, VL >750,000 copies/mL
- Let us assume that each patient has the same lipid profile
  - TC = 180 mg/dL, TG = 285 mg/dL, HDL = 30 mg/dL, LDL = 93 mg/dL
- Assuming a HAART regimen will be started, can you predict who will develop dyslipidemia? If so, how?
- Which patient do you think may have the worst lipid profile after starting on any antiretroviral regimen? And what order from worst to best?

Dyslipidemia in the HIV Population Over Time

- In the pre-HAART era, the main presentation of dyslipidemia was hypertriglyceridemia
  - Mainly caused by uncontrolled viremia with increased cytokine activity (eg. Increased α-interferon levels)
- In the early HAART era, the main presentation of dyslipidemia was still hypertriglyceridemia
  - Mainly driven by older PIs – indinavir, lopinavir/ritonavir
  - Some contribution by NRTIs – stavudine, zidovudine
- In the current HAART era, the main presentation of dyslipidemia is more likely to be hypercholesterolemia
  - Less driven by antiretroviral therapy
  - Likely driven by natural aging process, slowing metabolism, dietary choices, lack of exercise, development of diabetes or hypothyroidism, etc.

Mean Lipid Values Before & After HIV Infection (Treated & Untreated) from MACS Cohort



Adapted from Riddler et al. JAMA 2003;289:2978-82.

Factors Contributing to the Rise in Lipids Seen with Starting and/or Maintaining on any HAART Regimen

- "Return to Health" Phenomenon
  - HIV lowers lipids through effects on lipid metabolism
  - HAART leads to reduction of viral load and cytokine activity, thereby reversing this effect and leading to a rise back to preseroconversion levels
- Elevated preseroconversion lipid levels
  - Often unknown if patients already had elevated lipid levels before HIV infection, but a "return to health" effect after initiating HAART may lead to elevated lipids
- Direct and indirect effects of HIV and HAART on lipid metabolism
  - Increased production and decreased clearance of lipids (primarily triglycerides)
  - Older PIs may affect lipid and glucose metabolism
  - Older NRTIs may lead to mitochondrial toxicity in fat cells and lipoatrophy, thus leading to release of free fatty acids into the circulation → elevated triglycerides

Effect of Antiretroviral Therapy on Lipids

PIs

Contemporary ART	Impact on Lipids
Lopinavir/ritonavir	Increased TC/TG frequent
Fosamprenavir/ritonavir	Increased TC/TG
Atazanavir/ritonavir	Best lipid profile
Darunavir/ritonavir	Good lipid profile

NRTIs

Contemporary ART	Impact on Lipids
Zidovudine	Very increased TC/LDL-C
Stavudine	Very increased TC/TG
Abacavir	TC/HDL unchanged
Tenofovir	Decreased TC/LDL-C
Tenofovir alefenamide	No significant changes

NNRTIs

Contemporary ART	Impact on Lipids
Nevirapine	Can increase HDL-C
Etravirine	No significant change
Efavirenz	May increase lipids
Doravirine	No significant changes

Other

Contemporary ART	Impact on Lipids
Integrase inhibitor (raltegravir)	Low frequency of lipid changes
CK-receptor-5 antagonist (maraviroc)	No significant changes
Elvitegravir/cobicistat	Slight increase in TC/LDL-C
Dolutegravir	No significant changes
Biktegravir	No significant changes

Vachiat A, et al. *J Am Coll Cardiol*. 2017;69:73-82.

Factors Contributing to the Rise in Lipids Seen with Starting and/or Maintaining on any HAART Regimen (continued)

- Increased weight gain through poor diet and lack of exercise
  - Weight loss may be seen prior to initiation of HAART if infected for years
  - Patients may compensate by eating more food to maintain or gain weight
  - Patients may not exercise much due to having neuropathy, wasting, chronic fatigue, depression
  - These combined effects may lead to rapid weight gain, central obesity, lipohypertrophy, and dyslipidemia
- Development of glucose abnormalities
  - Impaired glucose tolerance, insulin resistance, or diabetes mellitus
- Development of fat abnormalities (lipodystrophy)
- Aging & Genetics

Case Scenario #1

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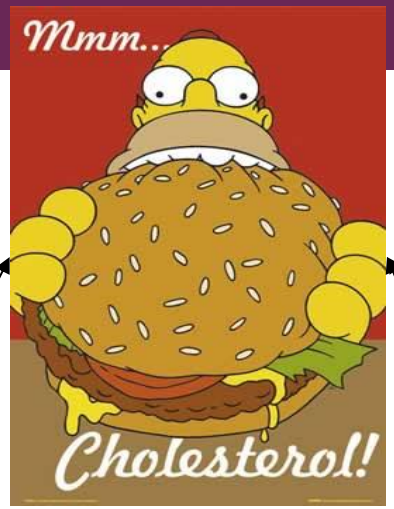
- Let us assume that each patient has the same lipid profile
  - TC = 180 mg/dL, TG = 285 mg/dL, HDL = 30 mg/dL, LDL = 93 mg/dL
- Assuming a HAART regimen will be started, can you predict who will develop dyslipidemia? If so, how? **YES**
- Which patient do you think may have the worst lipid profile after starting on any antiretroviral regimen? And what order from worst to best? **3 > 1 > 2**

Case Scenario #1

- What have we learned:
  - Factors which can help to predict dyslipidemia in patients starting HAART
    - "Actual" date of HIV infection vs. date of HIV diagnosis
      - Lower lipids may be seen with those who have actually been infected longer
      - May also have a more dramatic "return to health" rise in lipids
    - Lower CD4 count and higher VL
      - Typically associated with more advanced disease and longer time of HIV infection and thus, likely increased cytokine activity with associated metabolic effects (ie. α-interferon → ↑TG levels)
    - Choice of HAART regimen
  - Try asking the additional following questions
    - Do you know what your fasting lipids were <u>prior</u> to HIV infection?
    - How long do you <u>think</u> that you have been HIV-infected?
    - What is the lowest CD4 or highest VL you have had in the past?
    - Has anyone else in your family had high cholesterol or triglycerides?

Interrelationship Between Lipids, Glucose, & Fat



LIPIDS

GLUCOSE

FAT

Must keep in mind these relationships as these change over time with aging, HIV infection, and with HAART

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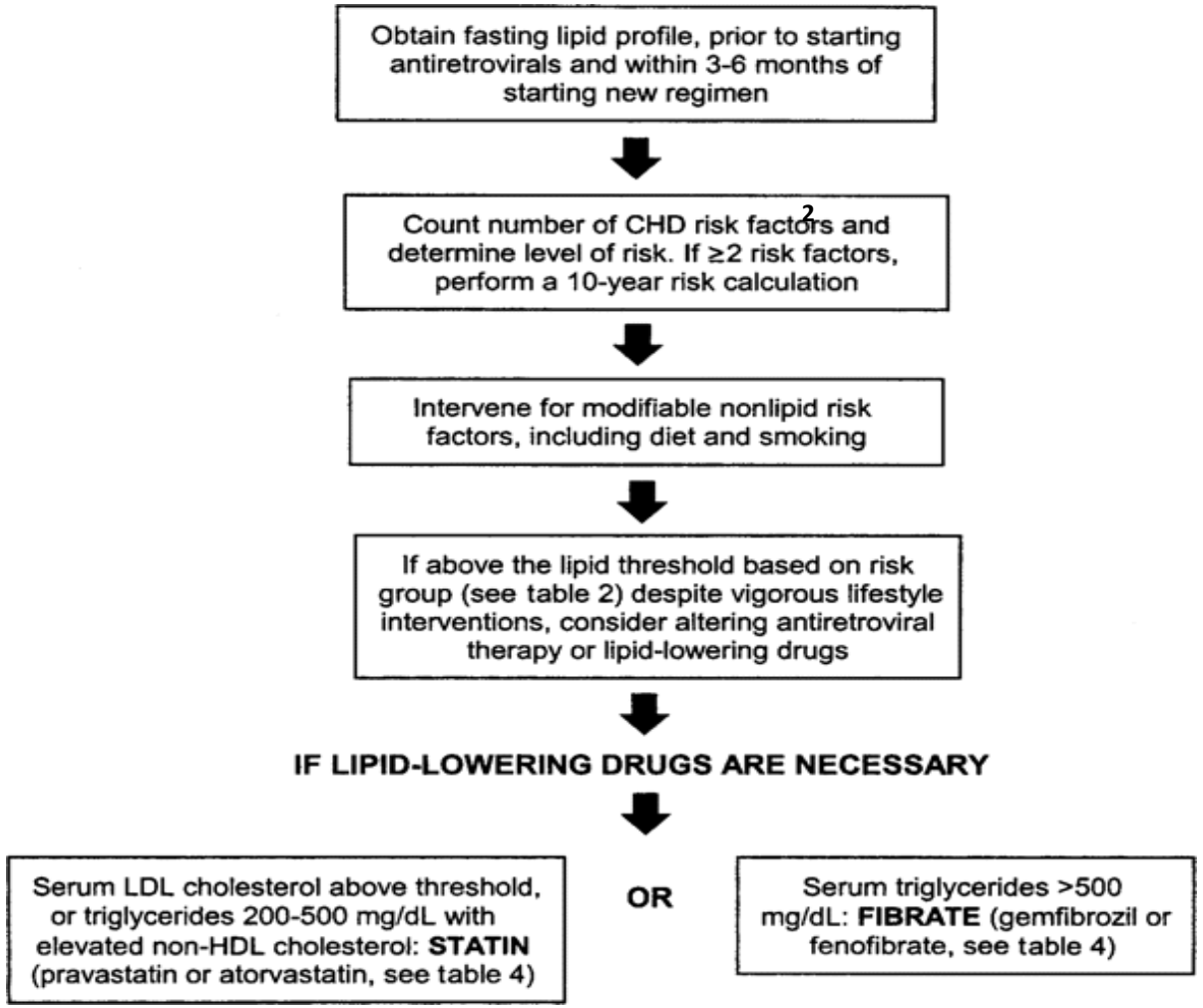
Managing Dyslipidemia in HIV Patients

- Screening for dyslipidemia
  - Experts recommend screening at baseline, prior to initiating antiretroviral therapy (ART), within 1-3 months after starting a new regimen, and every 6-12 months thereafter[1,2,3]
- Determine the cause(s) of dyslipidemia, evaluate cardiovascular disease risk factors, and address risk factors (eg. smoking cessation, start diet/exercise)
- If it is determined that the current antiretroviral therapy (ART) may be contributing to dyslipidemia, it is often best to try to switch ART, if options exist and can be safely done to maintain virologic control
- The indications for treatment of dyslipidemia is the same in people living with HIV as with people living without HIV
  - Based on 10-year Atherosclerotic Cardiovascular Disease (ASCVD) Risk Score[4]

1. Aberg JA, et al. CID 2014; 58: e1-34.
2. Dube MP et al. CID 2003; 37: 613-27.
3. Schambelan M, et al. JAIDS 2002; 31: 257-75.
4. Goff Jr DC, et al. Circulation. 2014; 129: S49–S73.

Managing Dyslipidemia in HIV Patients (continued)[1]



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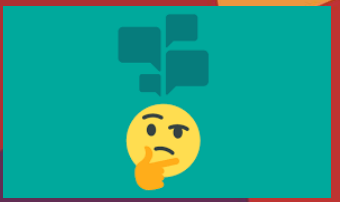
1. Dube MP et al. CID 2003; 37: 613-27.
2. Goff Jr DC, et al. Circulation. 2014; 129: S49–S73.

Treatment Options for Dyslipidemia

- Behavior Modification
  - Diet – more fish, less red meats, eggs, cheese, fast food
    - Less carbohydrates or carbohydrates w/low glycemic index, monounsaturated or polyunsaturated fats (vs. saturated fats)
    - Mediterranean diet (more nuts, olive oil, fruits, veggies)
  - Exercise – 150 minutes/week of moderate intensity or 75 minutes/week of vigorous intensity aerobic physical activity per American Heart Association[1]
  - Alcohol and Smoking Cessation
- Drug Modification or Substitution
  - Modifying HAART by switching out from a boosted-regimen to non-boosted regimen
  - Switching out offending HAART to a more lipid-neutral agent
    - NNRTI – Nevirapine, Etravirine, Rilpivirine, Doravirine
    - PI – Atazanavir, Darunavir
    - NRTI – Tenofovir, Abacavir, Lamivudine, Emtricitabine
    - INSTI – Raltegravir, Dolutegravir, Bictegravir
    - Other – Maraviroc, Enfuvirtide

1. https://www.heart.org/en/healthy-living/fitness/fitness-basics/aha-recs-for-physical-activity-in-adults

Question #1



- What is your primary choice for a statin in treating PLWH?
  - Pravastatin
  - Atorvastatin
  - Rosuvastatin
  - Pitavastatin
  - Other

Statin Intensity	%LDL-C Reduction	HMG-CoA Reductase Inhibitor						
		Rosuvastatin	Atorvastatin	Pitavastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin
High-Intensity (lowers LDL-C ≥ 50%)	63	40 mg ($196)						
	62							
	61							
	60		80mg ($9 gen, $236 br)					
	59							
	58							
	56	20 mg ($196)						
	54							
	52	10 mg ($196)						
	50		40mg ($9 gen, $236 br)					
Moderate-Intensity (lowers LDL-C 30% to < 50%)	48							
	46							
	44							
	42		20mg ($9 gen, $236 br)					
	40			4 mg ($81)	40 mg ($4 g, $202 br)			
	38					80mg ($4 gen, $306 br)	80 mg ($25 g, 173 br)	
	36							
	34				20 mg ($4 g, $202 br)			80mg ($95 gen, $300 br)
	32	5 mg ($196)		2 mg ($81)			40 mg ($25gen, 173 br)	
	30		10mg ($7 gen, $165 br)		10 mg ($4 g, $116 br)	40mg ($4 gen, $153)	20mg ($17 gen, 117 br)	
Low-Intensity (lowers LDL-C < 30%)	28			1 mg ($81)				
	26				5 mg ($4 g, $82 br)	20 mg ($4 gen, $43 br)		40mg ($95 gen, 150 br)
	24							
	22							
	20					10 mg ($4 gen, $43 br)	10mg ($19 gen, 58 br)	20mg ($95 gen, 150 br)
	18							

Note: The shading reflects doses listed in the ACC/AHA Guideline on Treatment of Blood Cholesterol (2013) as reflecting high-intensity therapy (≥ 50% reduction in LDL-C, darker shading) and moderate-intensity therapy (30% to 50% reduction in LDL-C, lighter shading).
*In one trial atorvastatin 40 mg was used for down-titration if unable to tolerate 80 mg.

