NATIONAL LGBTQIA+ HEALTH EDUCATION CENTER

A PROGRAM OF THE FENWAY INSTITUTE

# HIV and Diabetes

April 30th, 2021

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# About the National LGBTQIA+ Health Education Center

We offer educational programs, resources, and consultation to health care organizations to facilitate affirmative, high quality, cost-effective health care for lesbian, gay, bisexual, transgender, queer and intersex (LGBTQIA+) people.

- Training and Technical Assistance
- Grand Rounds
- Online Learning
  - Webinars, Learning Modules
  - CE and HEI Credit
- ECHO Programs
- Resources and Publications

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# Learning objectives

- Explore best practices for the management of co-occurring HIV and diabetes
- Discuss patient cases highlighting the risk of developing diabetes among patients with HIV
- Discover the metabolic side effects of antiretroviral medications and discuss drug interactions between anti-diabetic and antiretroviral medications

# Disclosures

## Janet Lo, MD, MMSc

- Gilead Sciences – Advisor for Medical Affairs Advisor Program
- Viiv Healthcare – Consultant, co-investigator on investigator-initiated research grant
- Shire, plc – Donation of teduglutide and matching placebo for an NIH-funded study

# Case 1

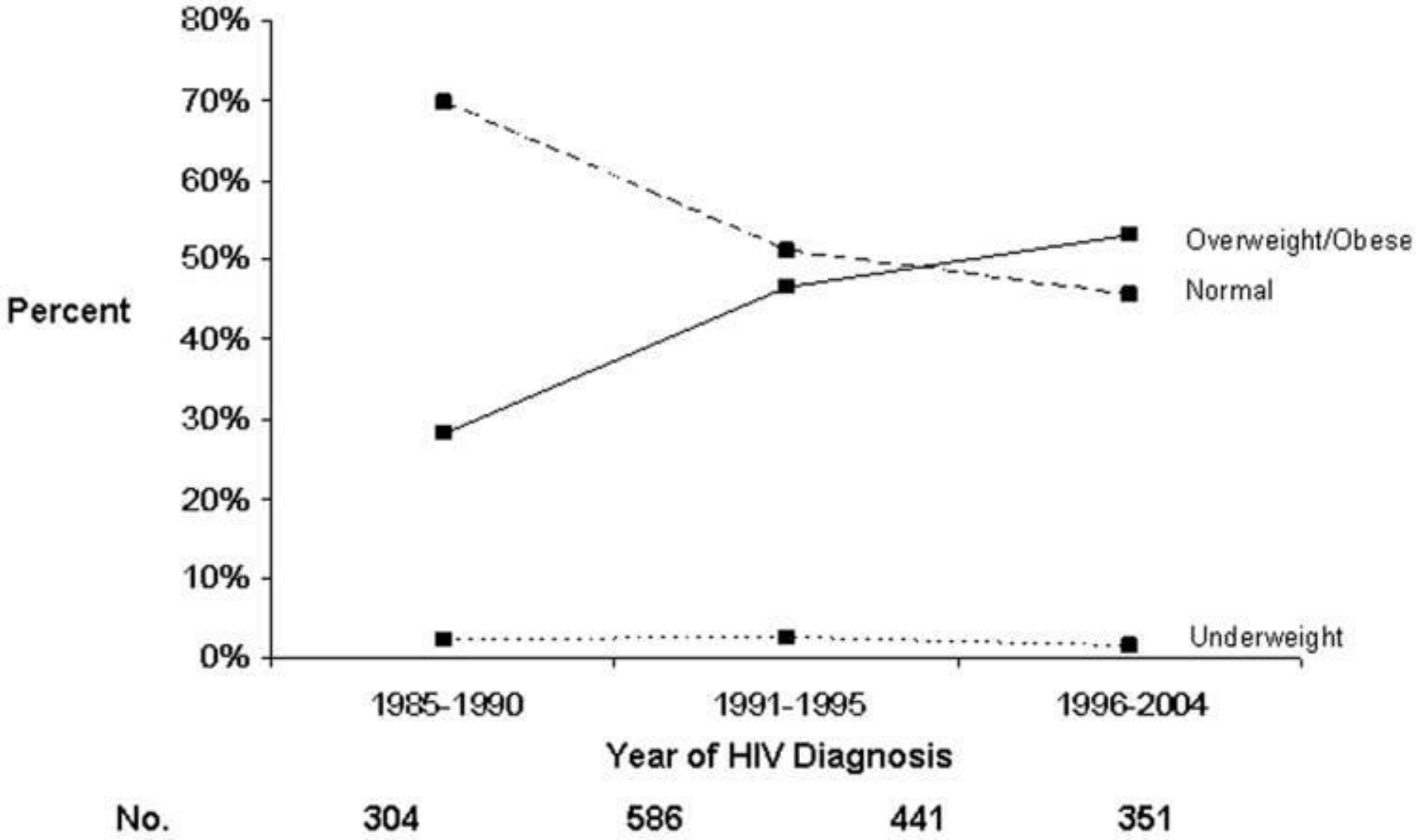
- A 32-year-old cisgender man was diagnosed with HIV on routine screening.
- Upon diagnosis, his HIV-1 RNA was 53,800 copies/mL, and his CD4 cell count was 281 cells/uL.
- He began emtricitabine-bictegravir-tenofovir alafenamide.
- Within 2 months, his viral load was suppressed, and his CD4 count increased to 596 cells/uL.
- Over the next 1.5 years, he gained 25 pounds (most recent BMI 32), and a hemoglobin A1C was 6.2%.

# Questions for case 1

1. What is the relationship between HIV, antiretroviral treatment (ART), weight gain, and metabolic disorders?

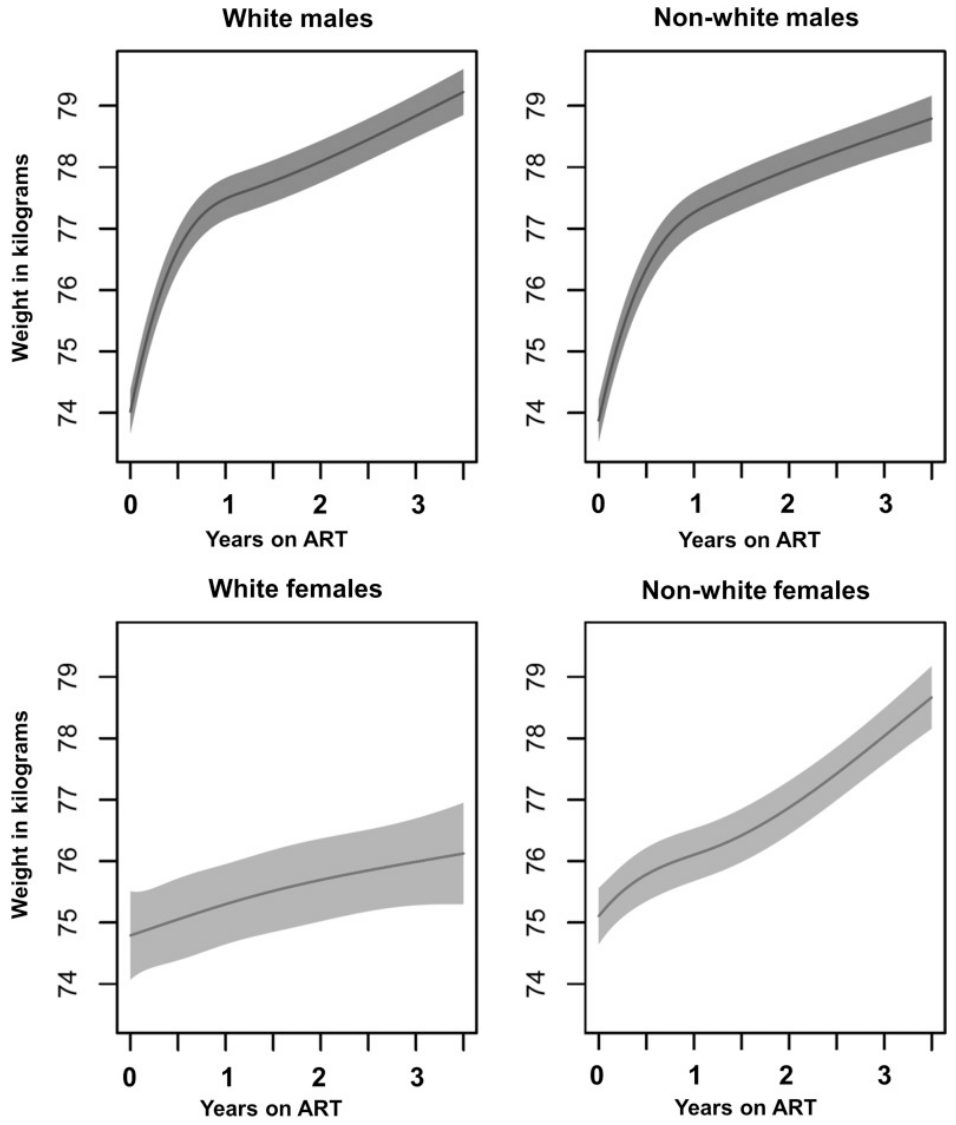
2. What is his risk for diabetes mellitus, and how can that risk be reduced?

