ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE - AIDS 2023

METABOLIC DISEASE IN PEOPLE LIVING WITH HIV

PRINCIPLES OF OBESITY AND DIABETES MANAGEMENT

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Disclosures

I am a site Principal Investigator for clinical trials funded by Regeneron Pharmaceuticals and GSK.

OVERVIEW

- Obesity and its link to diabetes in PLWH on modern ART
- Managing obesity and preventing diabetes in PLWH
- Diabetes care in PLWH – a few pearls…

Learning objectives

Learning objectives

1. Review what is known about the risk of obesity and its link to diabetes in PLWH on modern antiretroviral therapy regimens

2. Identify key strategies to manage obesity and prevent diabetes in PLWH

3. Describe several key principles of diabetes management and specific considerations in PLWH

Obesity and its link to diabetes in PLWH on modern ART

Case #1 (Part I)

47 year old man who was diagnosed with HIV in 2012

Off ART for 1 year, current HIV VL = 40,552

Started on TLD and achieved viral suppression within ~3 months

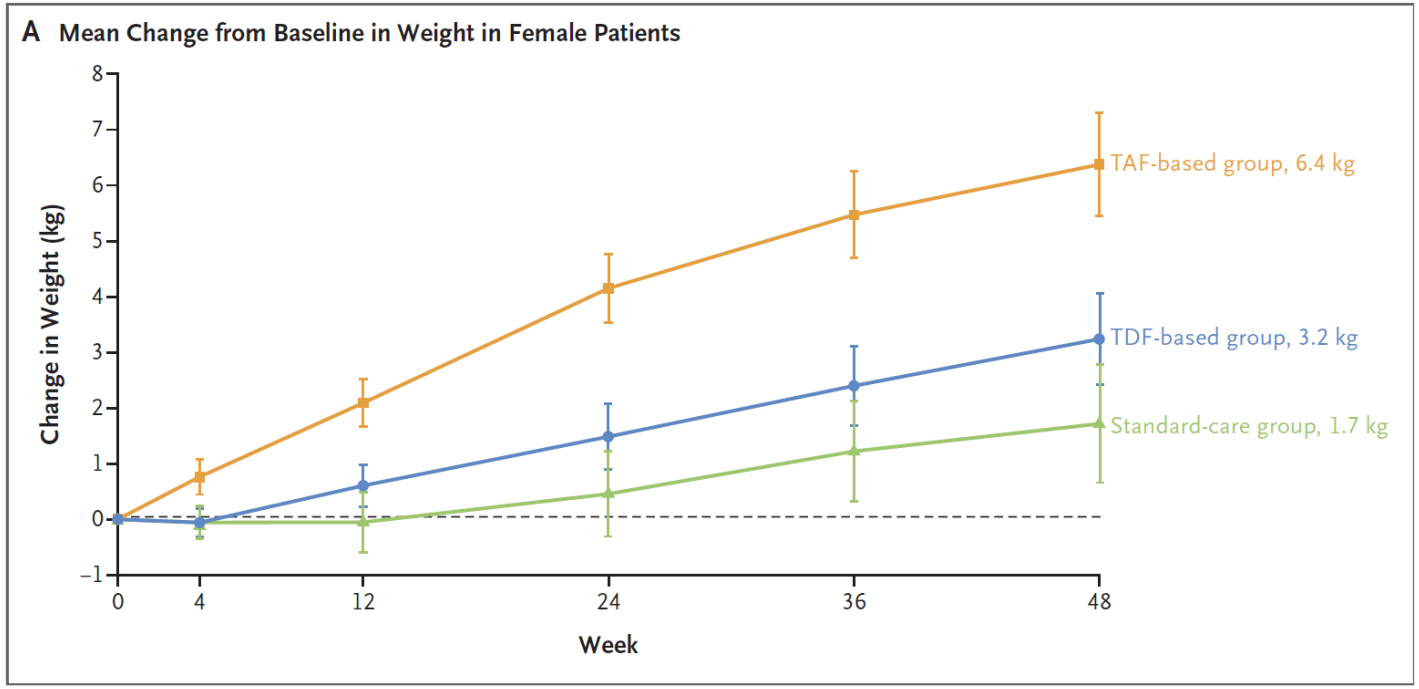
Over the next year, gained about 46 pounds…

Obesity & type 2 diabetes growing health threats for PLWH globally

Millions of PLWH now transitioned to "modern ART" (DTG, TAF, etc.)