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1. http://www.mqic.org/pdf/UMHS_Statin_Dose_Intensity_and_Equivalency_Chart.pdf

Treatment Options for Dyslipidemia (continued)

- Pharmacologic Therapy
  - Statins
    - Concern for muscle (myalgias, myopathy, rhabdomyolysis) and liver toxicity (hepatitis)
  - Fibrates
    - Fenofibrate may be more effective, QD, less drug interactions with statins compared to gemfibrozil
  - Niacin
    - Good for lowering triglycerides and total cholesterol, but flushing and insulin resistance may be an issue
  - Fish oil
    - Goal DHA + EPA = minimal dose 2 grams, optimal dose 4 grams
    - Dose-dependent response curve
    - Higher pill burden, but safe with minimal drug interactions
  - Ezetimibe
    - Synergistic effect with statins
  - PCSK9 Inhibitors
    - Injectable given every 2-4 weeks, issues with cost and insurance coverage

Unique Considerations for Treating Dyslipidemia in People Living with HIV

- Dyslipidemia is more difficult to treat in HIV+ vs. HIV- pts
  - May be drug-induced by antiretroviral therapy
  - Optimal treatment of any drug-induced dyslipidemia ought to be removal of the offending drug, but this is not always a viable option
- Decreased effectiveness of lipid lowering drugs
  - Confirmed by many clinical studies (ACTG 5087) & clinical experience
  - May require use of higher doses and more combination therapies leading to increasing toxicity (hepatitis and/or myositis)
- Potential P450 drug interactions with antiretroviral therapy and statins
  - May see increased toxicity with even standard doses
- Dyslipidemia may not necessarily occur immediately, but evolve over time
  - Changes in lipid, glucose, and fat metabolism with aging

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Questions?

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LIPODYSTROPHY

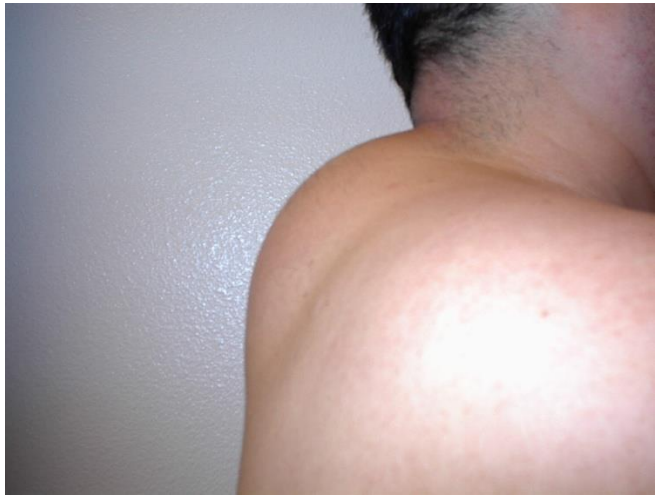
Case Scenario #2

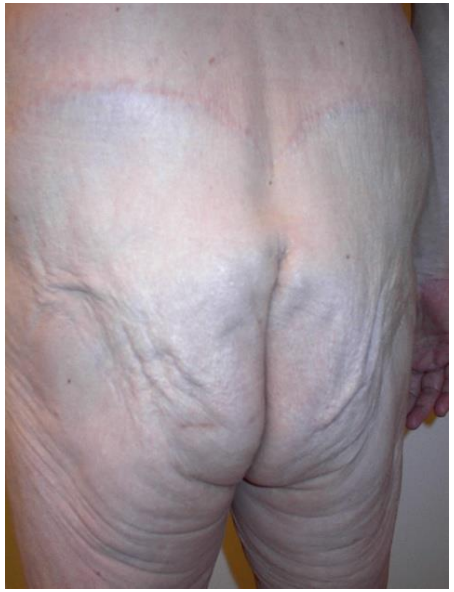
- 48 year old Caucasian male w/HIV w/CD4 = 310 cells, VL <50 c/ml
  - Current HAART includes darunavir/cobicistat 800 mg/150 mg daily, dolutegravir 50 mg daily, tenofovir alefenamide/emtricitabine 10 mg/200 mg daily
  - Pt has been HIV+ since 1993 and has been on multiple antiretroviral regimens with prior resistance to multiple medications over the years
  - Chief complaint is “lipodystrophy” and on physical exam…
  - Fat loss in arms, legs, and face and buttocks
  - Fat accumulation in abdomen, slight dorsocervical fat pad
  - He is interested in what is causing these body fat changes and what can be done to improve this
- What is/are the cause(s) of fat loss (lipoatrophy)?
- What is/are the cause(s) of fat accumulation (lipohypertrophy)?

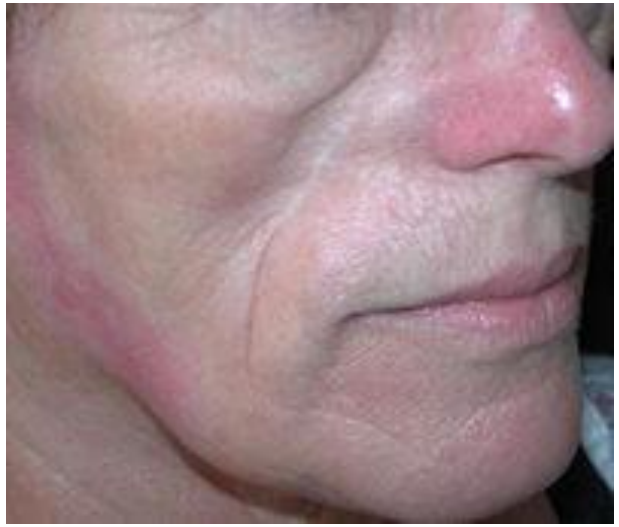
What is Lipodystrophy?

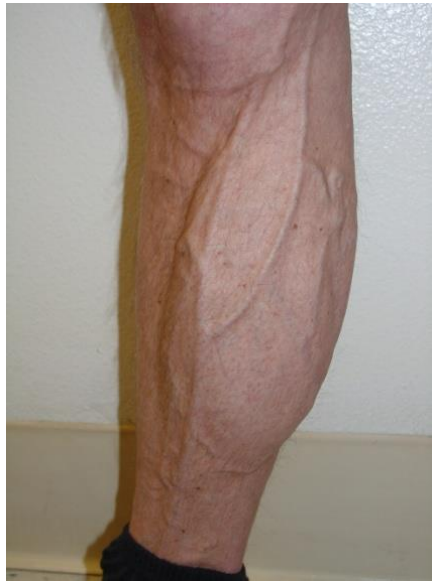
- Lipodystrophy refers to body **fat** changes that may occur in patients with HIV
- Primarily 3 main subtypes
  - Fat loss only (lipoatrophy)
    - Areas of white or subcutaneous adipose tissue (SAT) – face, arms, legs, buttocks
  - Fat gain only (lipohypertrophy)
    - Areas of brown or visceral adipose tissue (VAT) – central abdomen, upper trunk fat including dorsocervical hump
  - Both fat loss and fat gain (mixed)
- May be associated with
  - Cholesterol abnormalities
  - Glucose abnormalities
  - Lipomatosis

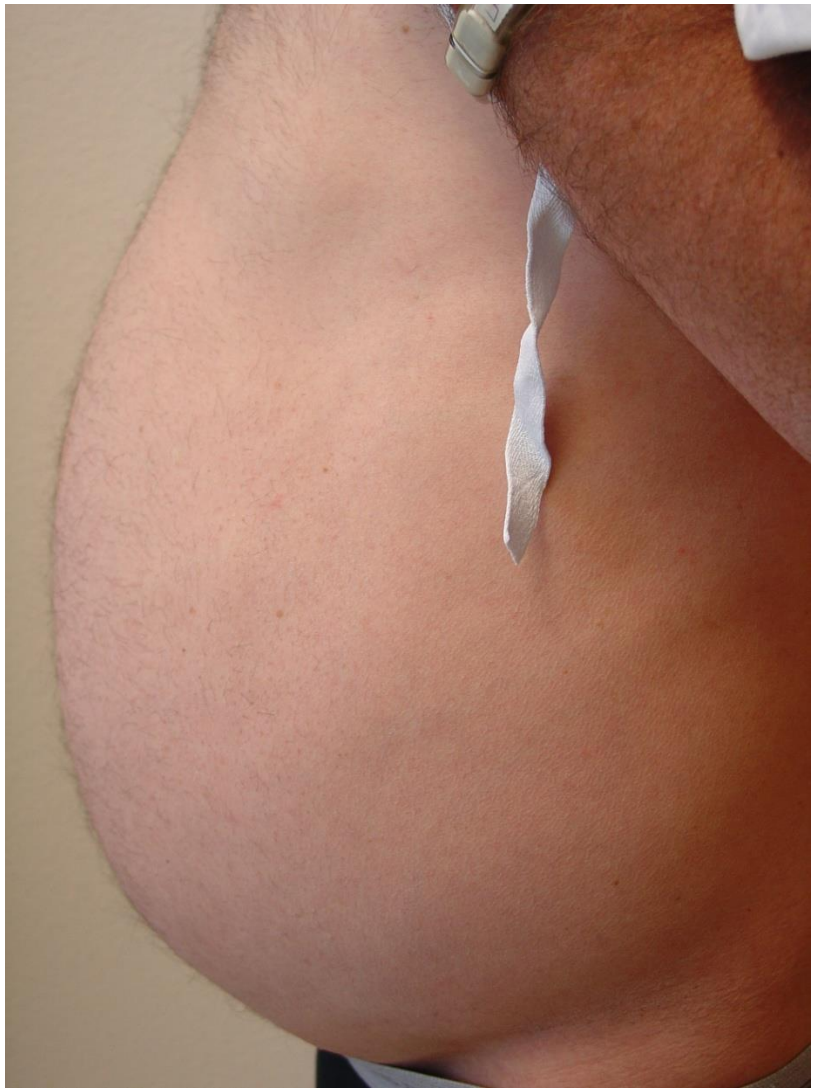
Lipodystrophy Syndrome











Factors Affecting Development of Lipodystrophy in HIV

- Internal Factors
  - Patient-specific factors
- External Factors
  - Viral factors
  - Drug/treatment-related factors

Proposed Causes of Fat Loss (Lipoatrophy)

- Patient factors
  - Older age
  - Race/Ethnicity - Caucasian
  - Male Gender
- HIV-related factors
  - Low CD4 count
  - High viral load
  - Duration of HIV infection
  - Disease progression
- Antiretroviral therapy-related factors
  - **Nucleoside Reverse Transcriptase Inhibitors (NRTI)**
  - Protease Inhibitors + NRTI
  - Duration of HIV treatment
- Other
  - **Mitochondrial toxicity**
  - Insulin resistance
  - Increased proinflammatory cytokine activity
  - Macrophage infiltration
  - Neuroendocrine dysregulation
  - Genetics

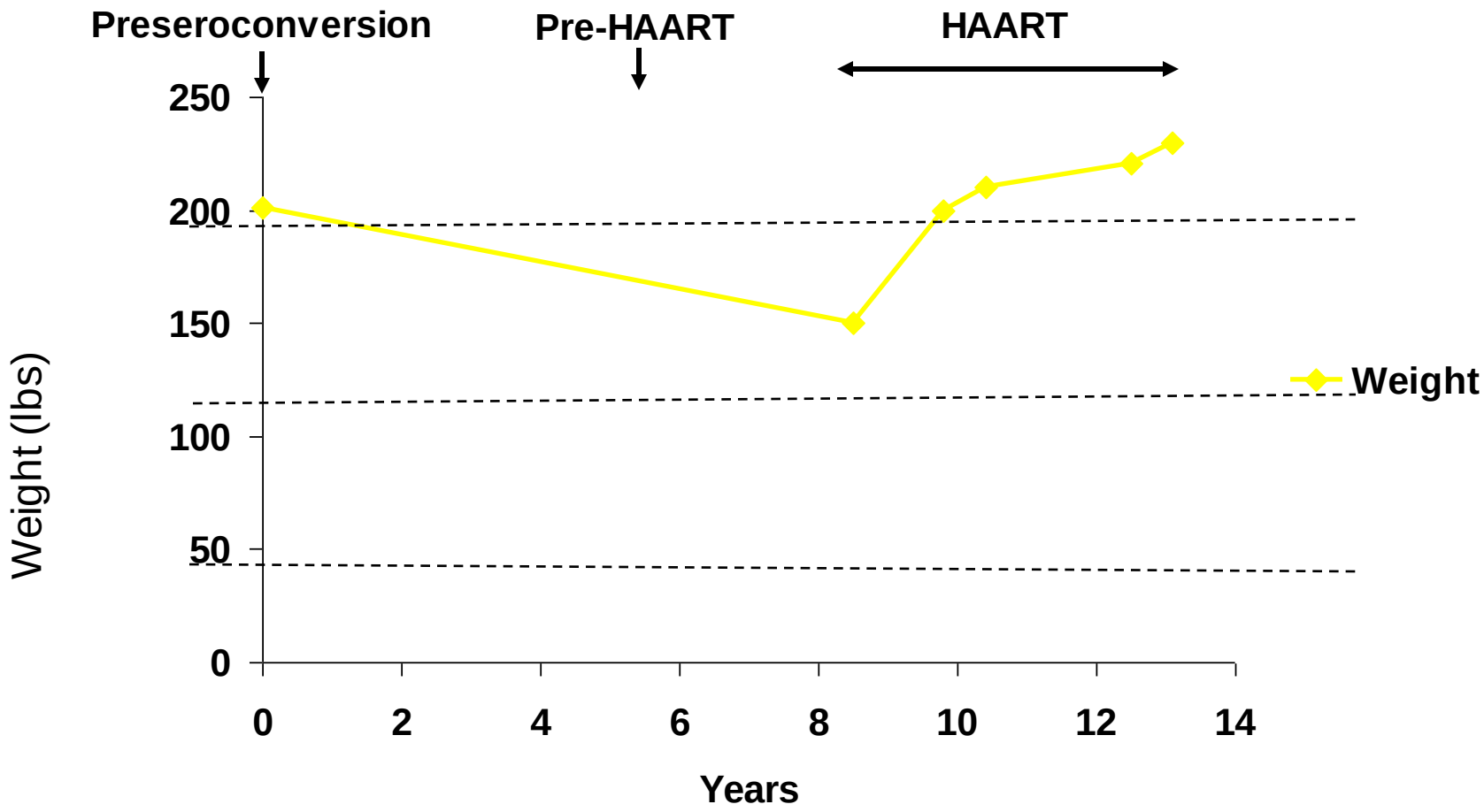
Patient-Specific Factors Affecting Development of Lipohypertrophy in HIV