# Weight is increasing in people with HIV



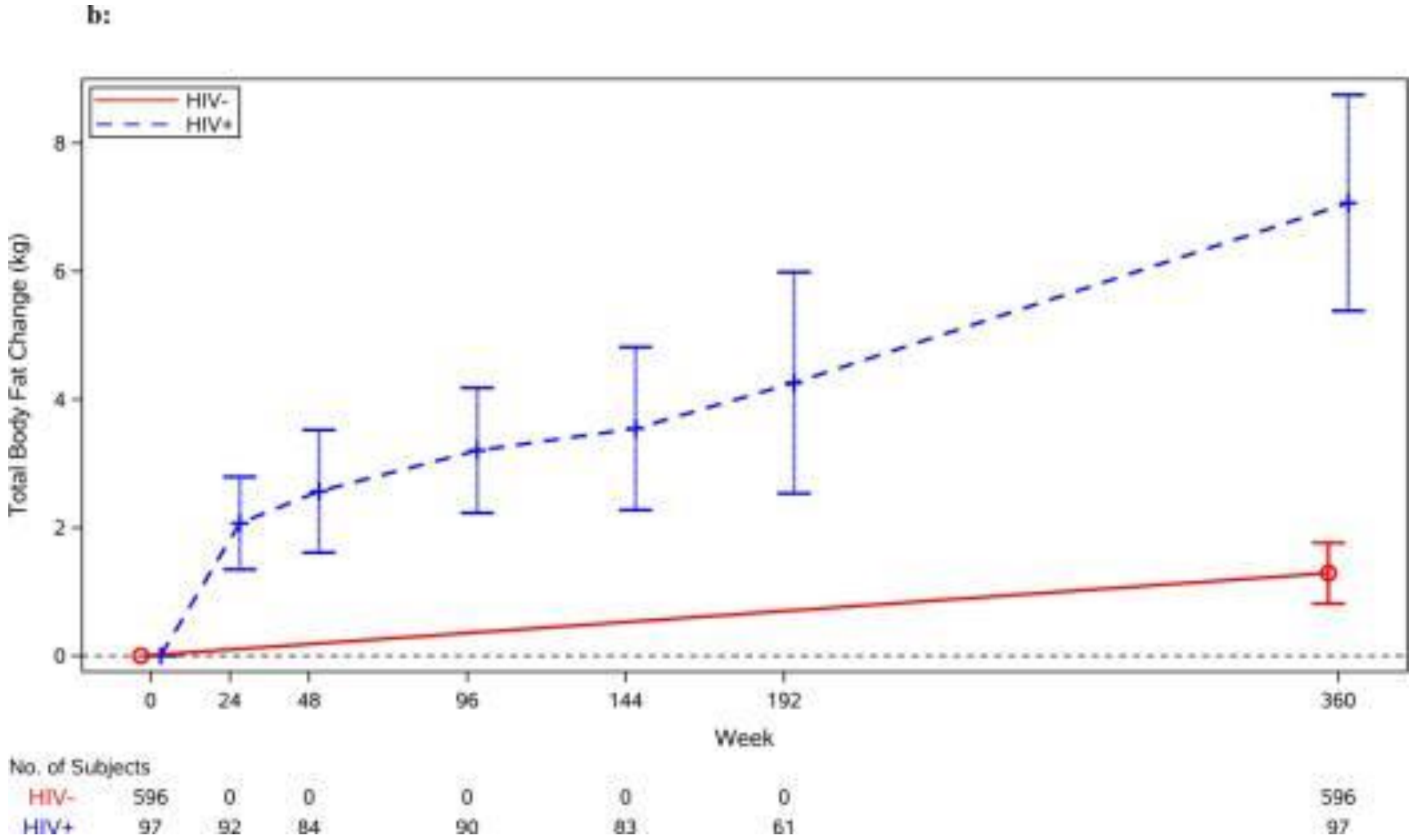

Crum-Cianflone et al. PLOS One 2010

# Weight gain after ART initiation (NA-ACCORD)



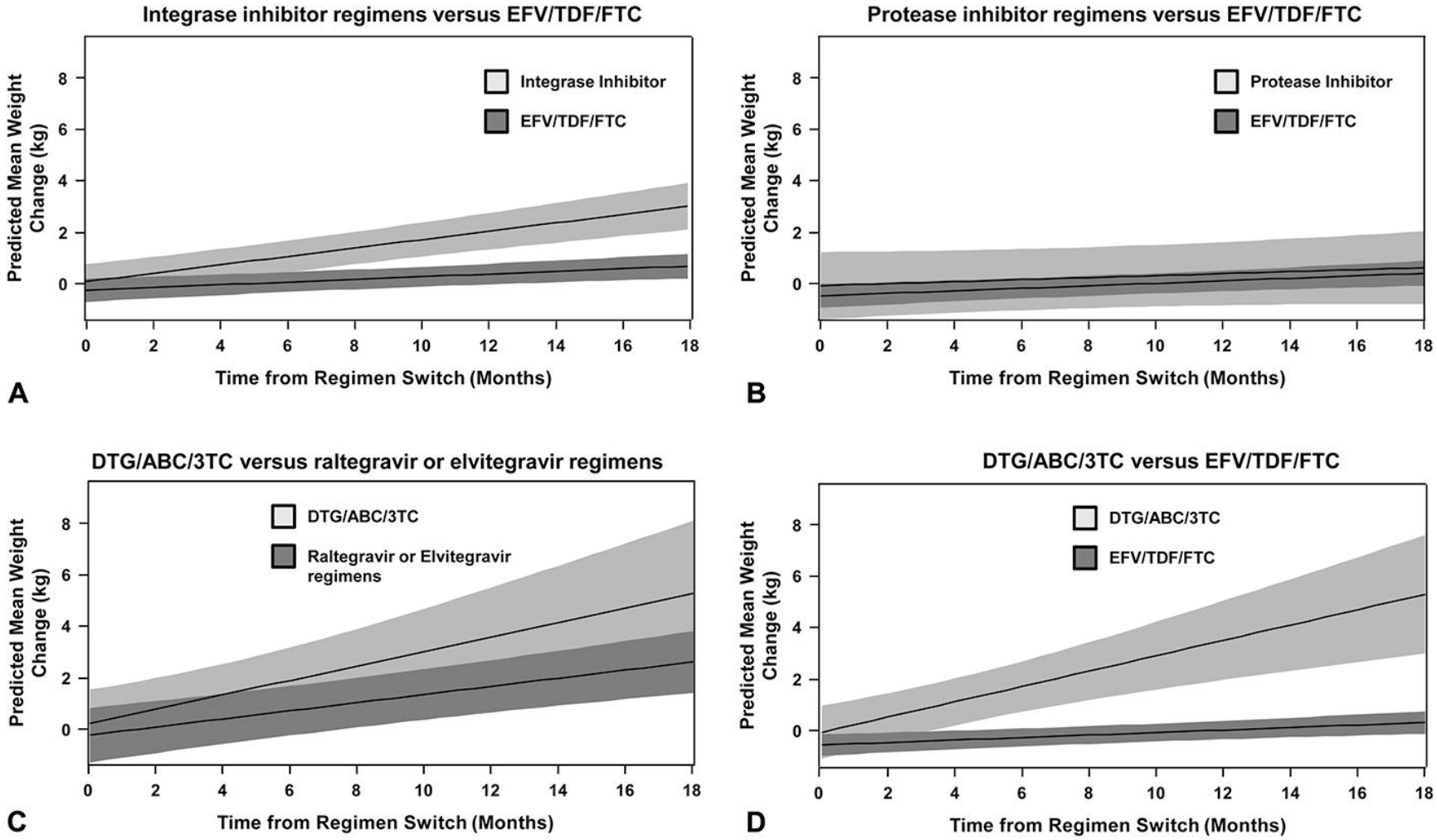

Koethe et al., *AIDS Res Hum Retroviruses 2016*

# Rising body fat in people with HIV




Grant et al. AIDS 2016

# Integrase inhibitors are associated with weight gain





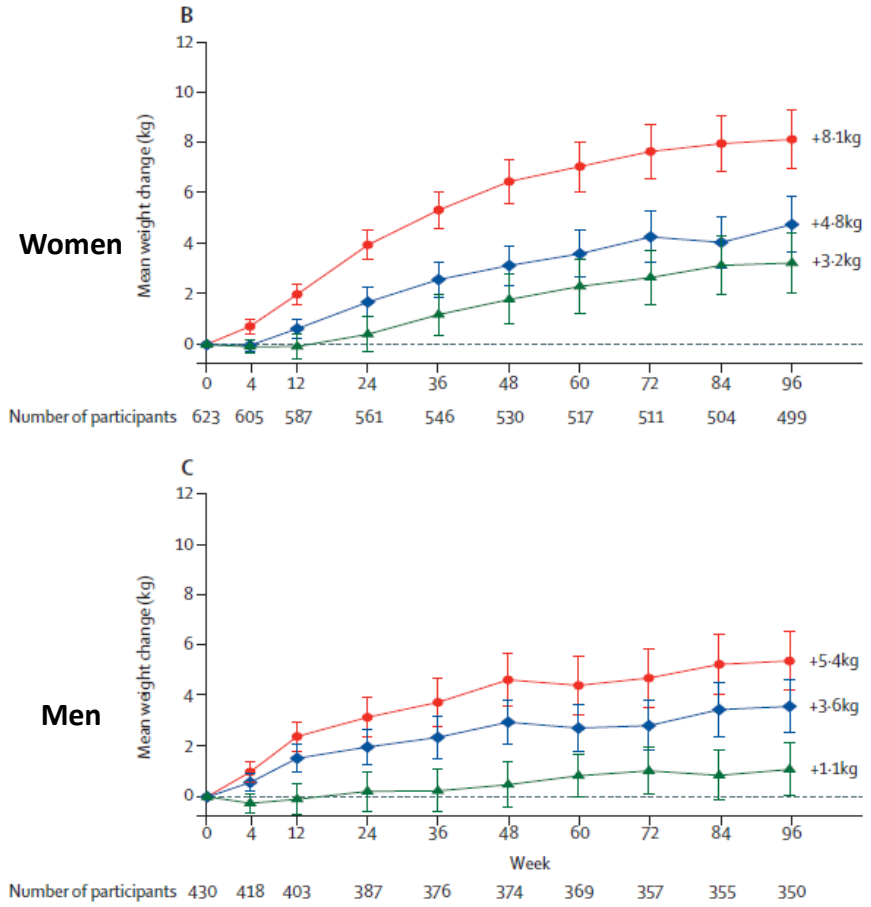

Norwood et al, *JAIDS 2017*

# INSTI and tenofovir alafenamide (TAF) vs. tenofovir disoproxil (TDF): Weight Gain and Metabolic Effects

- **DTG with TAF result in greater weight gain than with TDF, particularly among women**