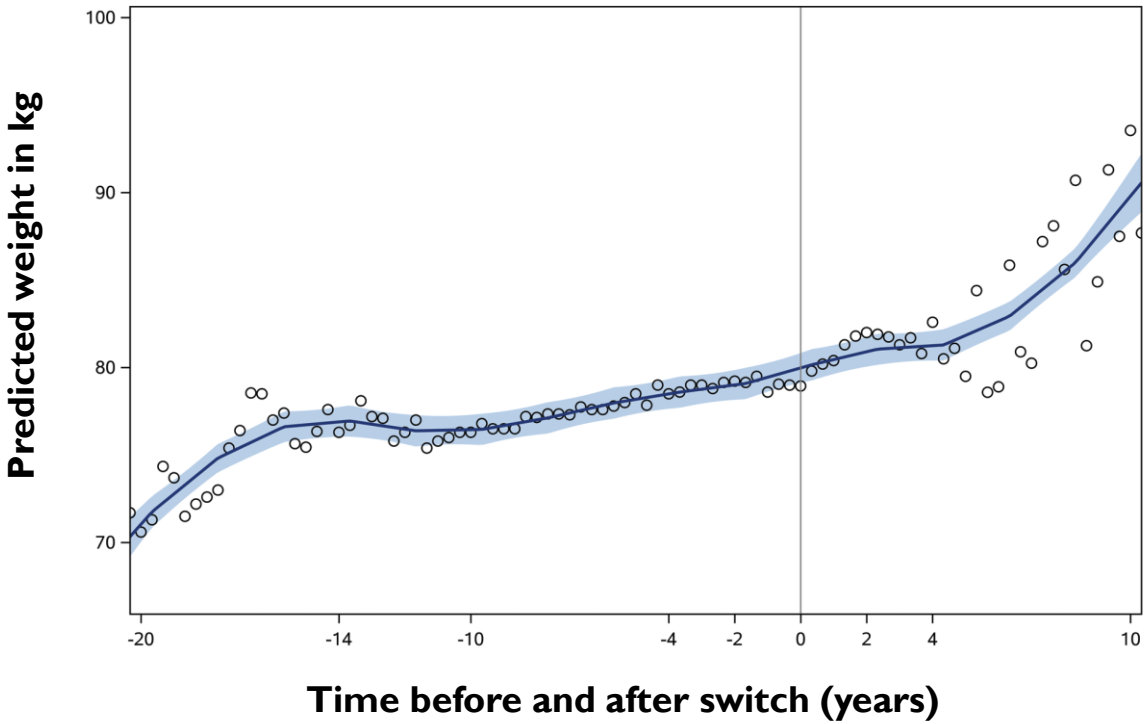
Obesity epidemic has high overlap with HIV epidemic, including in South Africa

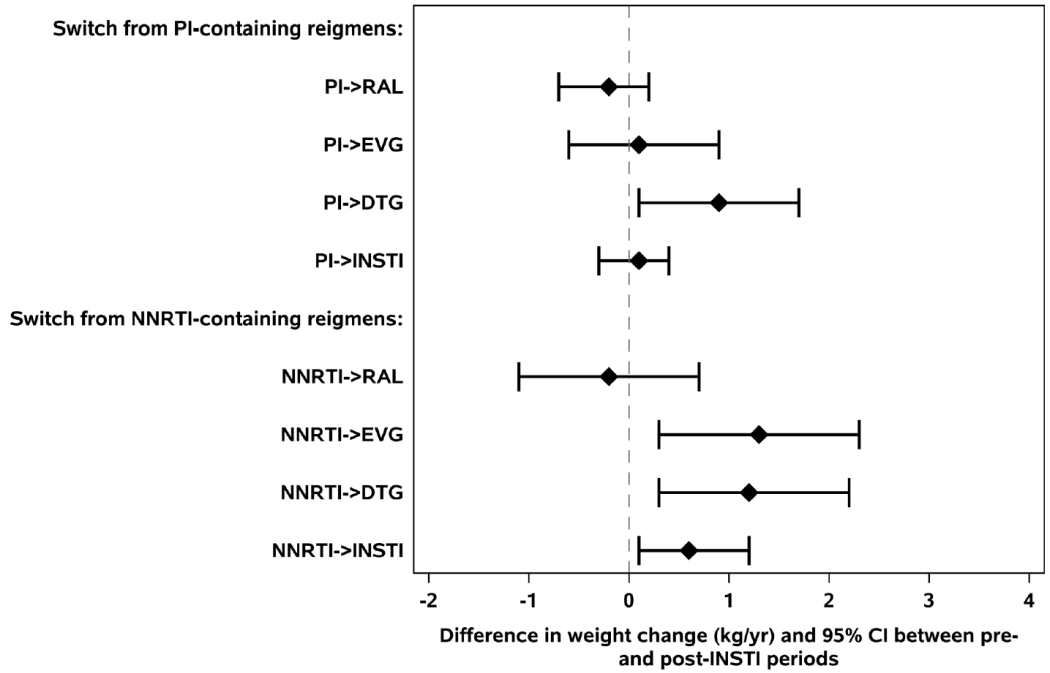
Weight gain places PLWH at higher risk of T2DM?