- Age
  - Older age → slower metabolism → fat accumulation
- Genetic susceptibility
  - Some people may be predisposed to fat accumulation
- Medical history
  - Presence of dyslipidemia, insulin resistance/diabetes, hypothyroidism, hypogonadism
- Resting energy expenditure (REE) & basal metabolic rate (BMR)
  - Affected by level of muscle mass and physical activity
- Caloric intake of food
- Adipocytokine production and growth hormone (GH) secretion
  - Leptin deficiency
  - Decreased adiponectin levels
  - Decreased GH levels

External Factors Affecting Development of Lipohypertrophy in HIV

- Viral factors
  - HIV
    - Effects on dyslipidemia (↑free fatty acid flux) and insulin resistance
    - Increased cytokine activity and its subsequent downstream effects
    - Likely many other unknown off-target effects?
  - Other infections (ie, hepatitis C and ↑ diabetes risk)
- Drug/treatment-related factors
  - Antiretroviral therapy
    - Protease Inhibitors → may affect glucose and lipid metabolism
    - Nucleoside Reverse Transcriptase Inhibitors → may cause irreversible lipoatrophy of subcutaneous fat, so fat gain may only be in areas of visceral fat
  - Other medications/drug interactions
    - Drugs affecting testosterone/estrogen balance (eg. megestrol acetate)
    - Inhaled corticosteroids with protease inhibitors
  - "Return to health" phenomenon

“Return to Health” Phenomenon Not Only Applies to Lipids, But Likely Also Applies to Fat and Weight Gain



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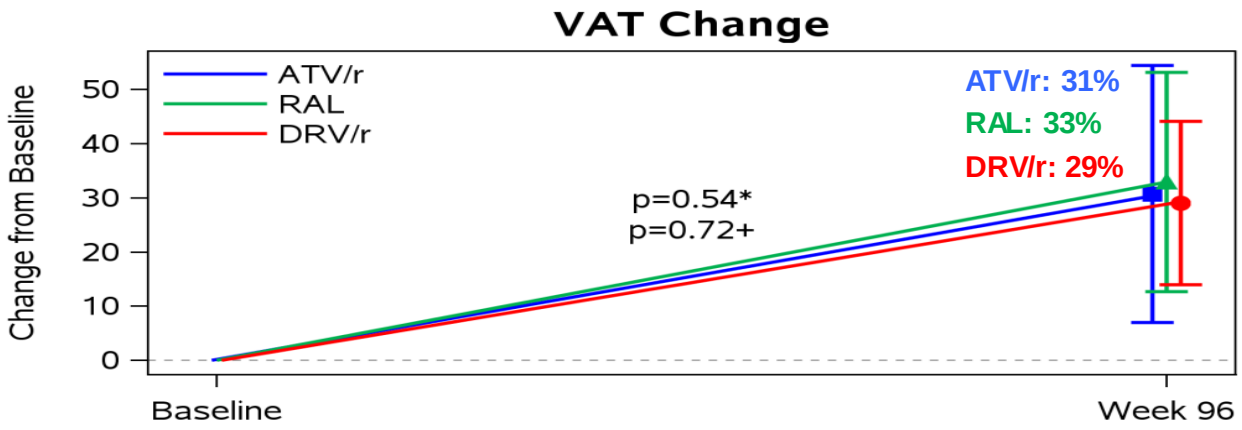
Adapted from Riddler et al. JAMA 2003;289:2978-82.

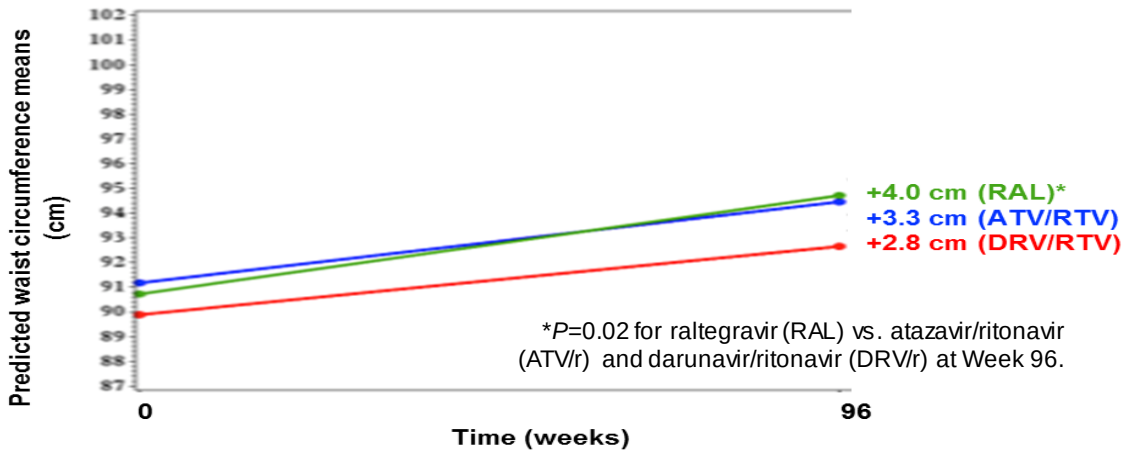
Abdominal Lipohypertrophy Remains Prevalent in the New ART Era: Results of the ACTG A5260s[1] and ACTG 5257[2] Studies

ACTG A5260s: VAT gains on Protease Inhibitors (PIs) vs an Integrase Strand Transfer Inhibitor (INSTI)



ACTG A5260s: a substudy of ACTG A5257 substudy (primary objective: change in CV markers).

ACTG A5257: Waist circumference increases on Protease Inhibitors (PIs) vs an Integrase Strand Transfer Inhibitor (INSTI)



ACTG A5257: Phase 3, prospective, multicenter, randomized, open-label trial (N=1809), ART-naïve HIV+ patients, with viral load ≥1000 copies/ml. Patients randomized 1:1:1 to 3 NNRTI-sparing regimens, 96-week follow-up.

1. McComsey G, et al. *Clin Infect Dis*. 2016; 62(7): 853-862.
2. Bhagwat P, et al. *Antiviral Therapy*. 2016;21: Suppl 1: A9

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Additional Common Causes of Abdominal Weight Gain in Everyone

- Aging
  - Slowing metabolism over time
- Stress
  - Cortisol promotes accumulation of body fat
- Overeating
  - Excess caloric intake > energy expenditure → weight gain
  - Poor diet
    - Saturated fats or trans fats (fatty red meat, whole milk, fried foods, dark meat poultry, poultry skin, butter, margarine, processed snacks)
    - Refined carbohydrates (enriched flour, table sugar, corn syrup)
- Physical Inactivity
  - Presence of lean muscle helps to burn fat

Evaluating Fat Accumulation in HIV Infection

- Questions you should consider asking the patient regarding his/her evolution of fat accumulation?
  - How long do you *think* you have been HIV-infected?
  - What was your normal weight before HIV infection?
  - Any significant weight loss in the past or prior to starting HAART?
  - Receiving HAART or not? Which prior medications?
  - When did the fat accumulation start?
  - Does the fat accumulation cause any discomfort?
  - Any history of dyslipidemia or insulin resistance?
  - Body habitus of family members?
  - Stress? Diet? Exercise?
  - Which fat depot on exam – subcutaneous and/or visceral fat accumulation?

Case Scenario #2

- What is this patient's evolution of fat accumulation?
  - How long do you *think* you have been HIV-infected? Probably since 1990
  - What was your normal weight before HIV infection? 170 lbs before HIV infection, now at 210 lbs.
  - Any significant weight loss in the past or prior to starting HAART? Yes, weight dropped to 150 lbs prior to HIV diagnosis in 1993, history of meth use intermittently in 2000-2002.
  - Receiving HAART or not? Which prior medications? Yes, darunavir/cobicistat 800 mg/150 mg daily, dolutegravir 50 mg daily, tenofovir alefenamide/emtricitabine 10 mg/200 mg daily. Prior HAART includes monotherapy zidovudine, indinavir, stavudine, many others (can't remember).
  - When did the fat accumulation start? 1996 after starting indinavir regimen
  - Does the fat accumulation cause any discomfort? Yes, difficulty breathing and tying shoes
  - Any history of dyslipidemia or insulin resistance? Yes, elevated triglycerides of 280 mg/dL
  - Body habitus of family members? Thin family members
  - Stress? Diet? Exercise? Chronic anxiety/depression, good diet, regular cardio at the gym
  - Which fat depot on exam – subcutaneous and/or visceral fat accumulation? Minimal pinchable SQ fat, massive amount of visceral fat present on exam

How Do We Evaluate Lipodystrophy?

- Patient self-report
- Physical examination
- Body Measurements
  - Skinfold caliper measurements
  - Circumference measurements
- Imaging studies
  - Ultrasound
  - Dual energy x-ray absorptiometry (DEXA)
  - CT scan / MRI
- Photographs/Digital Pictures

Patient Self-Report of Lipodystrophy

- Fat Loss (Lipoatrophy)
  - “My cheeks are getting thinner.”
  - “People at work or my friends are asking me if I am sick.”
  - “I’m losing my butt.”
  - “I don’t want to work out at the gym anymore because my legs are so skinny.”

- Fat Gain (Lipohypertrophy)
  - “I keep gaining weight and my waist size continues to grow even though I’m working out and dieting.”
  - “I can’t wear collared shirts anymore because of this hump”
  - “I wanted bigger breasts…but this is ridiculous!!”

Physical Examination of Lipodystrophy

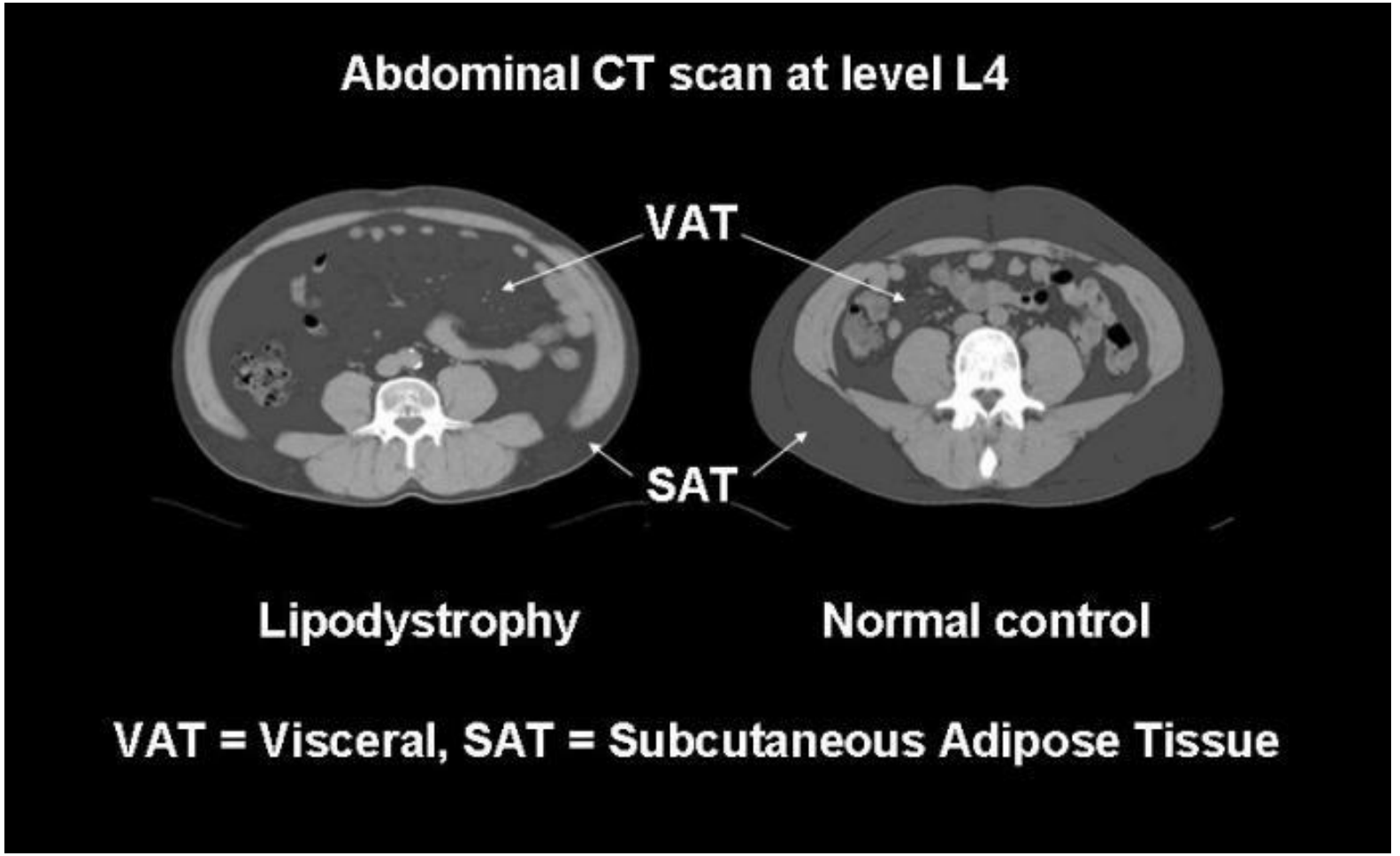
- Face
  - Fat loss in cheeks and temple area
  - Fat gain on sides of face (in front of ears) and under chin
- Neck/Back
  - Dorsocervical hump ("Buffalo hump") – size, shape, firmness
  - Lipomas (small fat deposits) – size, number, location
- Breast
  - Increase or decrease in breast tissue
- Abdomen
  - Size, shape, firmness
  - Location of fat accumulation – note whether above or below umbilicus
  - Presence of superficial fat to determine lipodystrophy versus obesity ("pinch test")
- Extremities (arms, legs, and buttocks)
  - Thinning in these areas with visible veins in arms/legs.