  - In the 96-week ADVANCE trial, people who started **TAF + emtricitabine + dolutegravir** experienced greater increases in overall **body mass** and **visceral adipose tissue** compared with people who started TDF-based regimens (**TDF + emtricitabine + dolutegravir** and **TDF + emtricitabine + efavirenz**)

  - Within each treatment group, a greater proportion of women developed obesity compared with men. For example, **28% of women vs. 5% of men** on TAF developed obesity

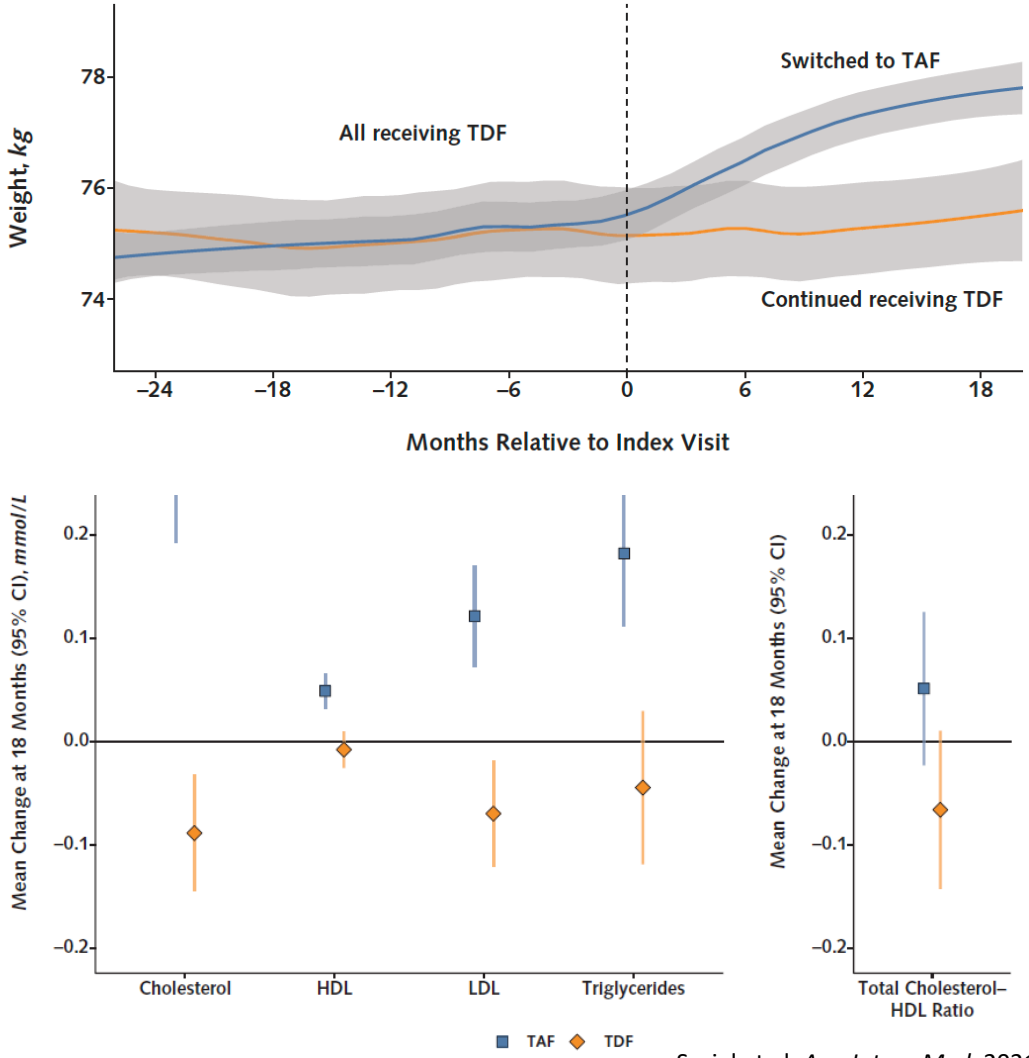



Venter et al. *Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial.* Lancet HIV. 2020 Oct.

# Tenofovir alafenamide (TAF) vs. Tenofovir disoproxil (TDF): Weight Gain and Metabolic Effects

- In a recent 18 month, 4375-participant study, transitioning treatment from TDF to TAF was found to result in increases in body mass, **particularly among women of African origin.** (Surial et al., 2021)

- **Long-term metabolic and cardiovascular effects of TA are not yet clear.**
  - Total cholesterol, HDL, LDL, and triglyceride levels were found to rise in people who transitioned from a TDF- to a TAF-based treatment regimen.
  - TAF was not, however, found to be related to a higher rate of diabetes development. (Surial et al., 2021)
  - ADVANCE trial: Found that total cholesterol and LDL levels increased more among people treated with TAF + dolutegravir than TDF + dolutegravir, but this was not true for HDL, triglycerides, or fasting glucose levels.

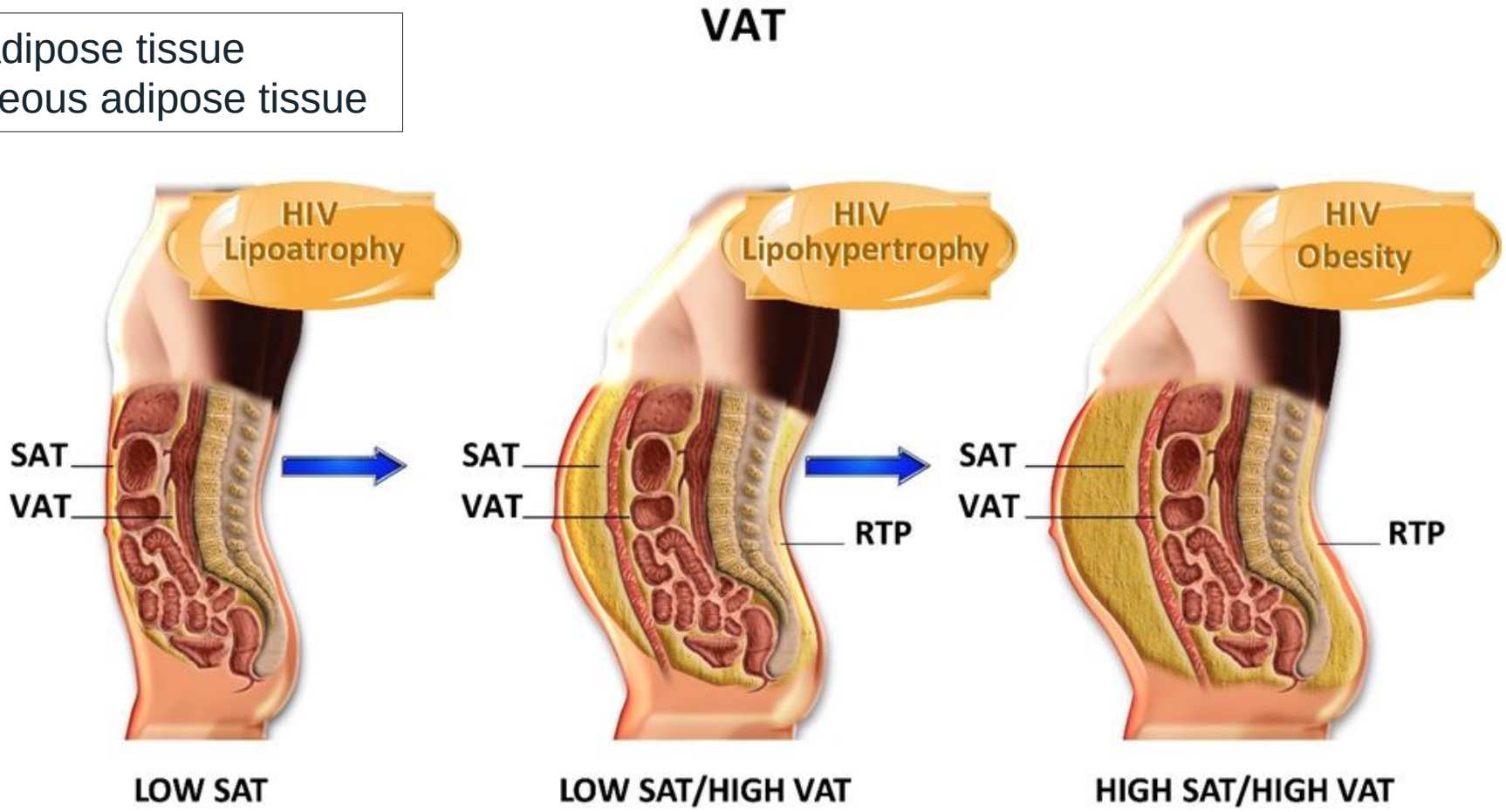





Surial et al. *Ann Intern Med*. 2021 Mar 16.