Source: Venter et al, *NEJM* 2019

Weight gain after transition to INSTI therapy





691 people in ACTG studies who were suppressed at the time of switch

Overall weight gain – 0.4 kg/yr pre-INSTI to 0.6 kg/yr post-INSTI

Subgroups: women =1.3 kg/yr, black race = 0.9 kg/yr and people >60 years = 1.2 kg/year

Source: Lake et al, *Clinical Infectious Diseases* 2021

Efavirenz metabolizer status and weight gain over 48 weeks

Loss-of-function polymorphisms in *CYP2B6* = higher efavirenz concentrations ("slow")

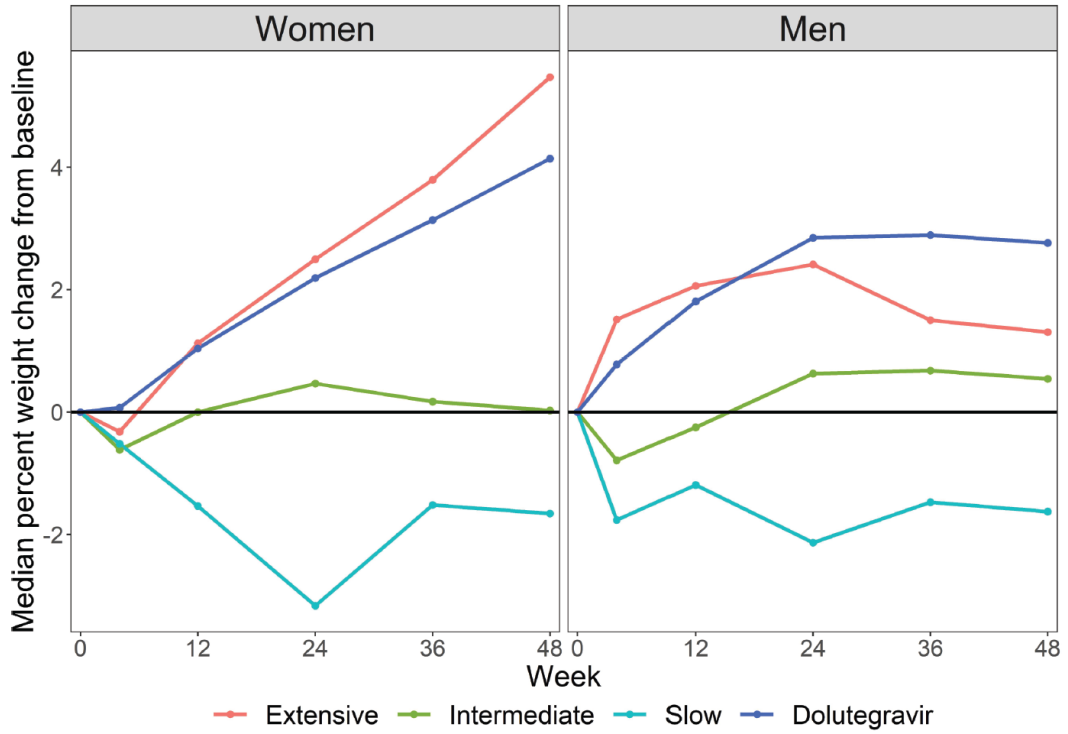
Sub-study of ADVANCE trial in South Africa