Body Composition Measurements and Imaging Studies

- Body Composition Measurements
  - Skinfold Calipers
  - Bioelectrical Impedance Analysis (BIA)
  - Hydrostatic Weighing
  - Circumference Measurements – longitudinal measurements of arms, legs, waist, hip, abdomen, neck
    - Live demonstration of measuring waist circumference and hip circumference

- Imaging Studies – mainly used in research settings
  - Ultrasound
    - Look for excess fat behind the neck or at lipomas
  - Dual Energy X-ray Absortiometry (DEXA) scan
    - Measures regional fat in extremities versus fat in trunk or abdomen
  - Computerized Tomography (CT) scan
    - Measures subcutaneous adipose tissue (SAT) versus visceral adipose tissue (VAT) in abdomen
  - Magnetic Resonance Imaging (MRI) scan
    - Measures subcutaneous adipose tissue (SAT) versus visceral adipose tissue (VAT) in abdomen

Lipodystrophy Imaging



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

Photographs and Digital Pictures for Tracking Lipodystrophy

- Old photographs may be useful to compare what a person looked like in the past to their current appearance
- Pictures can be repeated over time to track changes
  - May be useful in obtaining approval for surgery for lipodystrophy (eg. buffalo hump surgery or facial injections)
  - Advantages
    - Relatively easy to obtain/take digital pictures
  - Disadvantages
    - May be difficult to appreciate depth, shape, firmness of fat changes

Importance of Lipodystrophy

- Patient issues
  - Worsen body image, self-esteem, and quality of life
  - May cause or worsen anxiety and/or depression
  - Identification of HIV status
  - Physical effects
    - Neck pain, back pain, breathing problems, heartburn, abdominal pain, impaired range of motion

- Medical issues
  - May be associated with metabolic syndrome
  - May be associated with increased cholesterol and triglyceride levels
  - Possible increased risk of heart disease
  - Patients may not want to take HAART because they believe it will cause lipodystrophy

Strategies Evaluated in Treating Lipodystrophy

- Fat Loss
  - Avoidance of thymidine nucleoside reverse transcriptase inhibitors (NRTIs) that cause fat loss (zidovudine and stavudine)
  - Switching HAART
    - Switch offending thymidine NRTI to either tenofovir or abacavir
  - Insulin sensitizers
    - Thiazolidinediones
  - Surgical interventions
    - Facial fat loss
      - Injections/Fillers/Implants (eg. polylactic acid*)
      - Fat transfer
    - Fat loss of other body parts
      - Implants
      - Fat transfer

- Fat Gain
  - Lifestyle changes
    - Diet
    - Exercise
  - Insulin sensitizers
    - Metformin
  - Other drugs
    - Testosterone
    - Anabolic steroids
    - Recombinant human growth hormone
    - Growth hormone releasing factor (eg. tesamorelin*)
  - Surgical interventions
    - Liposuction
    - Surgical removal

*FDA approved

Wohl DA, et al. *Clin Infect Dis*. 2006;43(5): 645-653.

Case Scenario #2

- 48 year old Caucasian male w/HIV w/CD4 = 310 cells, VL <50 c/ml
  - Current HAART includes darunavir/cobicistat 800 mg/150 mg daily, dolutegravir 50 mg daily, tenofovir alefenamide/emtricitabine 10 mg/200 mg daily
  - Pt has been HIV+ since 1993 and has been on multiple antiretroviral regimens with prior resistance to multiple medications over the years
  - Chief complaint is "lipodystrophy" and on physical exam…
    - Fat loss in arms, legs, and face and buttocks
    - Fat accumulation in abdomen, slight dorsocervical fat pad
  - He is interested in what is causing these body fat changes and what can be done to improve this
    - We discussed the multiple possible causes for his lipodystrophy
      - Return to health phenomenon, older antiretroviral therapy, possibility of accelerated aging process with longstanding HIV infection
    - Treatment options were limited
      - Antiretroviral therapy was not changed as his options were limited by known prior resistance
      - Obtained tesamorelin (growth hormone releasing factor) for HIV-associated lipodystrophy with slight improvement in reduction of visceral fat (waist circumference was 110 cm and decreased to 105 cm)

What Have We Learned About Lipodystrophy

- Lipodystrophy is still an issue that concerns our patients (even in the era of Integrase Inhibitors)
  - Fat loss (Lipoatrophy)
  - Fat accumulation (Lipohypertrophy)
- The proposed causes of lipodystrophy are likely multifactorial and may be different from person to person
- A thorough clinical evaluation of lipodystrophy involves a more extensive history and physical exam, including various body composition measurements
- Lipodystrophy is not just purely cosmetic, but can have various effects on physical health, mental health, and quality of life
- Treatment of lipodystrophy should be targeted towards the underlying cause(s)

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Questions?

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WEIGHT GAIN AND OBESITY

Defining weight gain

- Weight gain is an increase in body weight
  - Muscle, fat, bone, water

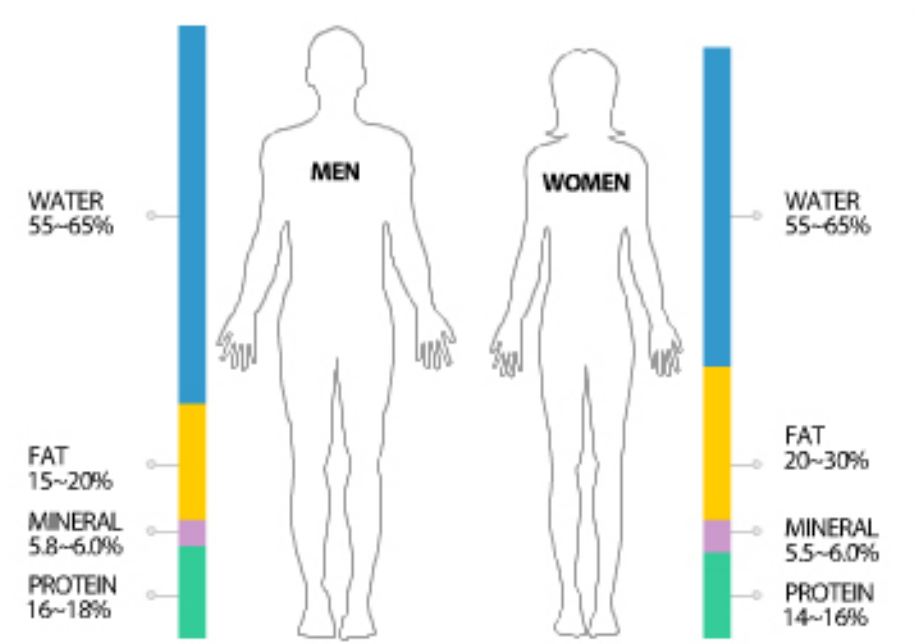
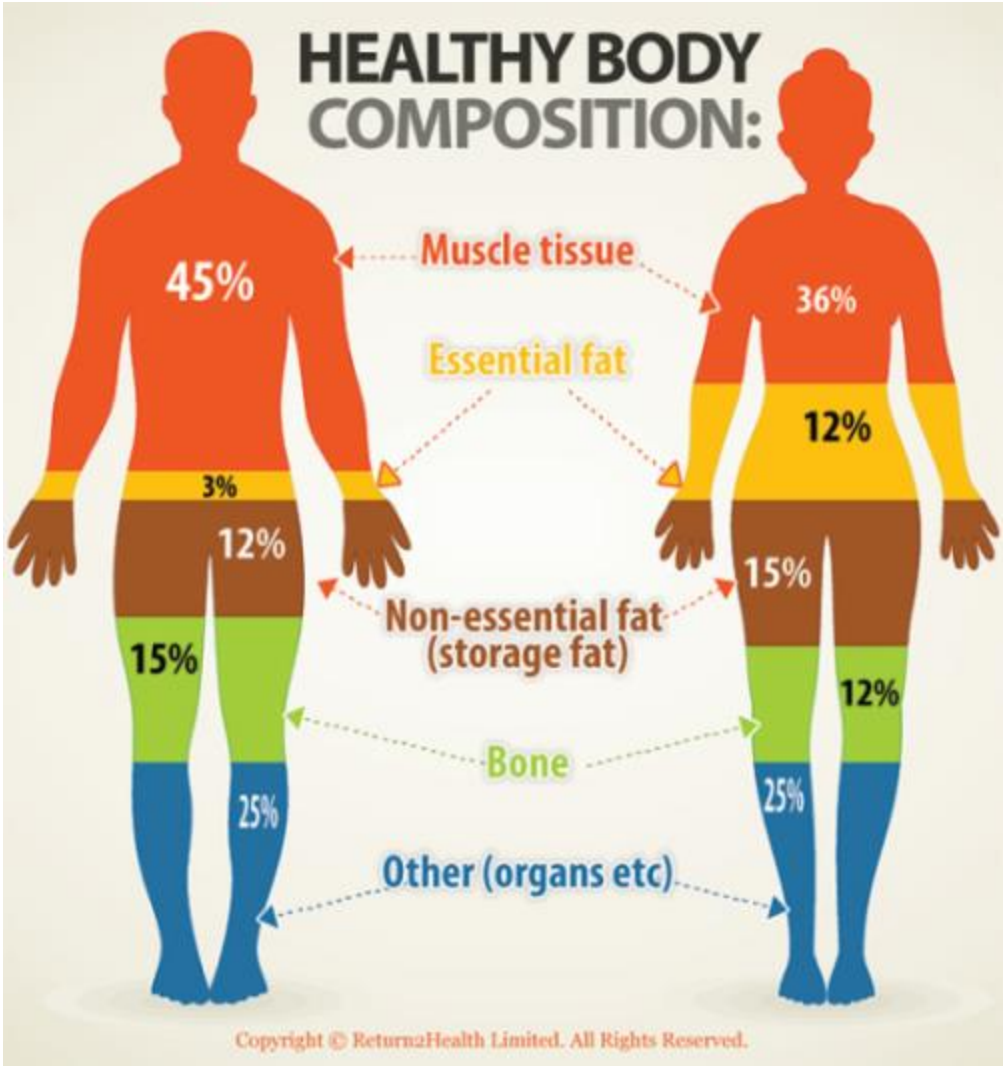


Image from: https://ucsdzone.tumblr.com/post/144555260332/body-composition



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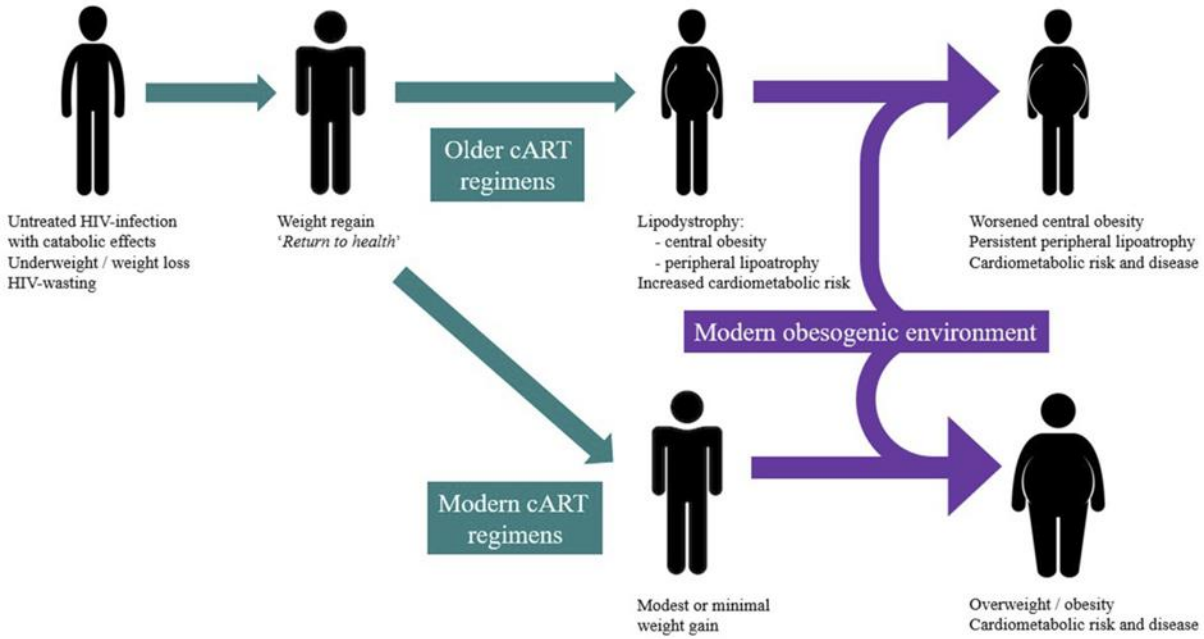
Factors Contributing to Weight Changes in HIV