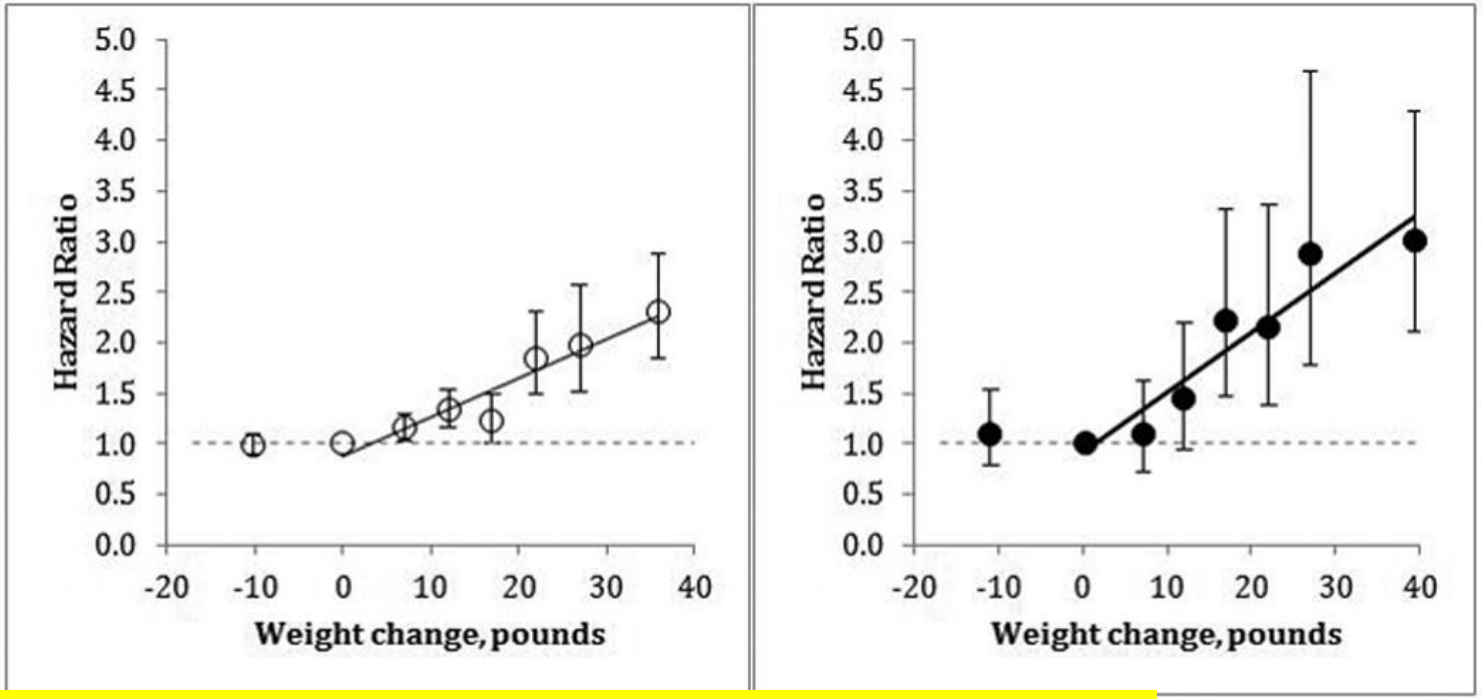
# Spectrum of Body Composition Changes in HIV - Past, Present and Future

VAT = Visceral adipose tissue
SAT = Subcutaneous adipose tissue




Godfrey et al. JID *2019*

# Compared to people without HIV, those with HIV have increased odds of DM as weight increases




For each 5 pounds of weight gained, HIV+ had 14% increased risk of DM (HR, 1.14; 95% CI: 1.10 to 1.17) and uninfected individuals had 8% increased risk (HR, 1.08; 95% CI: 1.07 to 1.10)

Herrin et al. JAIDS 2016

# People with HIV are at risk for poor diet quality

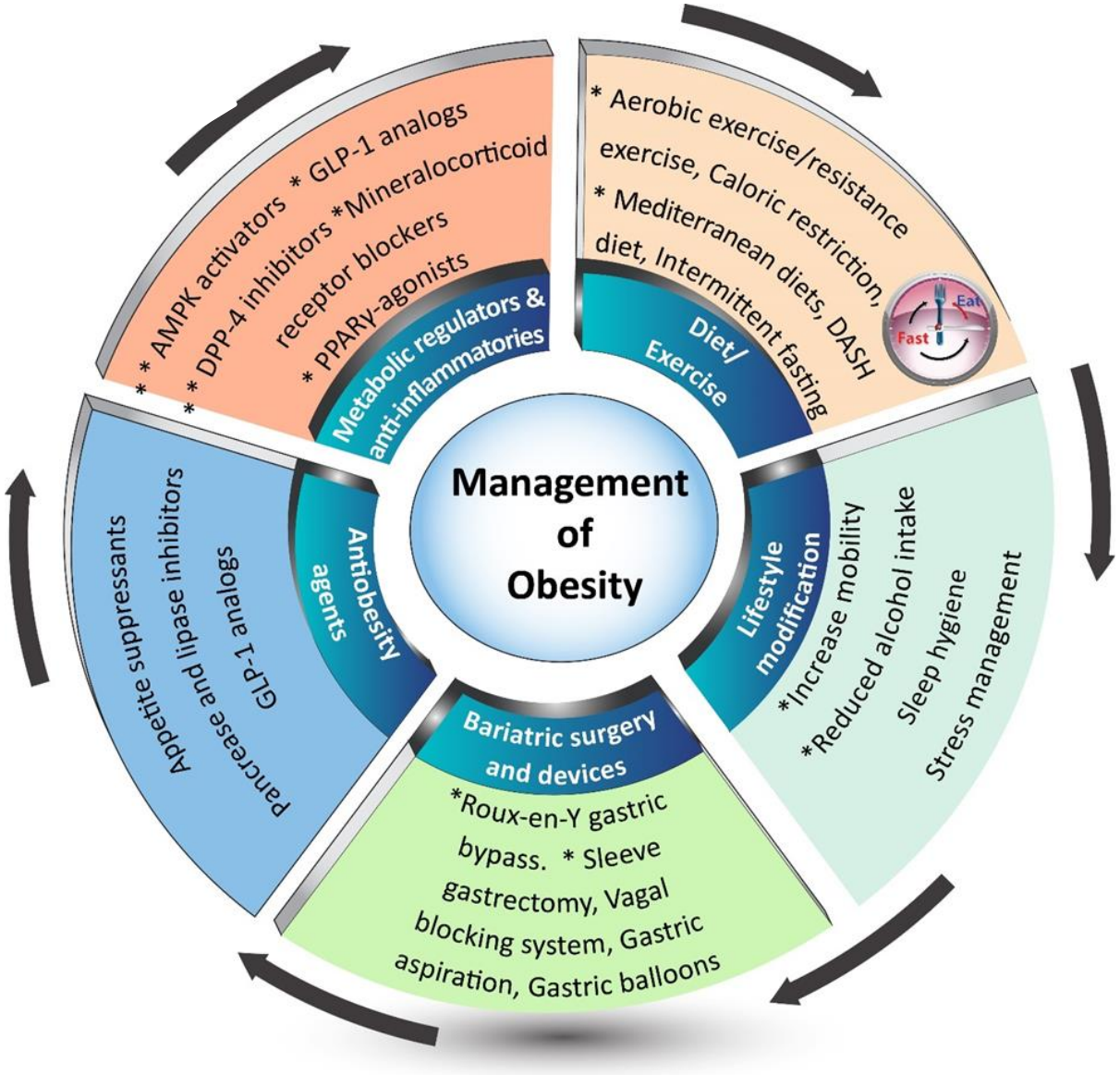
- Diet quality is poor (low for fruits, vegetables, dairy products and dietary fiber; and high for meats and eggs, total fat and cholesterol)
  - Duran et al. J Hum Nutr Diet. 2008

- Diet quality is lower among women with HIV and low diet quality was associated with higher sCD14
  - Weiss et al. J Nutr 2019 (diet quality was even lower among women with HIV)

- Men and women living with HIV consume more than recommended amounts of saturated fat
  - Klassen and Goff, Eur J of Clin Nutrition 2013

- Added sugar intake is also significantly higher among people with HIV
  - Hall et al. OFID 2017

# Treatment strategies for obesity

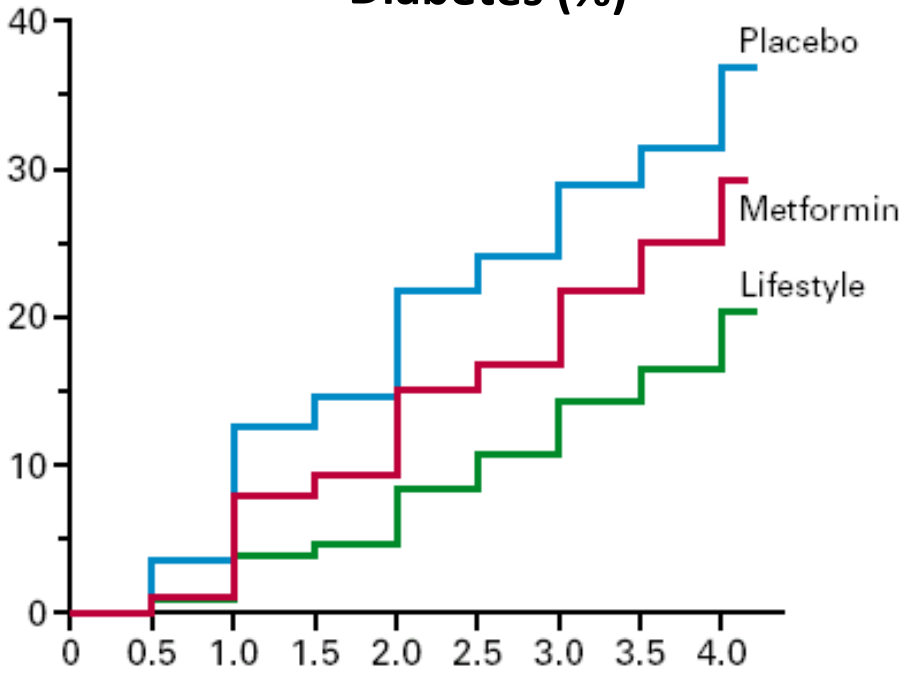



Godfrey et al. Journal of Infectious Diseases *2019*

# Diabetes Prevention Program

**Randomized study to prevent/delay diabetes in 3,234 nondiabetics with elevated fasting and post-load plasma glucose concentrations**