<u>Weight change</u>

Extensive – +3.5%, no difference to DTG group

Intermediate – 0.3%

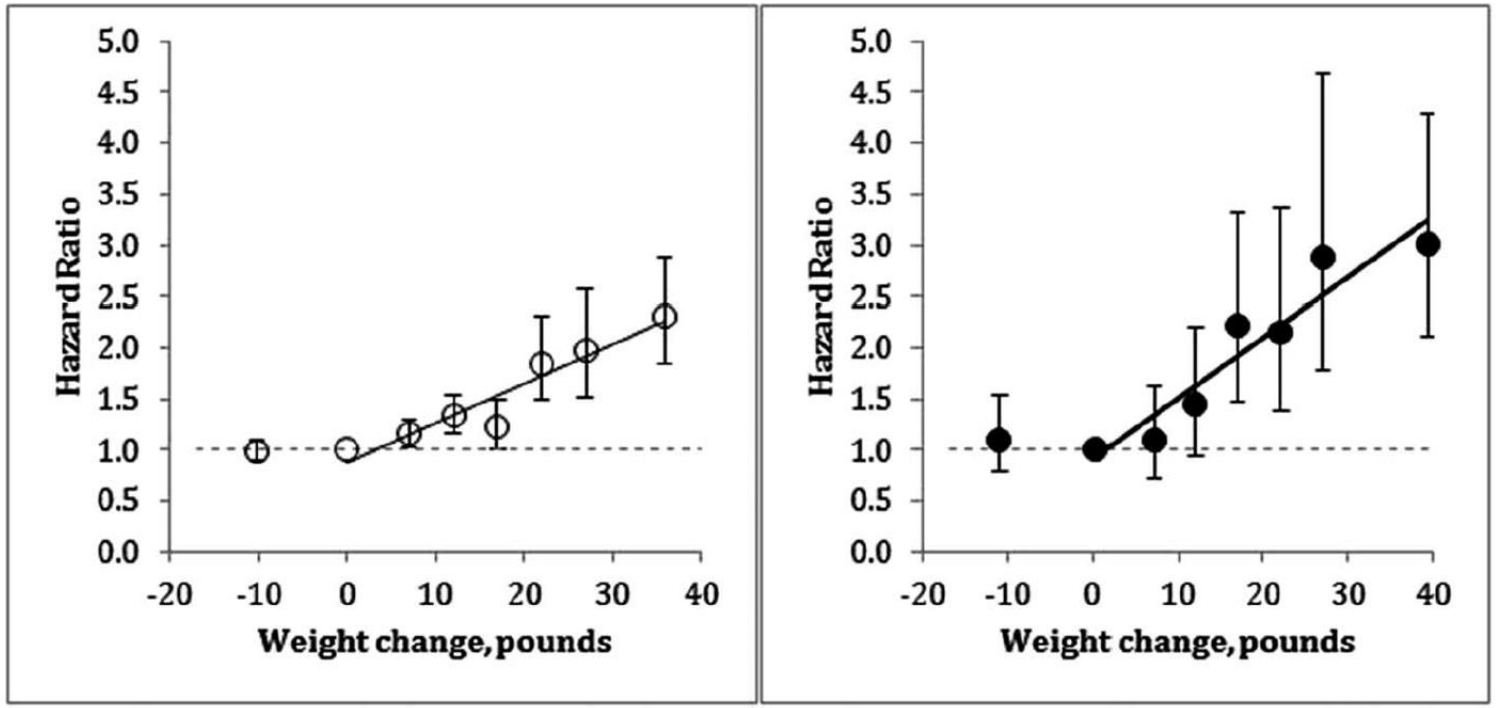
Slow – -1.7%



Source: Griesel et al, *2021 CID*

Link between weight gain and diabetes in PLWH

- Veterans Aging Cohort study (VACS) of PLWH matched 1:2 with uninfected controls
- From 2000 – 2011, weight assessed 1 year after ART initiation for PLWH, first available weight for uninfected group
- For every 5-pound weight gain:
  1. HIV+ = 14% inc. risk of DM
  2. HIV- = 8% inc. risk of DM