- HIV-related factors
  - Chronic Inflammation – increased proinflammatory cytokines
  - Microbial Translocation – effects on gut absorption
- Antiretroviral Therapy-related factors
  - Altered lipid trafficking
  - Abnormal adipose tissue distribution
- Patient/Host-related factors
  - Diet – food preferences, food insecurity, access to healthy foods (food deserts)
  - Energy Balance: Calories consumed = calories expended
  - Physical Activity – regularity of exercise, opportunities for physical activity, safety and walkability of community
  - Basal Metabolic Rate (BMR) – minimum number of calories needed to keep the body functioning at rest
  - Resting Energy Expenditure (REE) – number of calories that your body burns at rest
    - Accounts for 60% of total energy expenditure
    - Related most directly to amount of fat-free (lean) mass
  - Genetics – race/ethnicity, gender, family history
  - Other Comorbidities – thyroid abnormalities, diabetes, infections, malignancies
  - Concurrent Medications – psychiatric medications
  - Habits – smoking, alcohol, other illicit substances
    - Consequences of use vs. cessation

Weight Gain During ART: Return to Health vs. Obesity Trajectory

- Untreated HIV associated with weight loss/wasting
- Following ART initiation, weight gain is common, but need to distinguish weight gain due to:
  - "Return to health": desirable weight gain related to restoration of body nutrient stores
  - Clinically undesirable weight gain that leads to complications of overweight or obesity
- Gains in abdominal fat, weight, and BMI after ART may increase long-term risk for diabetes, CVD, other complications



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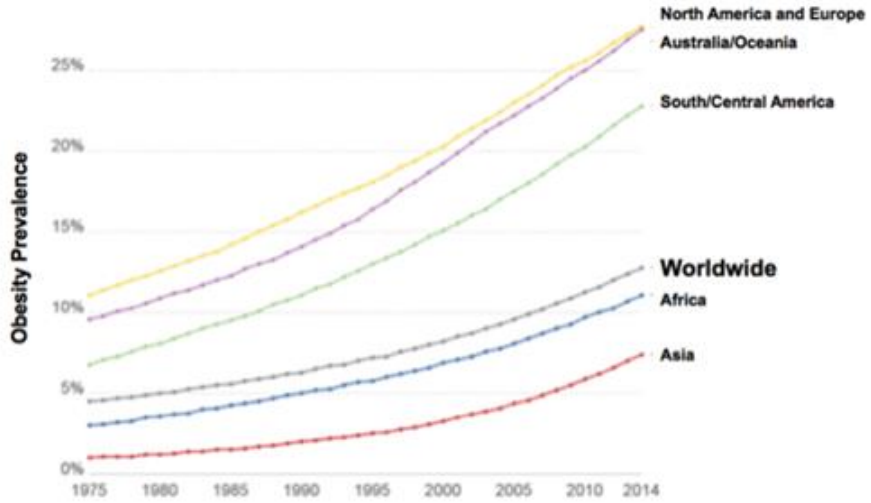
Kumar S, et al. *Front Endocrinol*. 2018;9:705.

Obesity: A Growing Problem in HIV

Obesity Prevalence is Rising Worldwide

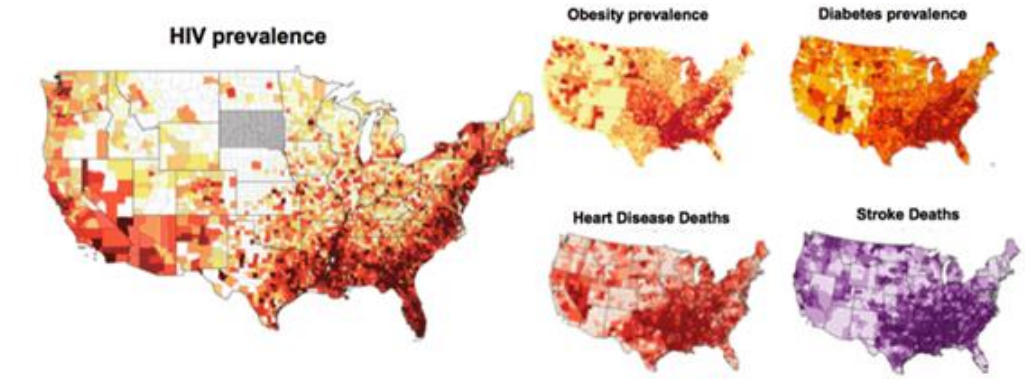


Source: WHO Fact Sheets 2018 & UN Food and Agricultural Organization

StartFragment

Worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults were overweight (BMI ≥25 kg/m^2). Over 650 million were obese (BMI ≥30 kg/m^2)

Overlapping Epidemics: HIV, Obesity, Diabetes, and Cardiovascular Diseases in the US



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

Overlapping Epidemics: HIV and Poverty in the US

Source: AIDSVu.com and US Census Bureau (Census.gov)

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Evaluating Body Weight

- Body weight
- Body mass index (BMI) = weight (kg) / height (m^2)
- Weight status - underweight, normal, overweight, obese

The standard weight status categories associated with BMI ranges for adults are shown in the following table.	
BMI	Weight Status
Below 18.5	Underweight
18.5 – 24.9	Normal or Healthy Weight
25.0 – 29.9	Overweight
30.0 and Above	Obese

Table from: https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

Challenges in Measuring Body Weight in Clinic/Studies

- Equipment
  - Choose appropriate scale(s)
    - Accuracy/precision of measurements
    - Reliability of measurements
  - Check and calibrate scales regularly
- Measurement protocols
  - Use same scale(s)
  - Train and standardize data collectors
  - Standardize how measurements are obtained
    - Gowned vs. ungowned
    - Time of day
    - Relationship to meals (fasting vs not fasting)
- Other

Himes JH. Pediatrics 2009. 124 Suppl 1: S3-22.

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What is the relationship between antiretroviral therapy and weight gain/obesity?

INSTIs?

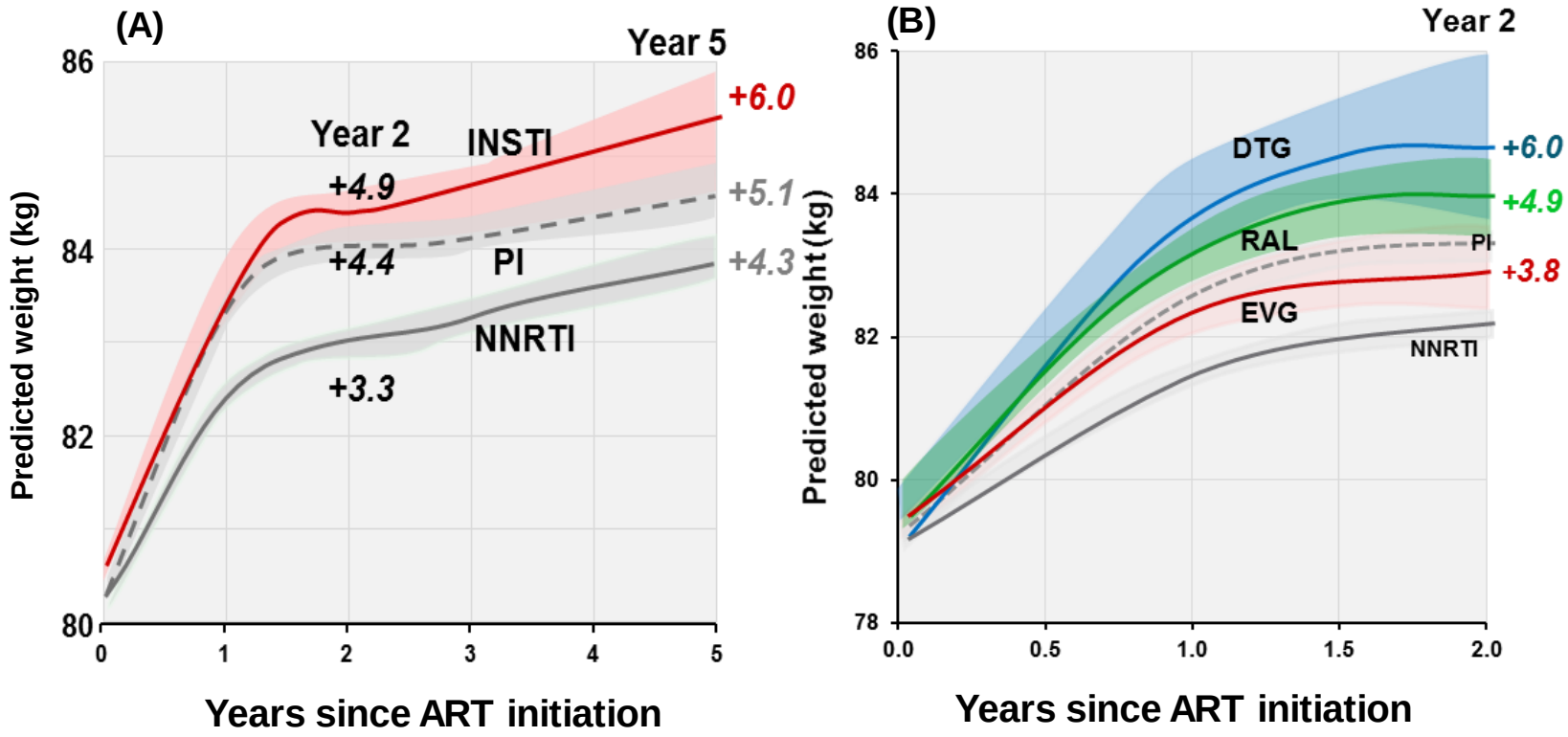
TAF?

Initial vs. Switch Therapy

NA-ACCORD: Impact of Initial Antiretroviral Therapy on Body Weight

- **Adult, treatment-naïve PLWH (n=24,001) initiating ART between January 2007 and December 2016 in US/Canada**
- **Method:** Linear effects modeling evaluated associations of weight over time with ART class
- **Primary Outcome Measures:**
  - A. Weight by ART class within 5 years of ART initiation
    - INSTI: 20%
    - PI: 31%
    - NNRTI: 49%
  - B. Weight by INSTI drug (n=4740) within 2 years of ART initiation
    - DTG: 20%
    - EVG: 45%
    - RAL: 35%

Predicted Weight Changes within:
(A) 5-years of ART initiation by ART class
(B) 2-years of ART initiation by INSTI drug and ART class



ART class predicted weight changes at 2 and 5 years (INSTI > NNRTI and PI > NNRTI)
Weight gain associated with INSTI-based regimens did not vary by sex (male vs. female) or race (white vs. non-white)

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Bourgi K, et al. CROI 2019. Seattle, WA. Poster 670

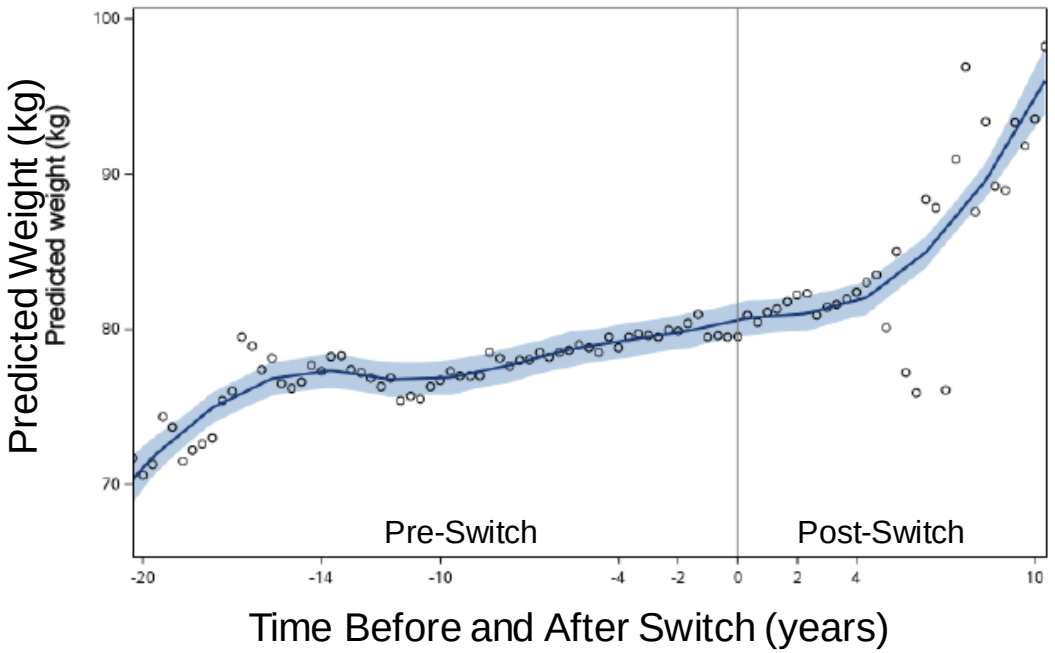
ACTG A5001 and A5322: Risk Factors for Weight Gain Following Switch to INSTI-Based ART

Prospective, observational follow up of virologically-suppressed PLWH (n=691) previously enrolled in ACTG randomized interventional trials from 2007-2017

ART Pre-Switch

	%
ART Prior to Switch	
PI	63%
NNRTI	35%
NRTI Prior to Switch	
ABC	25%
TDF	49%
TAF	14%

Change in Weight Before and After Switch to INSTI



Annual Rate of Weight Change Pre-Post Switch to INSTI

	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2	0.5	0.5
Post-INSTI	1.3	0.9	0.3
Pre-post difference	1.0 (0.0009)	0.5 (0.11)	-0.2 (0.37)