**Cumulative Incidence of Diabetes (%)**

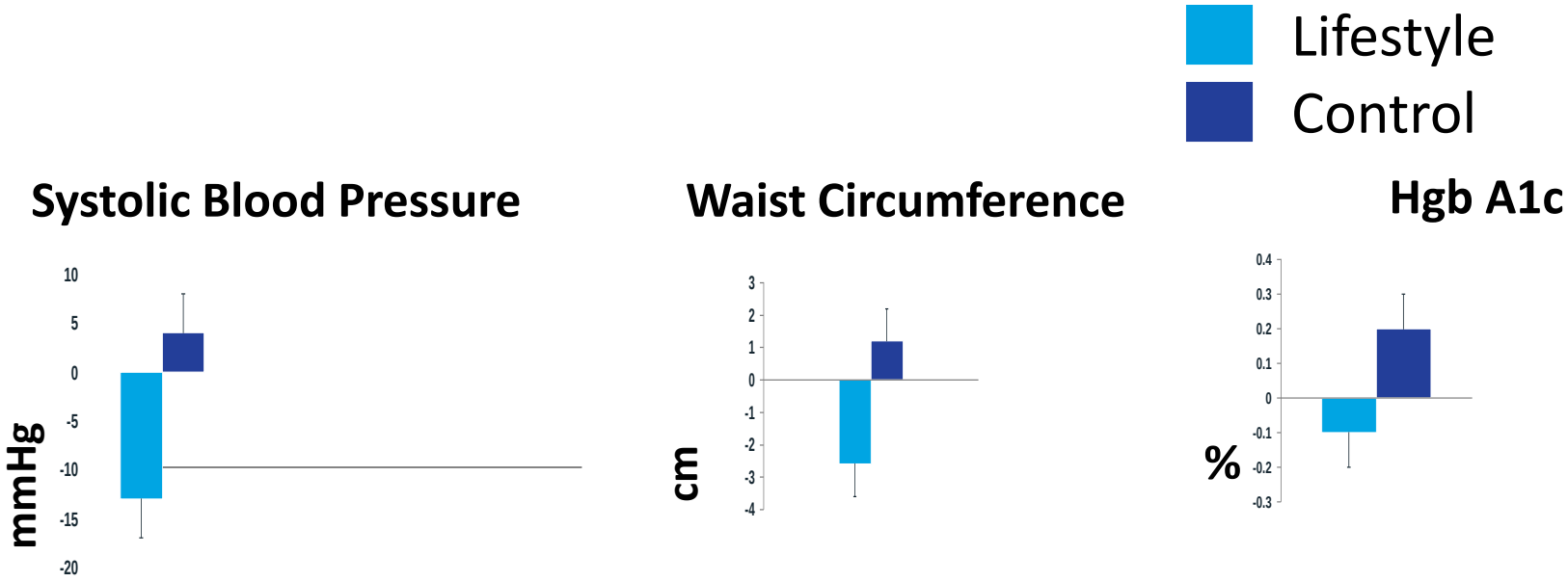



**Lifestyle Goals:** ≥ 7% weight loss/weight maintenance & ≥ 150 min of physical activity (intensity of brisk walking)

1) Individual case managers
2) Frequent contact
3) Behavioral self-management strategies for weight loss and physical activity
4) Supervised physical activity sessions
5) More flexible maintenance intervention of group & individual approaches, motivational campaigns, and "restarts"
6) "Toolbox" of adherence strategies
7) Tailoring of materials and strategies to address ethnic diversity
8) Extensive network of training, feedback, and clinical support


Diabetes Prevention Program Research Group, *NEJM* 2002
Diabetes Prevention Program Research Group, *Diabetes Care* 2002

# A 6-month lifestyle intervention for people with HIV improved metabolic parameters




**p=0.008**

**p=0.022**

**p=0.017**



Fitch et al. *AIDS* 2006

# Diet and physical activity for 6 months in people with HIV with impaired fasting glucose

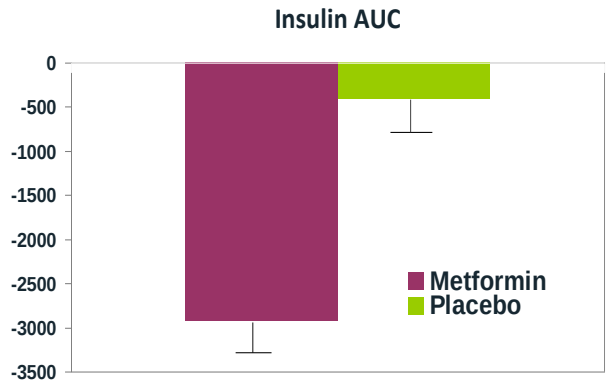
28-person exploratory study in the UK showed that intensive diet and physical activity targeting weight loss can reduce glucose, insulin and waist circumference

| | Standardized goal |
|---|---|
| 1. Energy restriction | Daily energy deficit of 600 kcal |
| 2. Weight reduction | Achieve 7% weight loss in 6 months, or until BMI of 22.5 kg/m$^2$ achieved |
| 3. Waist reduction | Aim to reduce waist size to achieve International Diabetes Federation target: < 90 cm for Asian, 94 cm other men; < 80 cm for women |
| 4. Limit saturated fat | Saturated fat to comprise <10% of mean total daily energy intake |
| 5. Monounsaturated fat | Monounsaturated fat to comprise >15% of mean total daily energy intake |
| 6. Wholegrains | >50% of carbohydrate intake from wholegrains |
| 7. Restrict added sugar | Restrict added sugar to 25g per day or less |
| 8. Sodium restriction | <6 g salt daily (<2.5 g sodium per day) |
| 9. Fruit and vegetables | ≥7 portions fruit and vegetables daily |
| 10. Steps per day | 10 000 steps per day, building gradually by 1000 steps per day until goal achieved or exceeded |

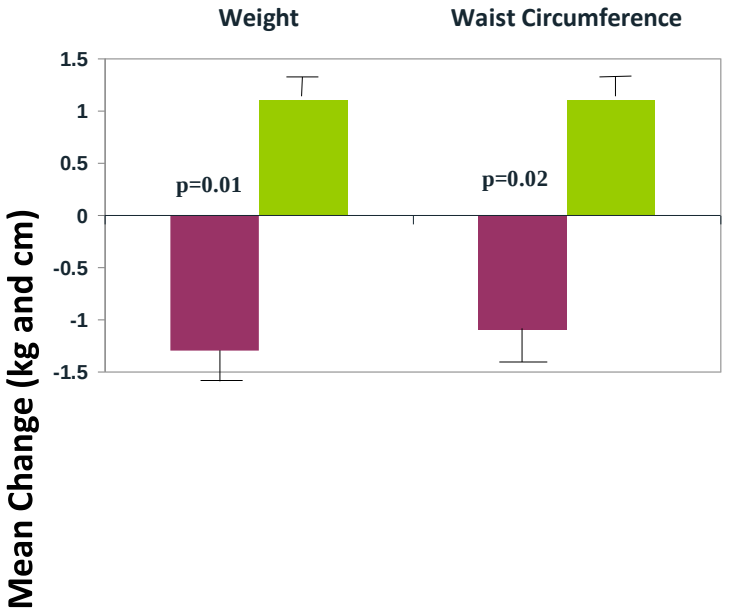
Duncan et al. *Diabetic Medicine* 2019

# Response to metformin in people with HIV with central fat accumulation and insulin resistance

## Metformin 500mg BID versus placebo for 3 months




p=0.01






Hadigan et al. *JAMA* 2000

# Summary of this case

- Weight tends to increase after ART initiation, more so with integrase inhibitor- and TAF-containing regimens than other common ART regimens.

- As weight increases, people with HIV have higher odds of developing diabetes than those without HIV.

- Lifestyle interventions and/or metformin can improve metabolic parameters and prevent diabetes.

# Case 2

- A 65-year-old transgender woman with HIV presents in follow-up. Her HIV has been well-controlled (HIV-1 RNA undetectable, CD4 cell count > 500 cells/uL) on emtricitabine-tenofovir alafenamide and dolutegravir.
- She has a history of cured hepatitis C infection, osteoarthritis, and orchiectomy.
- Routine blood testing shows a fasting glucose of 179. A follow-up hemoglobin A1C is 7.6%.

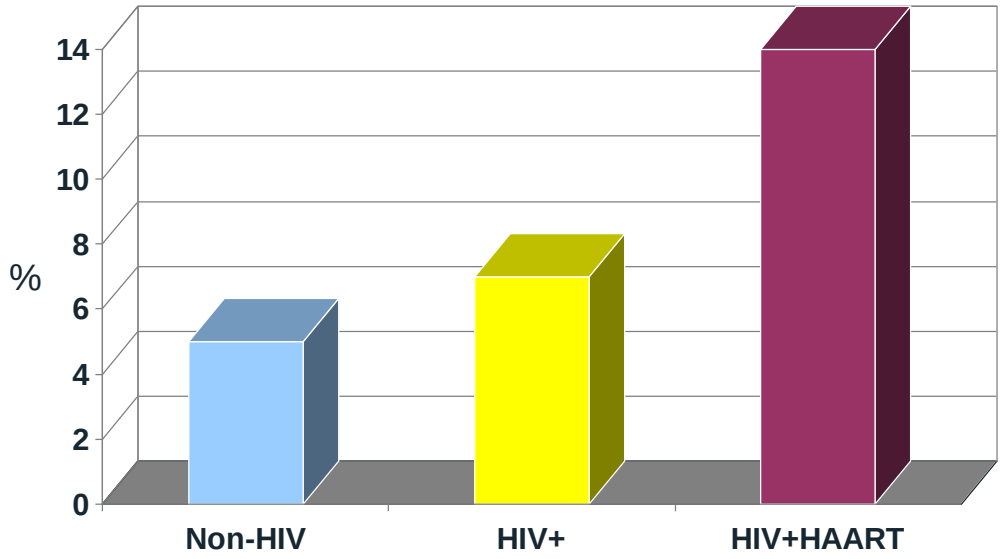
# Questions for case 2

1. What is the next best step in management for the diagnosis of diabetes?

2. Are there drug interactions between antiretrovirals and diabetes medications that need to be considered?

# Prevalence of diabetes by HIV and treatment status

PR= 4.6 *
(CI 3.0-7.1)




Prevalence Ratio = 2.2 *
(CI 1.1-4.4)

* age-BMI adjusted



Brown et al, *Arch Intern Med 2005*

# Prevalence of diabetes mellitus in MMP vs National Health and Nutrition Examination Survey (NHANES)

- Among a nationally representative US sample of adults with HIV receiving medical care in the Medical Monitoring Project (MMP), the prevalence of diagnosed diabetes mellitus (DM) was **10.3%.**
- This was 3.8% higher than the general population in NHANES after adjusting for age, sex, race/ethnicity, education, poverty level, obesity, and HCV infection.
- People with HIV develop DM at younger ages and in the absence of obesity compared with the general US adult population.
- HIV-care providers should screen for diabetes prior to and after starting ART.