Source: Herrin, et al *JAIDS* 2016

Weight gain and diabetes risk in PLWH (continued)

1,544 PLWH switched to TAF; 2,629 to INSTI; 918 to TAF+INSTI

≥10% weight gain in 8.8%, 10.6% and 14.4% of these individuals

Those with ≥10% weight gain had modest increases in glucose + lipids

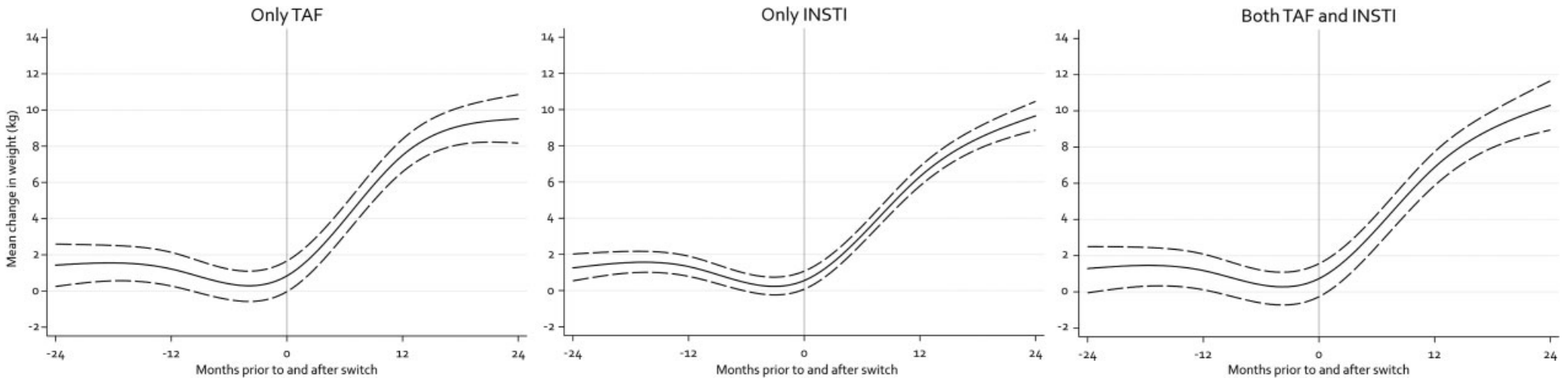


Figure. Mean change in weight in 24 months before and after ART switch among those with ≥10% weight gain

Source: Verburgh et al, *OFID* 2022

Challenge: one BMI does not fit all

"The best BMI" for HEALTH likely differs across populations…

$$BMI = \frac{weight\,(kg)}{height^2\,(m^2)}$$

Original Article
EPIDEMIOLOGY/GENETICS

Obesity

BMI and All-Cause Mortality in a Population-Based Cohort in Rural South Africa

Jennifer Manne-Goehler[1,2,3], Kathy Baisley[4,5], Alain Vandormael[6,7], Till Bärnighausen[5,6,8], Frank Tanser[5,9,10], Kobus Herbst[5,11], Deenan Pillay[5,12], and Mark J. Siedner[1,2,3,5]