Weight changes in kg/year (p-value) for 2 years before and after switch to INSTI

Rate of weight change following switch was significant for DTG

Increases in weight gain following switch to INSTI were most prominent for women, blacks and persons age ≥ 60

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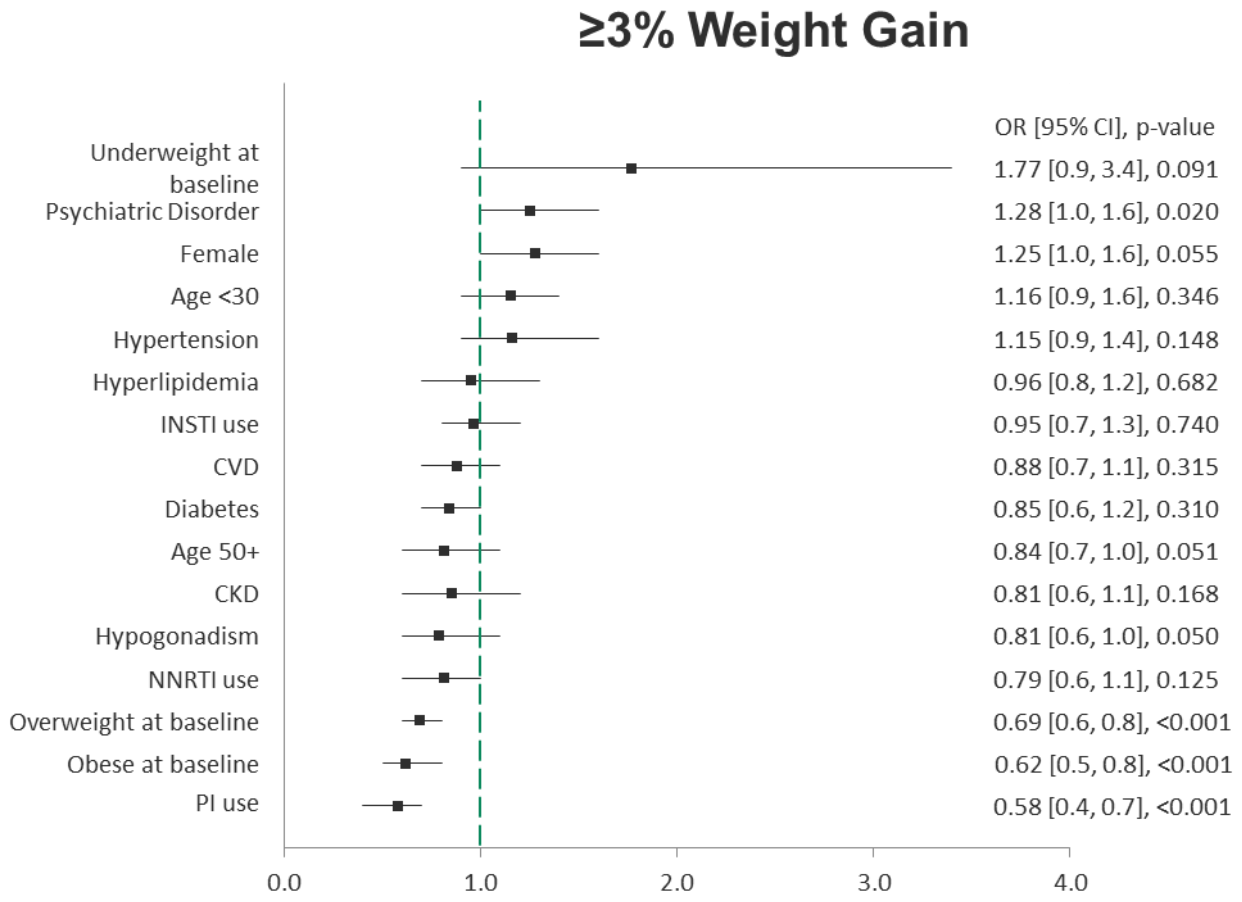
Lake J, et al. CROI 2019. Poster 669

TRIO: Weight Gain Among Treatment-Experienced Adults with HIV

- TRIO: Retrospective, observational cohort study (n=3468; 2013-2017)
  - Virologically suppressed with BMI measures at baseline and between 365-730 days on ART
- Baseline characteristics
  - Mean age (48 years), male (81%), white/black (61%/28%), mean CD4 (656 cells/mm^3), BMI >30 kg/m^2 (39%)
  - CVD (12%), diabetes (8%), hyperlipidemia (36%), hypogonadism (19%), psychiatric disorder (16%)
- Linear regression analysis of factors associated with ≥3% weight gain
  - Negative association: overweight/obese at switch, hypogonadism, PI-containing ART
  - Positive association: psychiatric disorder
  - INSTI-based ART: no longer significant



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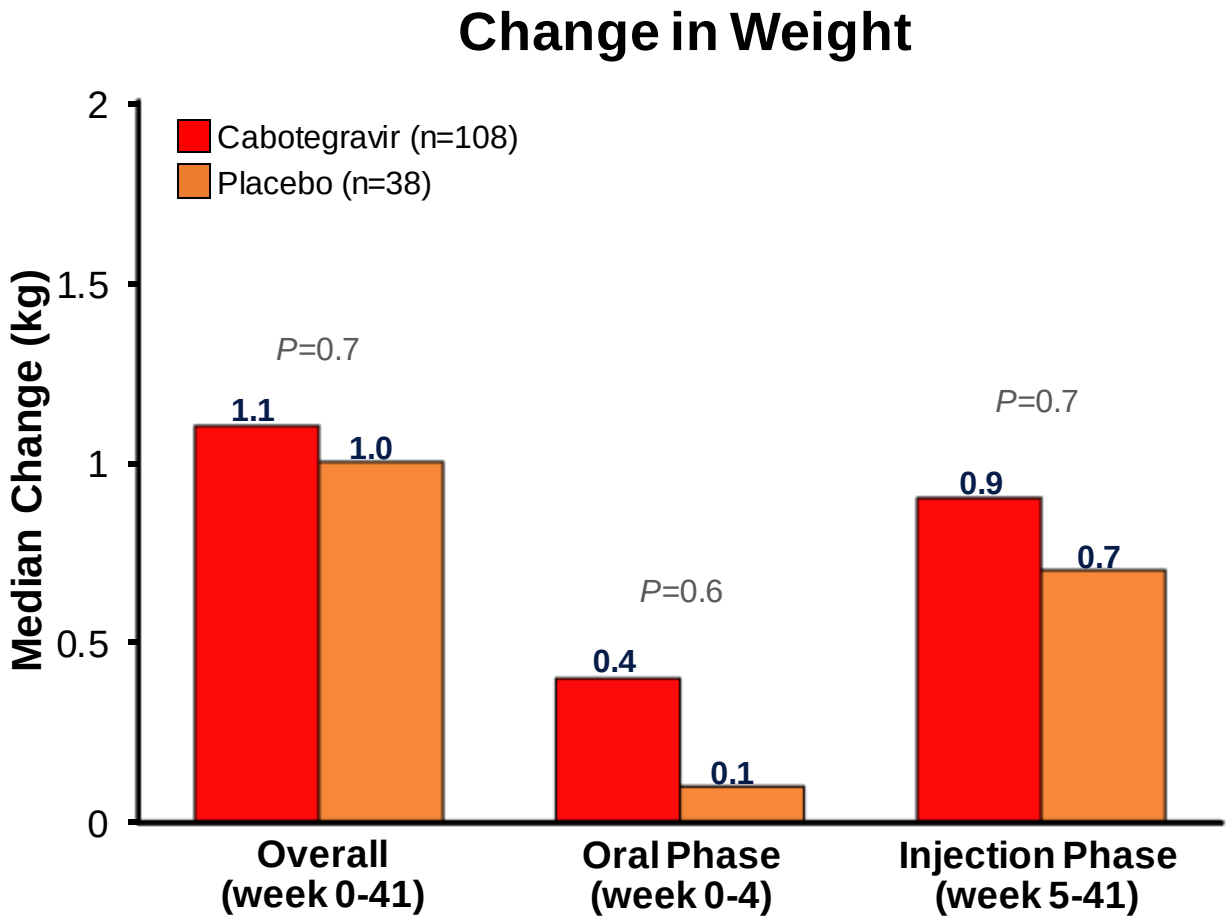
McComsey GA, et al. 26th CROI. Seattle, 2019. Abstract 671.

HPTN 077: Subanalysis of Weight Change with Cabotegravir

- HPTN 077: Phase 2 study of Pre-Exposure Prophylaxis in HIV-negative individuals
  - Week 0-5 (oral cabotegravir), week 5 to 41 (cabotegravir 800 mg IM q12 weeks or 600 mg IM q8 weeks)
  - Matching placebo
- Weight gain with cabotegravir was small and not statistically different compared to placebo
  - No difference by subgroups (sex, dosing cohort, age, race/ethnicity, smoking status, BMI category)
- Changes in fasting glucose and fasting lipids were similar between both arms
- Limitations
  - Non-standardized weight measurement, modest sample size (ie, sample size powered to rule out a minimum difference in weight change of 2.4 kg)



McComsey GA, et al. 26th CROI. Seattle, 2019. Abstract 671.

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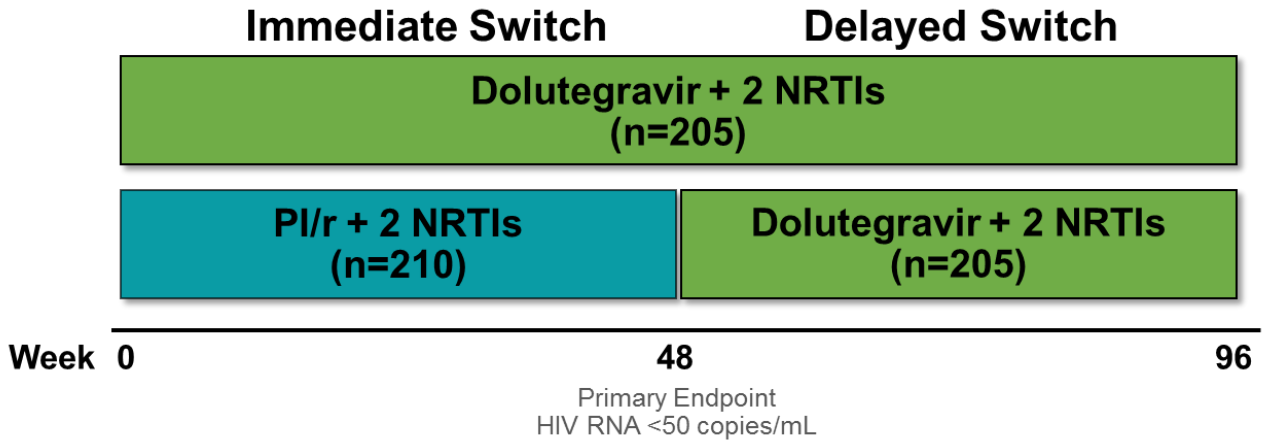
INSTIs and Weight Gain

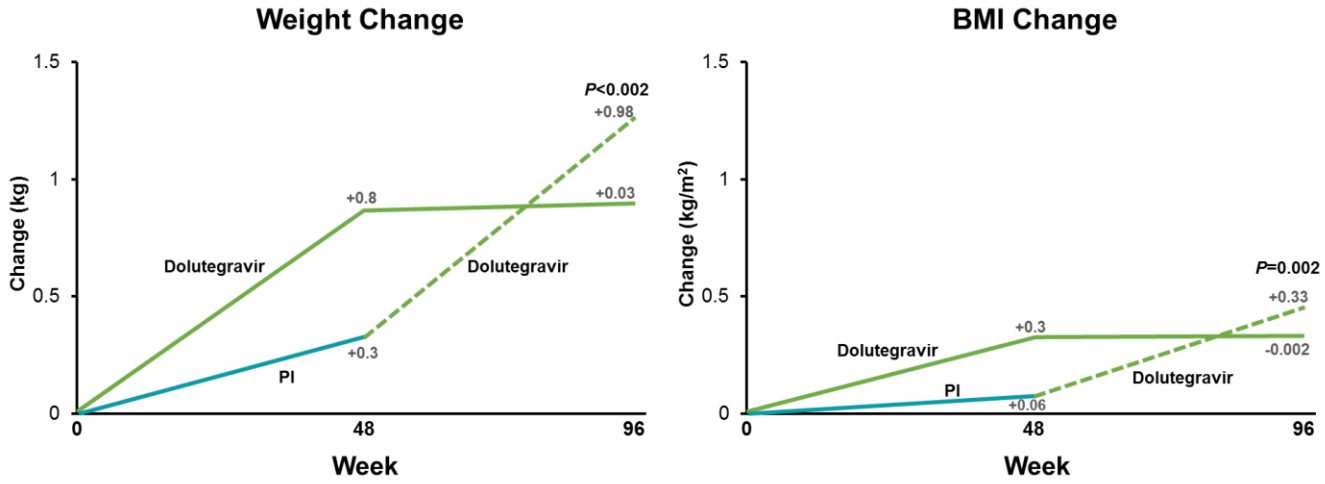
- Positive Association
  - NA-ACCORD (initial therapy): CROI 2019 abstract 670 – INSTI (DTG > RAL > EVG) > PI > NNRTI
  - ACTG long-term cohort (switch): CROI 2019 abstract 669 – DTG > EVG > RAL
    - Women, black race, older age ≥ 60 were at greater risk of weight gain

- No Association Found
  - TRIO retrospective cohort (switch): CROI 2019 abstract 671
  - HPTN 077 - Cabotegravir in HIV PrEP studies (HIV-negative): CROI 2019 abstract 34

NEAT 022 Study: Switching From a Boosted PI- to Dolutegravir-Based Regimen in Patients With High CVD Risk

- Randomized Trial – 6 European Countries
  - Open-label
  - Treatment-naïve
- Entry Criteria
  - HIV RNA<50 copies/mL on ritonavir-boosted PI-based regimen
  - ≥50 years of age and/or 10-year Framingham risk score >10%
  - No resistance and no previous virologic failure
- Baseline Demographics: Male: 89%, Family history of CVD: 43%, Diabetes: 6%, Current smoker: 38%, Framingham score >10% at 10 years: 74%, Age >50 years: 88%, CD4: 617 cells/mm^3, Receiving lipid-lowering agents: 30%
- Baseline boosted PI: darunavir (51%); atazanavir (37%); lopinavir/r (9%); other (4%).