Hernandez-Romieu et al, BMJ Open Diabetes Res Care 2017

# Which test would you use to screen for diabetes mellitus in patients with HIV?

1. Fasting glucose
2. Random glucose
3. Oral glucose tolerance test
4. Hemoglobin A1c

# American Diabetes Association Diagnostic Criteria

**Measures of Glucose Homeostasis:**

**Normal:** Fasting glucose (FG) <100mg/dL
2h OGTT glucose <140

**Prediabetes:**
**IFG:** Fasting glucose 100-125mg/dL
**IGT:** 2h glucose 140-199
**Prediabetes:** A1C range of 5.7–6.4%

**Diabetes mellitus:** FG ≥126 or 2h OGTT glucose≥200, Hemoglobin A1c ≥ 6.5%



American Diabetes Association Diagnostic Criteria, *Diabetes Care* 2015

# Primary care guidelines recommend diabetes screening for people with HIV.

"Random or fasting blood glucose and hemoglobin A1c (HbA1c) should be obtained prior to starting ART. If random glucose is abnormal, fasting glucose should be obtained. After initiation of ART, only plasma glucose criteria should be used to diagnose diabetes. Patients with diabetes mellitus should have an HbA1c level monitored every 6 months with an HbA1c goal of <7%, in accordance with the American Diabetes Association Guidelines."

Thompson MA, Clin Infect Dis, 2020

# Hemoglobin A1c in people with HIV

**Caveat: Hemoglobin A1c may be inaccurate and underestimate serum glucose in PWH**

It is also important to consider age, race/ethnicity, and anemia/hemoglobinopathies when using the A1C to diagnose diabetes.

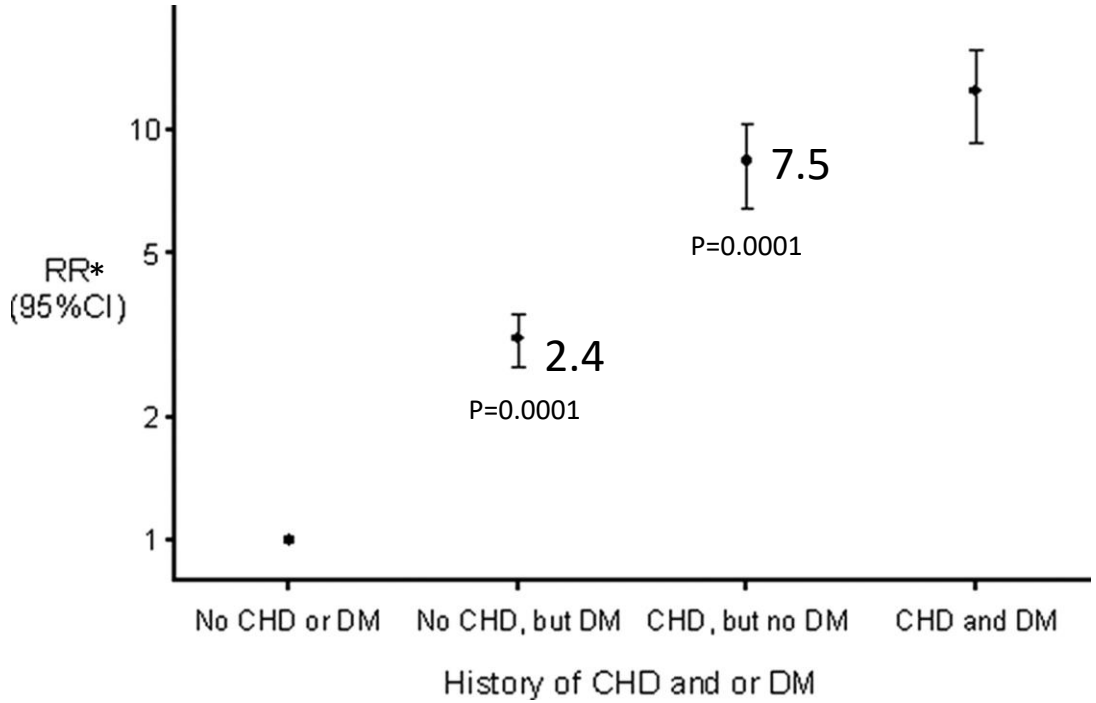
Kim et al. *Diabetes Care* 2009;
Diop et al. *AIDS Res and Hum Retrov* 2006;
Slama et al. (MACS study) *Journal of Antimicrobial Chemotherapy* 2014;
Muchira et al. Int J STD AIDS. 2019

# The oral glucose tolerance test (OGTT) may improve sensitivity for diabetes among women with HIV.

- In Women's Interagency HIV study, DM prevalence was 5.6% in women with HIV vs. 2.8% in HIV negative control women
- Adding 2h OGTT glucose $\geq$ 200 increased prevalence to 7.4% in HIV+ women
- OGTT identified 31% relative increase in number of diabetes cases in HIV + women
- No additional cases were diagnosed by OGTT in HIV negative women

Seang et al., *J AIDS Clin Res 2016*

# DM Increases Risk of coronary heart disease (CHD) Event in HIV




Evaluation of the impact of DM and preexisting CHD on the development of a new CHD episode
among 33 347 HIV+ pts in D:A:D Study with over 159,971 person-years and 698 CHD events

- **Risk of new CHD event is 2.4x higher in those with DM and no pre-existing CHD**

* After adjustment for gender, age, cohort, HIV transmission, ethnicity, family history of CHD, smoking, and calendar year, the rate of a CHD episode

Worm et al, *Circulation 2009*

# Potential Mechanisms of Insulin Resistance and Diabetes in HIV

- Fat redistribution and altered adipokines
- Obesity
- PI and NRTI associated with DM (Swiss HIV Cohort Study, Ledergerber et al. *CID* 2007)
- Protease inhibitors reduce glucose transporter (Glut 4)
- Increased inflammation and inflammatory cytokines
- Hepatitis C co-infection is associated with higher risk of diabetes in HIV patients (Veterans Aging Cohort Study, Butt et al. *AIDS* 2009)

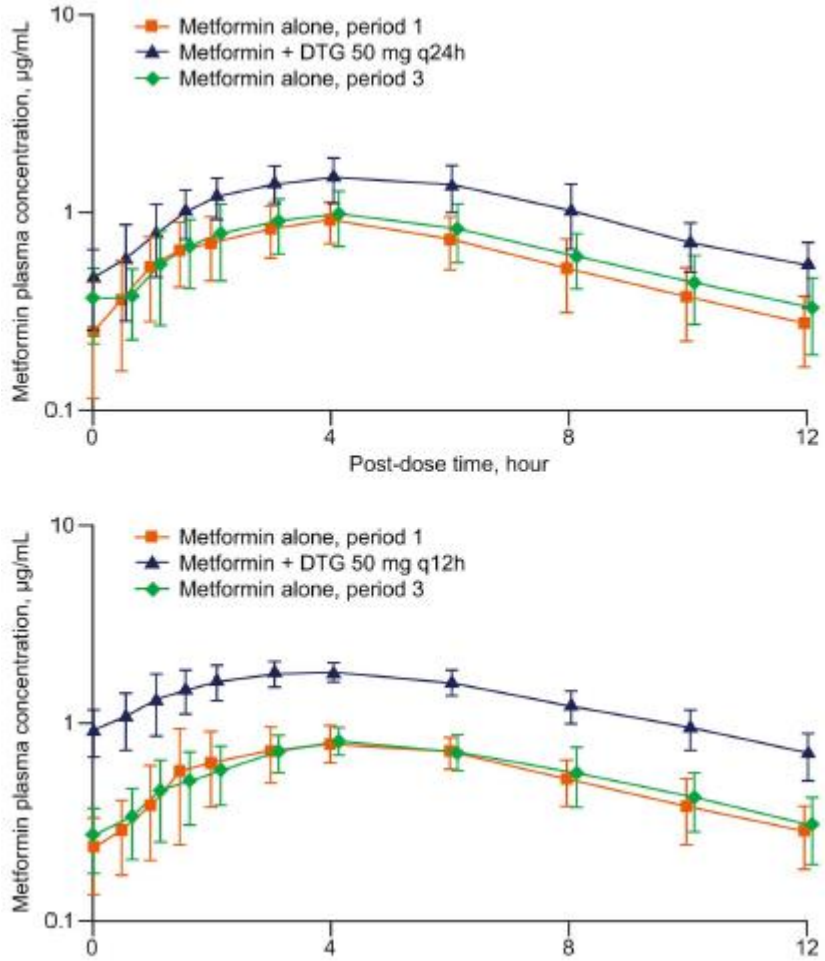
# Treatment Strategies for those with Prediabetes and Diabetes