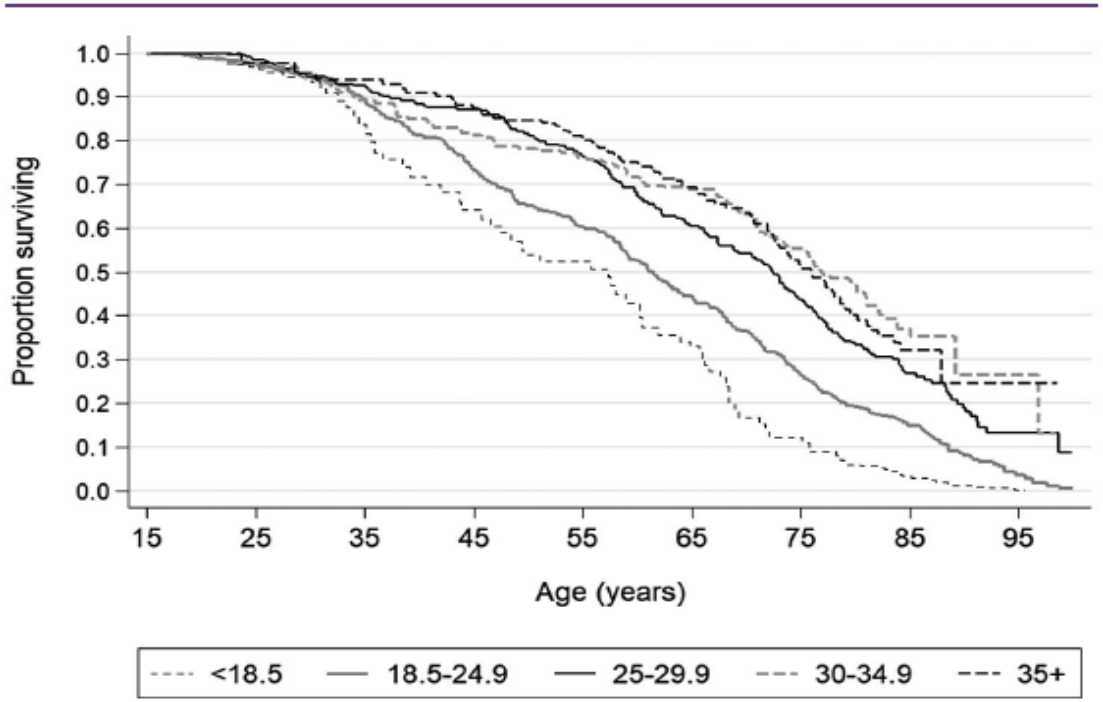


Figure 1 Kaplan-Meier estimates of survival, by BMI group.

Source: Teufel et al, *The Lancet* 2021

Challenge: the "obesity epidemic" differs across contexts

Stage 4 is still theoretical …

No country has "reversed its obesity epidemic"