Gatell JM, et al. *Clin Infect Dis.* 2019;68:597-606.
Waters L, et al. *J Int AIDS Soc*. 2018;21(suppl 8):77. Abstract P102.

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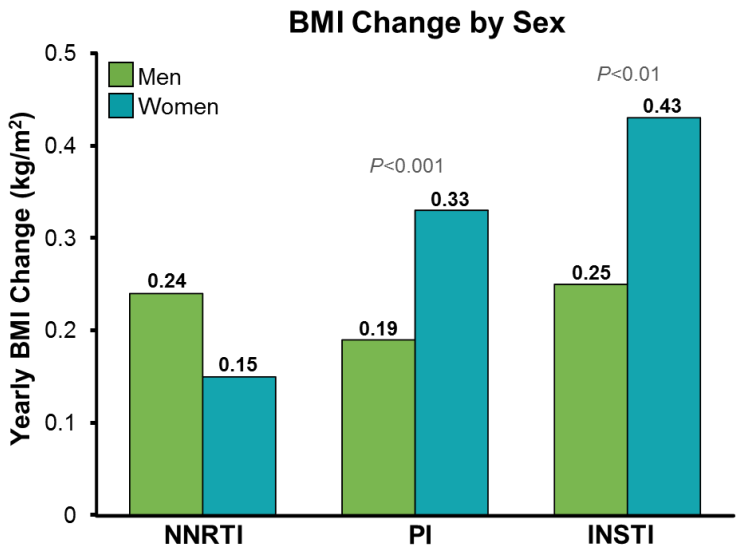
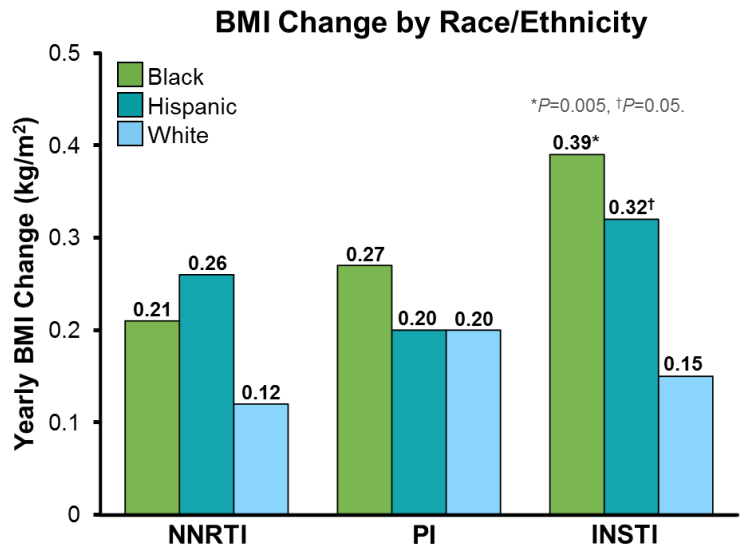
Parkland Cohort Study: Change in BMI and INSTI-Based ART

- Single-center cohort in Texas exposed to ART between 2009-2017 (n=4048)
  - Received ART with 2 NRTIs and either an NNRTI (n=1364), PI (n=2087), INSTI (n=2264)
- Median follow-up: 6.7 years
- Primary Outcomes:
  - Multivariate analysis of yearly BMI changes on ART in patients with baseline HIV RNA ≥400 copies/mL (n=3208)

Baseline Characteristics

	Cohort (n=4048)
Age (years)	46
Race/ethnicity (%)	
Black	53
Hispanic	28
White/other	16/3
Male (%)	69
BMI (kg/m^2)	27
Regimen exposure (person-years)	
NNRTI	3546
PI	6184
INSTI	3090





INSTI-based ART was associated with greater increases in BMI in blacks and Hispanics. Women had greater BMI gains than men on PI and INSTI.

Bedimo R, et al. *Open Forum Infect Dis*. 2018;5 (suppl 1):S199. Abstract 538.

AMERICAN ACADEMY OF HIV MEDICINE

INSTIs and Weight Gain

- Positive Association
  - NA-ACCORD (initial therapy): CROI 2019 abstract 670 – INSTI (DTG > RAL > EVG) > PI > NNRTI
  - ACTG long-term cohort (switch): CROI 2019 abstract 669 – DTG > EVG > RAL
    - Women, black race, older age ≥ 60 were at greater risk of weight gain
  - ***NEAT 022 study (initial therapy and switch): Waters et al. – DTG > PIs***
  - ***Parkland, Texas Cohort study (all, including switches): Bedimo et al. – INSTI > PI or NNRTI***
    - ***Women, blacks, and Hispanics were at risk for higher BMI change***

- No Association Found
  - TRIO retrospective cohort (switch): CROI 2019 abstract 671
  - HPTN 077 - Cabotegravir in HIV PrEP studies (HIV-negative): CROI 2019 abstract 34

Munich, Germany: Weight Change with Switch from a TDF to a TAF-containing Regimen

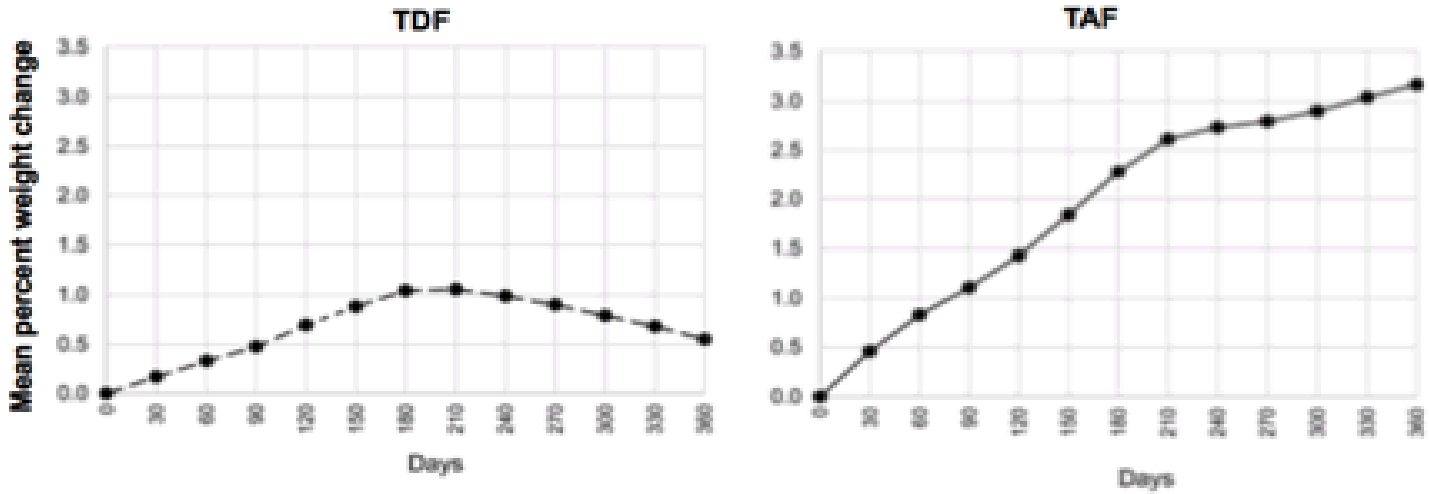
241 treatment-experienced adults treated with TDF or TAF from 2015-2017

- N=129 switched TDF to TAF
- N=112 remained on TDF (control)

Analyses:

- Weight over time for TDF vs. TAF recipients
- Repeated measures general linear model for patients switching TDF → TAF

Retrospective, single-site analysis of patients switched from a TDF- to a TAF-containing regimen



Weight change over 360 days

- Patients switched to TAF had a mean 3.17% weight increase through 360 days
- Patients on a TDF-containing regimen had a mean 0.55% increase over same period

Gomez M, et al. Infection 2018

AMERICAN ACADEMY OF HIV MEDICINE

Slide from Koethe JR. Obesity: A Growing Problem in Antiretroviral Therapy. 26th CROI. Seattle, 2019. Abstract 158.

Munich, Germany: Weight Change with Switch from a TDF to a TAF-containing Regimen

241 treatment-experienced adults treated with TDF or TAF from 2015-2017

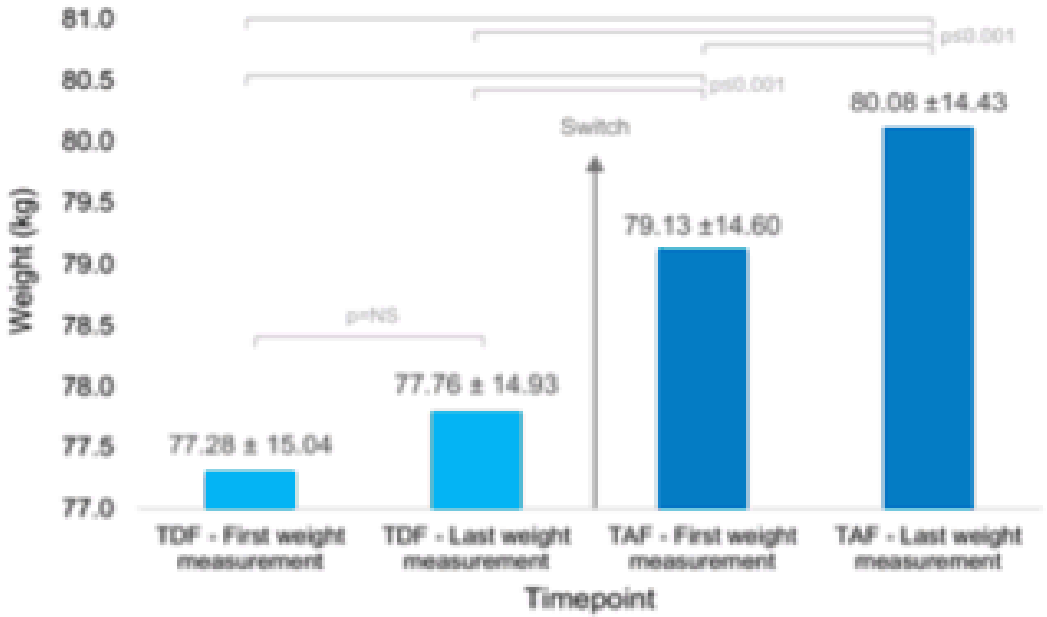
- N=129 switched TDF to TAF
- N=112 remained on TDF (control)

Third agent switches in the 129 also occurred:

- 13 NNRTI → INSTI
- 7 PI → INSTI
- Weight change with TDF → TAF switch significant in these 21, but lower (78.8 kg at first TAF measurement and 79.8 kg at second TAF measurement)

Gomez M, et al. Infection 2018

Retrospective, single-site analysis of 129 patients switched from a TDF- to a TAF-containing regimen



Weight increased after TDF → TAF switch

- Last TDF to first TAF measurement: 77.8 to 79.1 kg ($p<0.001$)
- First TAF to last TAF measurement: 79.1 to 80.1 kg ($p<0.001$)

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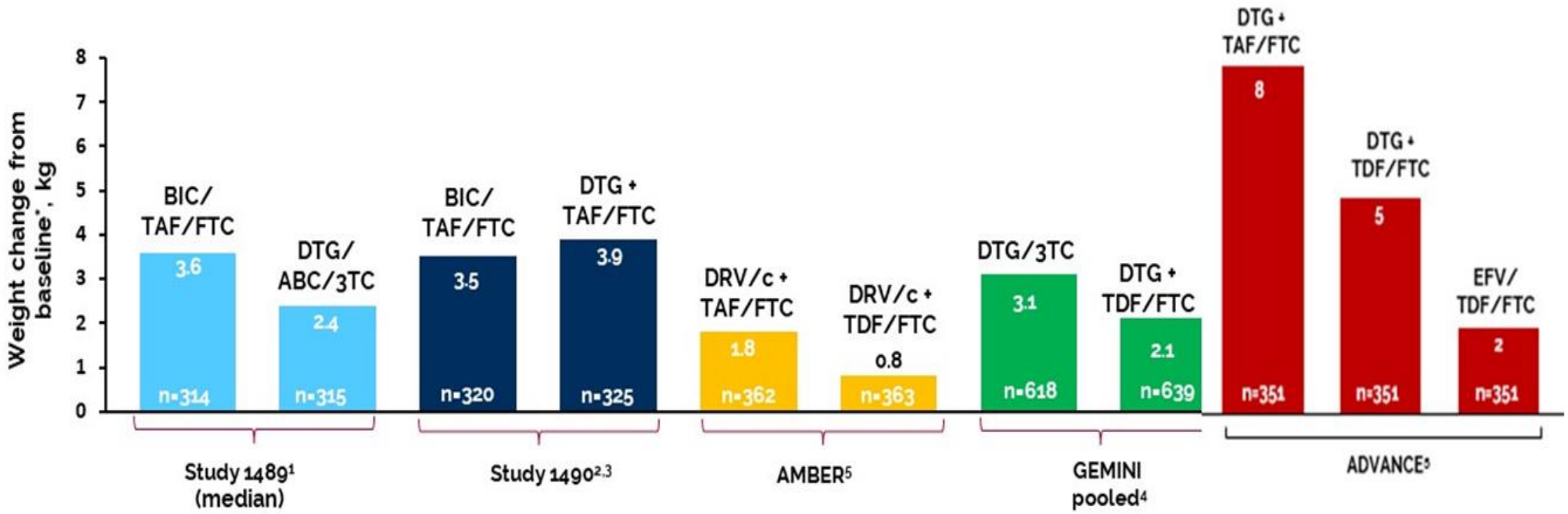
Slide from Koethe JR. Obesity: A Growing Problem in Antiretroviral Therapy. 26th CROI. Seattle, 2019. Abstract 158.