- **Diet and exercise**, first and foremost
- **Metformin** for IFG, IGT or type 2 DM
- **GLP-1 agonists and other second-line antidiabetic agents** when metformin alone fails

GLP-1: Glucagon-like peptide-1

Approved **GLP-1 agonists**:
exenatide (Byetta/Bydureon), approved in 2005/2012
liraglutide (Victoza, Saxenda), approved 2010
ixisenatide (Lyxumia), approved in 2016

# Metformin-dolutegravir Interaction




| Dolutegravir (DTG) | |
|---|---|
| **Study Design** | Open-label, parallel-group, multi-dose, 3-period crossover study in healthy adults |
| **Mechanism** | partially explained by OCT2 inhibition |
| **Pharmaco-kinetics** (metformin) | DTG 50 mg q24h<br>• ↑ AUC 79% & Cmax 66%<br>DTG 50 mg q12h<br>• ↑ AUC 145% & Cmax 111% |
| **Management** | Metformin dose adjustment should be considered when starting or stopping DTG<br><br>Avoid metformin >1000mg per day |



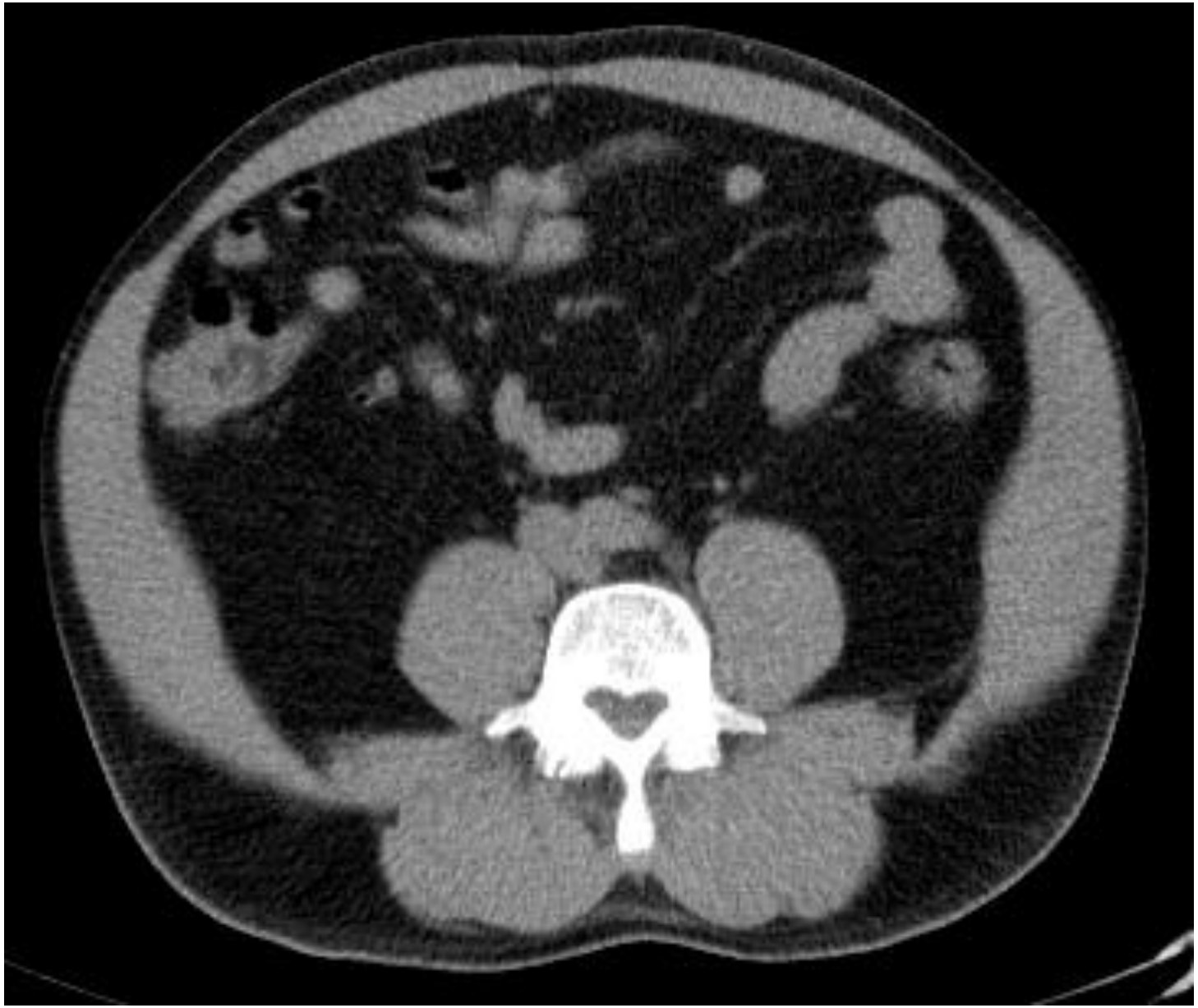
Song IH, et al. JAIDS 2016;72:400–407

# Summary of this case

- Screen all patients with HIV for diabetes mellitus
- Glucose should be assessed before initiating ART and during follow-up.
  - IDSA recommends fasting glucose and/or hemoglobin A1c prior to starting ART, and fasting glucose only while on ART.
- Hemoglobin A1c may underestimate glucose in people with HIV.
- Diet and exercise can improve glucose control.
- Treatment of diabetes should follow current guidelines for the general population.
- Caution regarding high-dose metformin and dolutegravir

# Case 3

- A 68-year-old cisgender man with longstanding but well-controlled HIV (HIV-1 RNA undetectable, CD4 cell count 381 cells/uL) on lamivudine, raltegravir, and maraviroc presents for monitoring while on tesamorelin for visceral fat accumulation.
- He has taken tesamorelin for 4 months, losing 3.3 kg.
- Laboratory studies show an increase in hemoglobin A1C from 5.9% prior to initiation of tesamorelin to 6.7% today.



**CT (performed for research purposes) showing limited subcutaneous fat but extensive visceral fat**

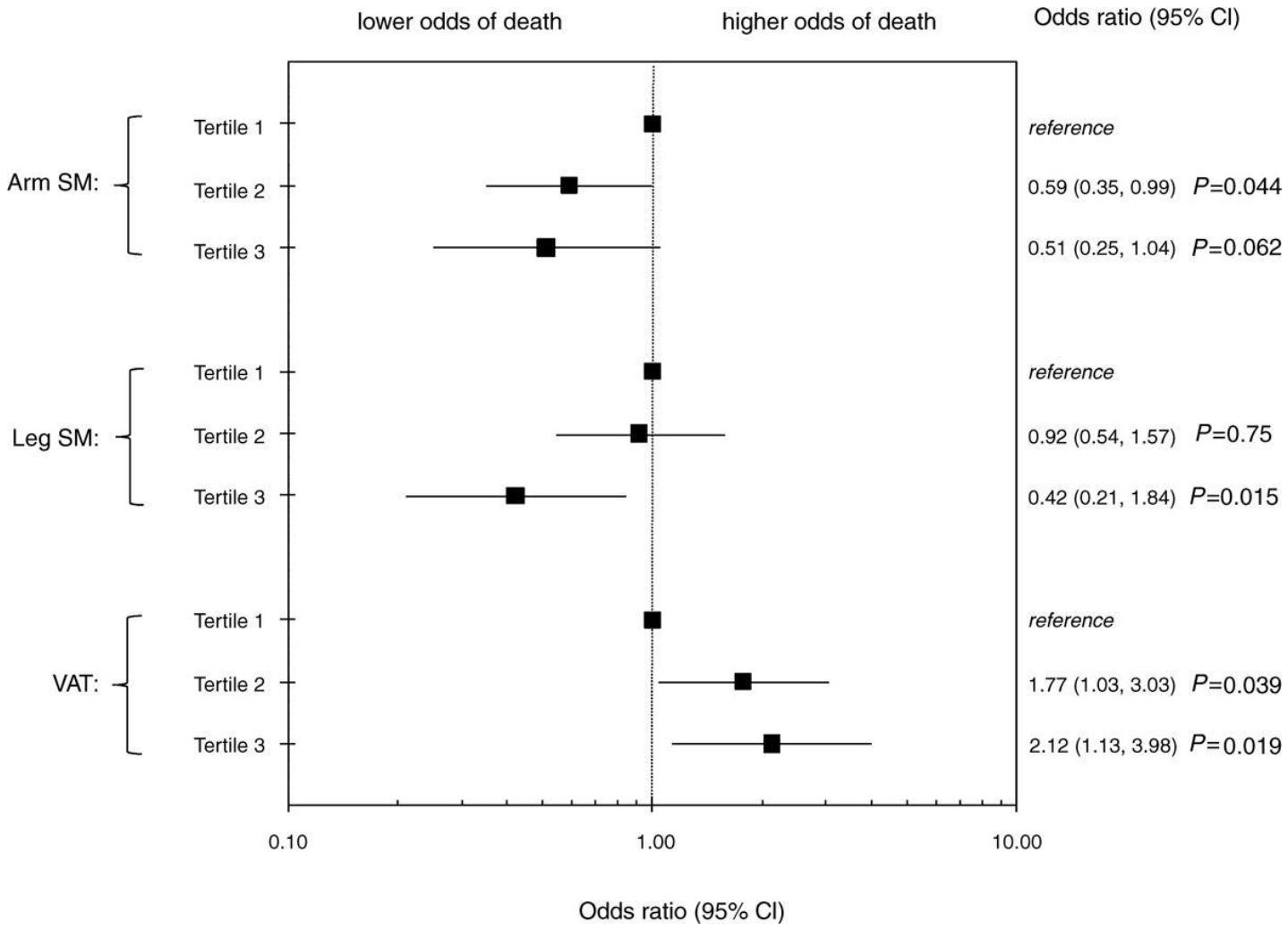
# Questions for case 3

1. What is tesamorelin and what is its role in managing HIV-associated visceral fat accumulation?

2. What is the relationship between tesamorelin and blood glucose?

3. What is the next best step in management for this patient?

# Increased VAT is independently associated with higher mortality risk



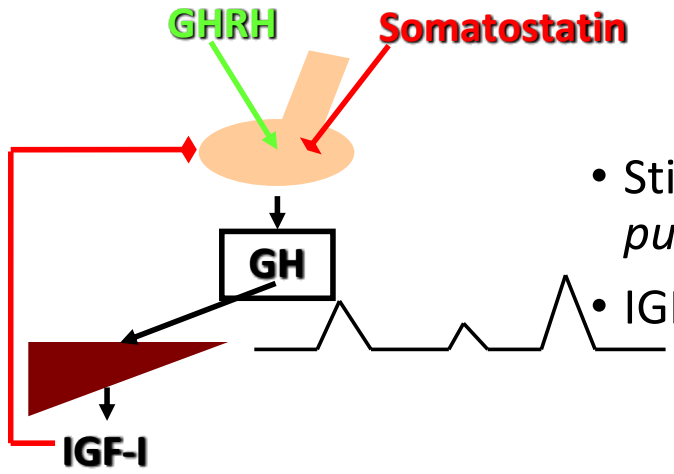

Estimates from multivariable adjusted models controlling for age, sex, race, traditional CVD risk factors, HIV-related factors, CRP, fibrinogen, GFR, albuminuria, arm SM, leg SM, and VAT



Scherzer et al (FRAM). *AIDS* 2011

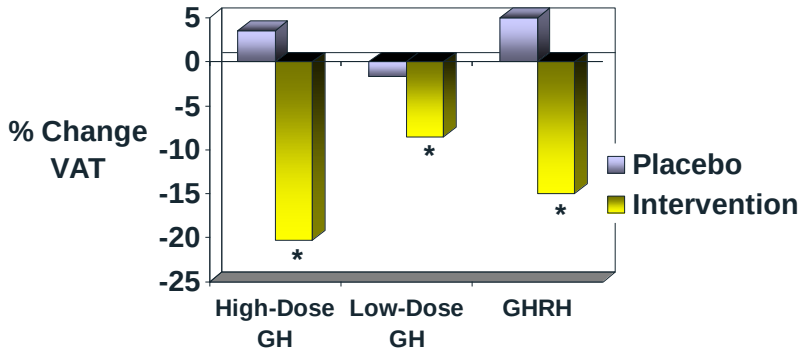
# Tesamorelin

- Synthetic analogue of human 1-44 growth hormone-releasing factor
- Induces secretion of growth hormone (GH) in a pulsatile manner
- FDA-approved to reduce excess abdominal fat in HIV-infected patients with lipodystrophy




- Stimulates endogenous *pulsatile* GH release
- IGF-1 feedback intact

# Comparison of High Dose GH, Low Dose GH and GHRH

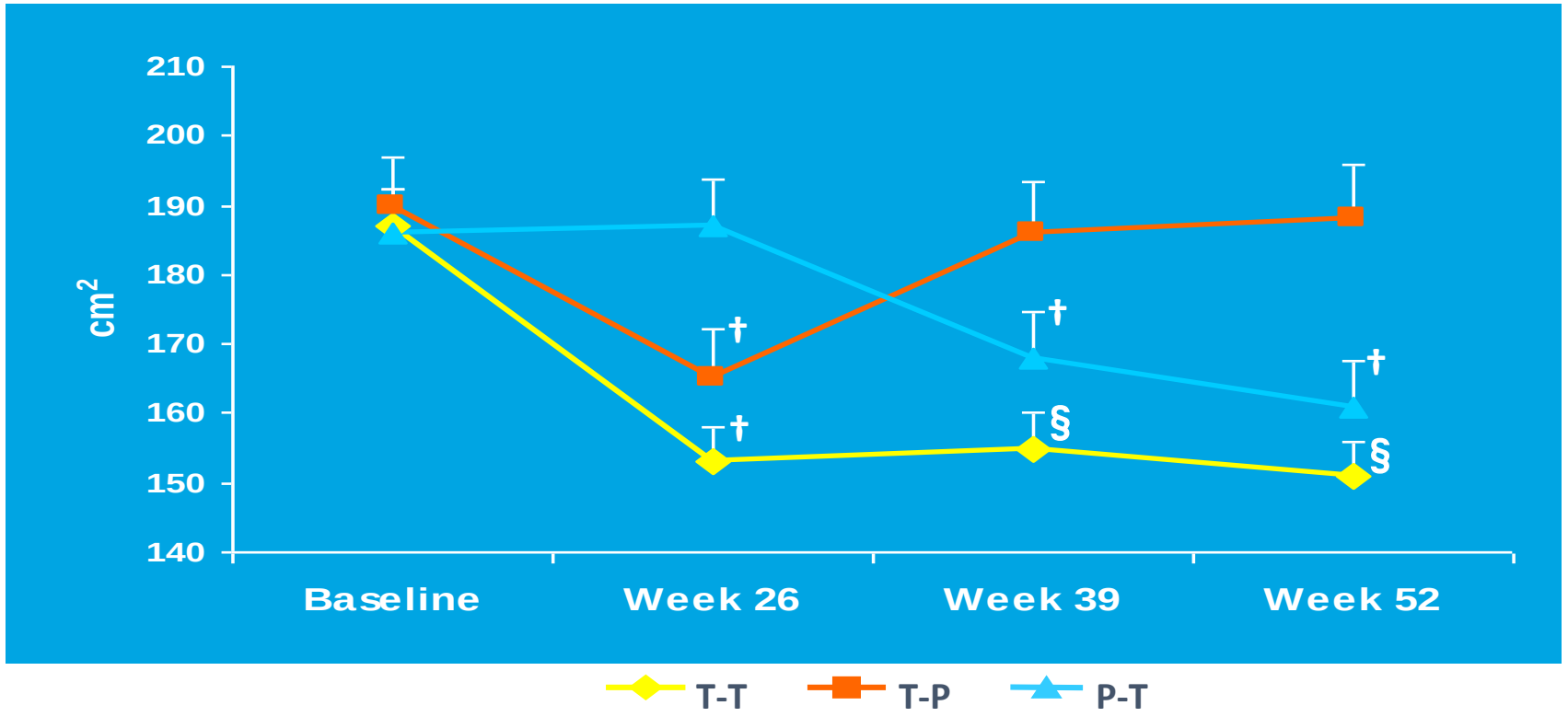



| | High-Dose GH[1] | Low-Dose GH[2] | GHRH[3] |
|---|---|---|---|
| Dose | 4 mg/d | 0.3 mg/d | 2 mg/d |
| Duration | 3 Months | 18 Months | 6 Months |
| IGF-I | Supra-physiologic | Physiologic | Physiologic |
| Triglycerides | Improved | Improved | Improved |
| Glucose | Worsened | Worsened | No change in initial trials |
| Side Effects | Significant | Well-tolerated | Well-tolerated |



[1]Grunfeld et al. JAIDS 2007, [2]Lo et al. JAMA 2008, [3]Falutz et al NEJM 2007

# Tesamorelin's effects on VAT




**Data are Mean ± SEM. § P<0.001 vs. Baseline and vs. T-P. †P<0.001 vs. BL.**



Falutz et al., NEJM 2007, AIDS 2008, JAIDS 2010, JCEM 2010

# Tesamorelin

- Treatment with 2 mg tesamorelin daily:
  - Reduces VAT
  - Improves lipids
  - Preserves SAT
  - Reduces liver fat
  - Improves body image
- Treatment with tesamorelin is overall well tolerated, however, it can worsen glucose in susceptible individuals
- Tesamorelin may be a useful strategy, with an acceptable benefit/risk profile, to preferentially decrease VAT and improve body image, while improving lipids in HIV-infected patients with excess abdominal fat

# FDA Label for tesamorelin (Egrifta)

- EGRIFTA treatment can result in glucose intolerance.
- During clinical trials, the percentages of patients with elevated HbA1c (≥ 6.5%) from baseline to Week 26 were 5% and 1% in the EGRIFTA and placebo groups, respectively.
- An increased risk of developing diabetes with EGRIFTA (HbA1c level ≥ 6.5%) relative to placebo was observed [intent-to-treat hazard odds ratio of 3.3 (CI 1.4, 9.6)].
- Evaluate glucose status prior to initiating EGRIFTA. Monitor all patients treated with EGRIFTA periodically to diagnose those who develop impaired glucose tolerance or diabetes. If patients treated with EGRIFTA develop glucose intolerance or diabetes, consider discontinuing EGRIFTA in patients who do not show a clear efficacy response.
- EGRIFTA increases IGF-1, monitor patients with diabetes who are receiving treatment with EGRIFTA at regular intervals for potential development or worsening of retinopathy.

# Summary of this case

- Tesamorelin is an FDA-approved treatment for HIV-associated lipohypertrophy.

- However, it can worsen glucose control

# Conclusions

- **Significant weight gain occurs with ART even in the current era of modern ART and normal BMI at initiation**
- **Weight and visceral fat can increase in the first years after ART**
- **All people with HIV should be screened for DM**
- **Glucose:**
  - IDSA recommends fasting glucose and/or hemoglobin A1c prior to ART and fasting glucose thereafter
  - *Caveat is A1c may underestimate glucose in HIV patients*
  - *Suggest following fasting glucose at least once a yr in those at risk for DM*
- **Dietary and lifestyle counseling first and foremost**
- **Pharmacologic therapy depending on co-morbid conditions**
  - **Metformin**
  - **Tesamorelin may be effective in lowering VAT, TG, and liver fat in patients with HIV-associated lipohypertrophy**