Cross-Study Comparison of Treatment-Naïve Studies Evaluating Weight Changes From Baseline To Week 96

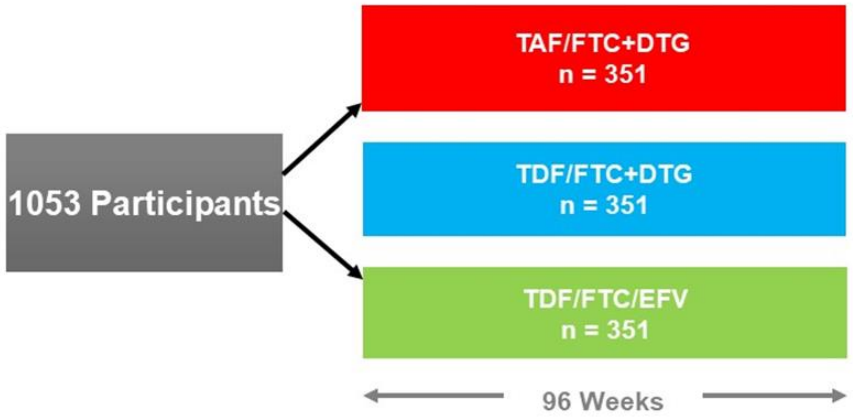


*Mean change data shown for all studies except 1489, which shows median change

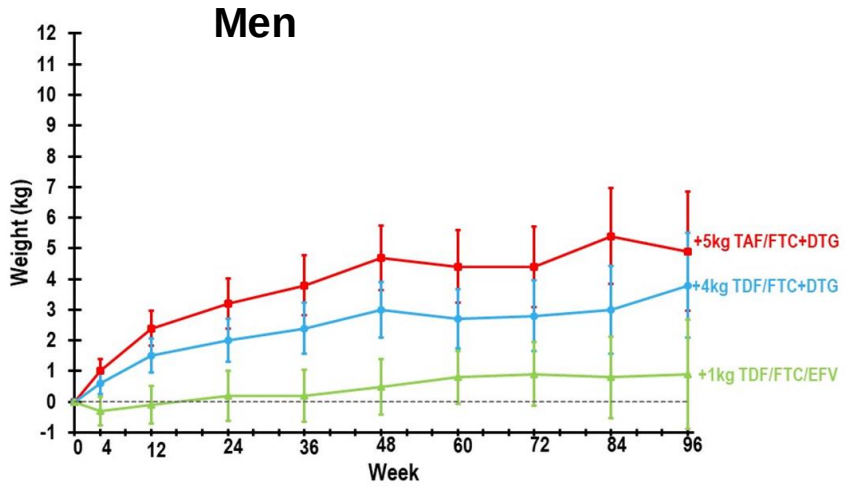
1. Wohl DA, et al. Lancet HIV 2019;6:e355-e363; 2. Hill A, et a. J Vir Erad 2019;5:41–3 3. Sax P, et al. Lancet 2017:390;2073–82; 4. ViiV Healthcare. Data on file. DTG Clinical Data and Safety Update, June 2019; 5. . Orkin C, et al. HIV Glasgow. October 2018. Glasgow, UK. Abstract O212

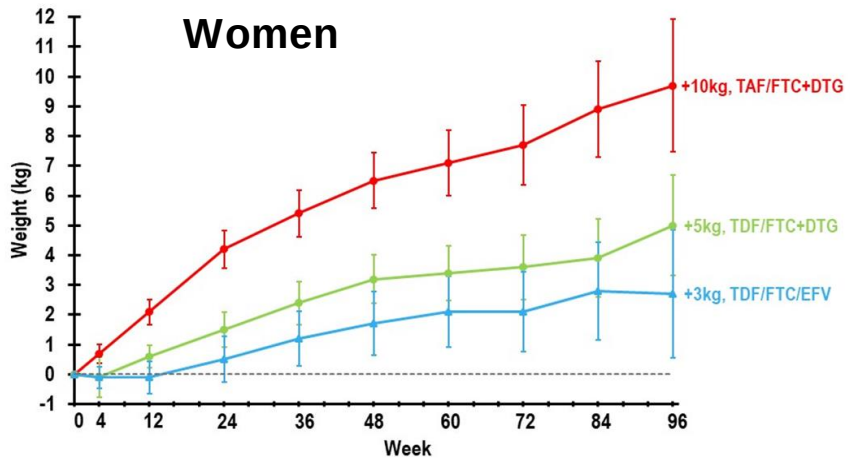
ADVANCE: Progressive Rise in Weight and Obesity for TAF/FTC/DTG and TDF/FTC/DTG versus TDF/FTC/EFV

- ADVANCE: Treatment-naïve, open-label study



	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Mean age (years)	33	32	32
Female	61%	59%	57%
Black	99%	100%	100%
Weight (mean, kg)			
Male	67.9	67.1	67.3
Female	68.8	69.5	70.2
BMI (kg/m²)			
Male	21.7	21.6	21.8
Female	25.6	26.1	26.1
Categories of BMI, n(%)			
Underweight (<18.5)	42 (12)	35 (10)	37 (11)
Normal (18.5-25)	177 (51)	190 (54)	193 (55)
Overweight (25- 30)	96 (27)	78 (22)	77 (22)
Obese (>30)	35 (10)	48 (14)	44 (12)





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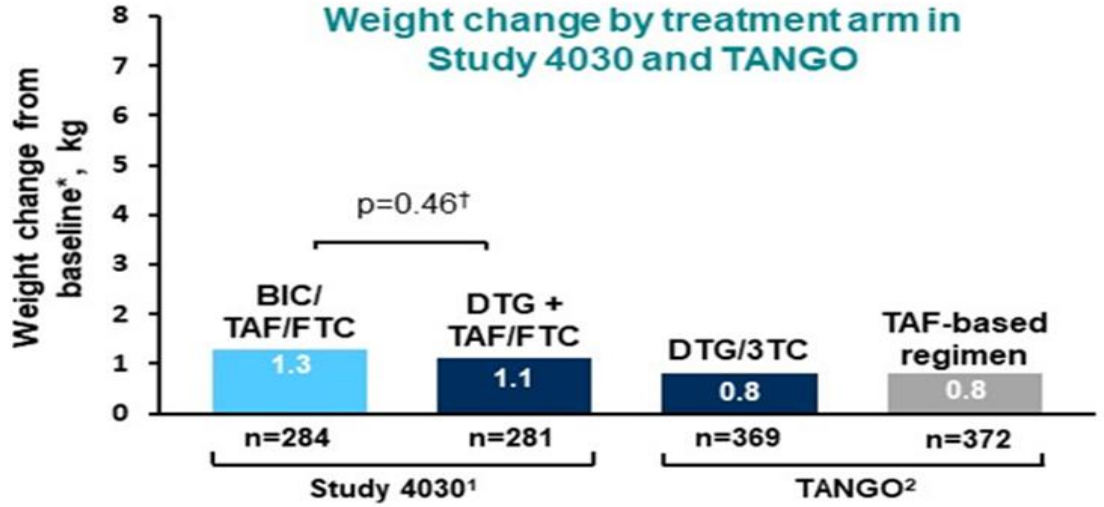
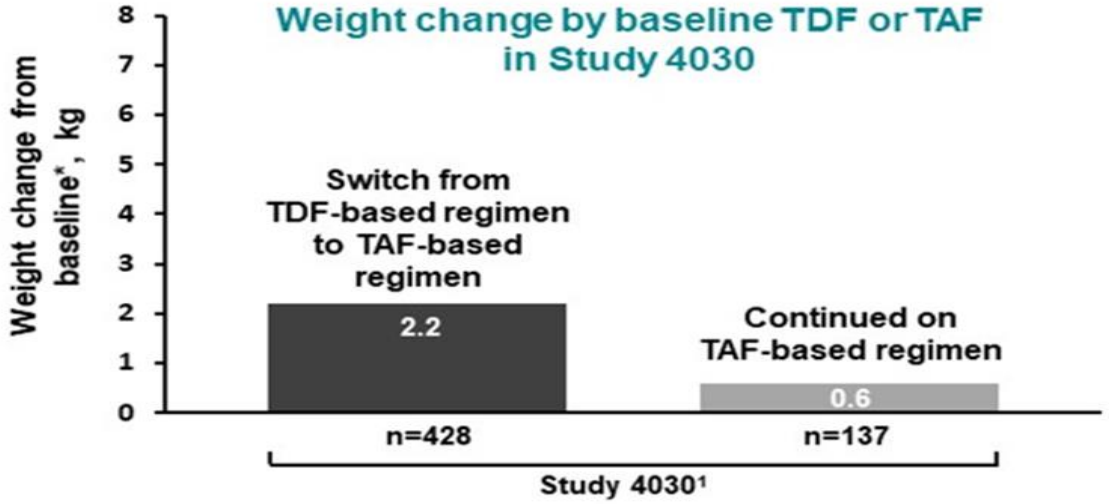
Hill A, et al. IAS 2019. Mexico City, 2019. Oral MOAX0102LB.

Cross-Study Comparison of Switch Studies Evaluating Weight Changes From Baseline To Week 48

- No significant difference in weight change from baseline to Week 48 between BIC/TAF/FTC vs DTG + TAF/FTC in Study 4030[1], or between DTG/3TC vs TAF-based regimens in TANGO[2]
- Participants in Study 4030 who switched from a TDF-based regimen to a TAF-based regimen had a greater increase in weight from baseline than those who continued on a TAF-based regimen, with no difference in weight gain by BIC/TAF/FTC and DTG + TAF/FTC treatment arms[1]





1. Sax P, et al. IAS 2019. Oral MOAB0105; 2. van Wyk J, et al. IAS 2019. Oral WEAB0403LB 3. Gomez M et al. Infection (2019) 47:95–102
*Values were not specified as median or mean; †p-value from Fisher exact test

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Tenofovir Alefenamide (TAF) and Weight Gain

- Possible Association
  - Munich, Germany (switch): Gomez M et al. – switch from TDF to TAF
  - Study 1489 (initial therapy): Wohl et al. – TAF > ABC
  - AMBER study (initial therapy): HIV Glasgow 2018 abstract O212 – TAF > TDF
  - ADVANCE study (initial therapy): Hill et al. – DTG + TAF > DTG + TDF > EFV + TDF
  - Study 4030 (switch): Sax et al. – switch from TDF to TAF

- No Association Found
  - No studies

INSTIs and Weight Gain

- Positive Association
  - NA-ACCORD (initial therapy): CROI 2019 abstract 670 – INSTI (DTG > RAL > EVG) > PI > NNRTI
  - ACTG long-term cohort (switch): CROI 2019 abstract 669 – DTG > EVG > RAL
    - Women, black race, older age ≥ 60 were at greater risk of weight gain
  - NEAT 022 study (initial therapy and switch): Waters et al. – DTG > PIs
  - Parkland, Texas Cohort study (all, including switches): Bedimo et al. – INSTI > PI or NNRTI
    - Women, blacks, and Hispanics were at higher risk for weight gain
  - ***ADVANCE Study (initial therapy): Hill et al. – DTG + TAF > DTG + TDF > EFV + TDF***

- No Association Found
  - TRIO retrospective cohort (switch): CROI 2019 abstract 671
  - HPTN 077 - Cabotegravir in HIV PrEP studies (HIV-negative): CROI 2019 abstract 34
  - ***Study 4030 (switch): Sax et al. – No difference between Dolutegravir and Bictegravir***

Unanswered Questions: Is Weight Gain/Obesity Associated With INSTI or TAF-Based Regimens?

- Recent data suggest that possibly INSTI or TAF-based regimens may be associated with greater weight gain than some other regimens; however, randomized data from initial therapy trials still needed
  - Whether there are differences between INSTIs remains uncertain
- What body composition is increased in association with weight gain?
  - Visceral or subcutaneous fat gain versus muscle?
- What is/are the mechanisms of weight gain?
  - Does not appear to occur via typical mechanisms of dyslipidemia or insulin resistance
  - Off-target effects? Greater drug efficacy? Complete "return to health" with INSTIs?
- Are there differences between the weight gain seen after initiation of antiretroviral therapy and weight gain after switching of ART regimens?
- What are the risk factors for weight gain? Who is at risk for weight gain?
- What are the clinical consequences of weight gain?
- What are potential treatment options in those with significant weight gain?
  - Does changing to another INSTI or to a non-INSTI based regimen lead to weight loss?

Conclusions

- The overall picture regarding the risk factors and causes of various metabolic complications is slowly becoming clearer over time as research continues to evolve
- Dyslipidemia, lipodystrophy, and weight gain/obesity are common comorbidities seen with ongoing HIV infection
- As people with HIV live longer, we can only expect to see more comorbidities
- Understanding the relationship between lipids, fat, and glucose is helpful in managing these metabolic complications
- Weight gain/obesity is increasing in prevalence in people living with HIV, but the exact etiology remains unclear
  - Tracking weight and waist circumference (in a standardized way) may be helpful if we are to begin to study this phenomenon more in depth
- Ultimately, the management and treatment of all of these metabolic complications need to be individualized

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Questions?

What do we do as a community?

- Bullet one goes here.
- More information can go around this
  - Who are we reaching?
  - Why are they targeted?
  - When will we launch?
- One more tidbit then it's complete.