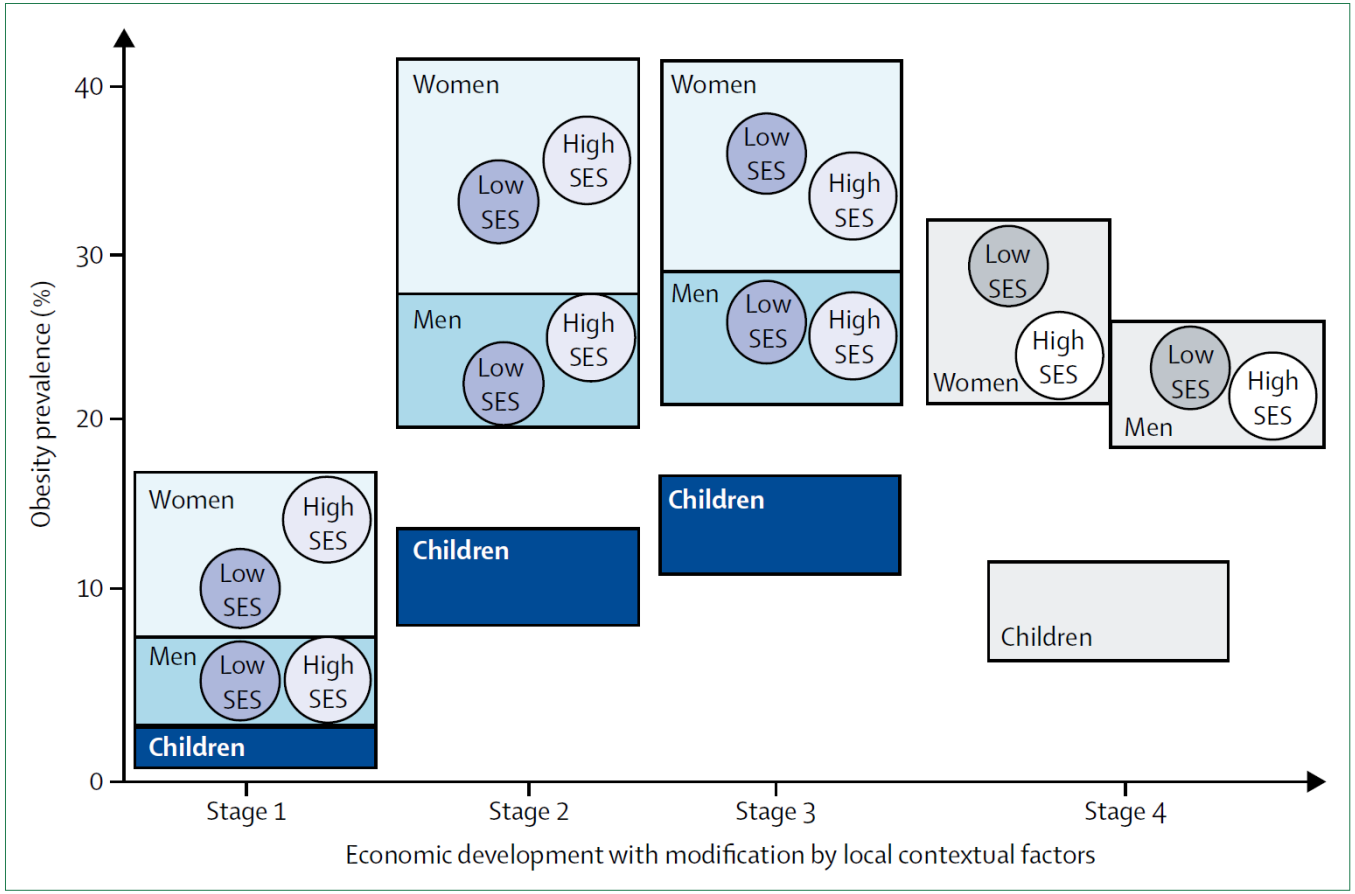


Figure 1: **Conceptual model of the stages of the obesity transition**
SES=socioeconomic status.

Source: Jaacks et al, *The Lancet Diabetes and Endocrinology* 2019

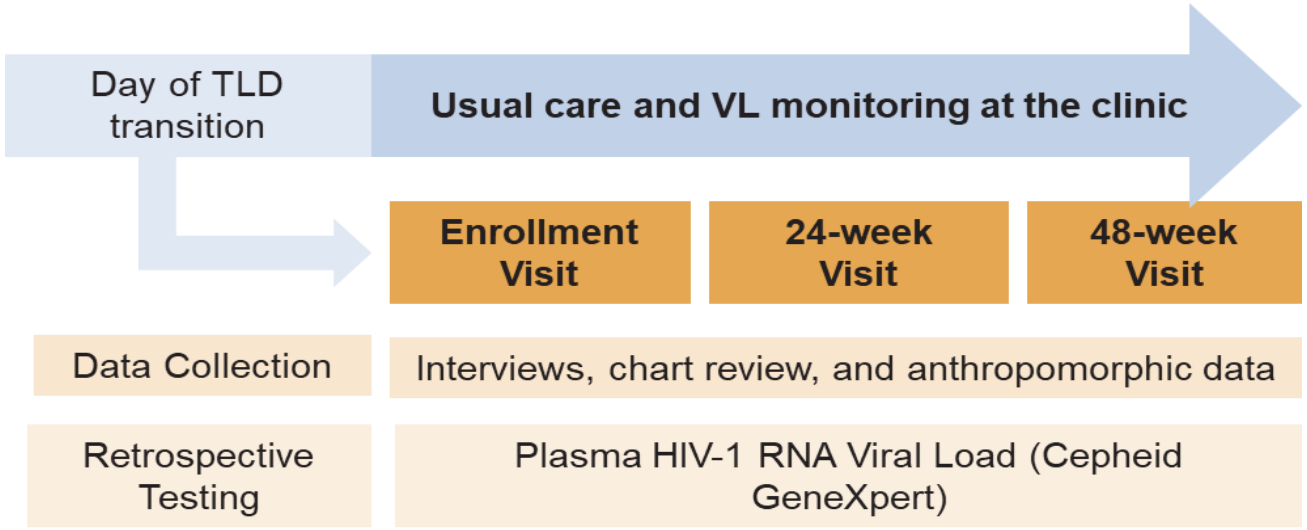
The DISCO Metabolic Study in Uganda and South Africa

Study design

- *Population Effectiveness of Dolutegravir Implementation in Sub-Saharan Africa*
- Prospective, observational cohort
- 1,000 people in rural Uganda + South Africa

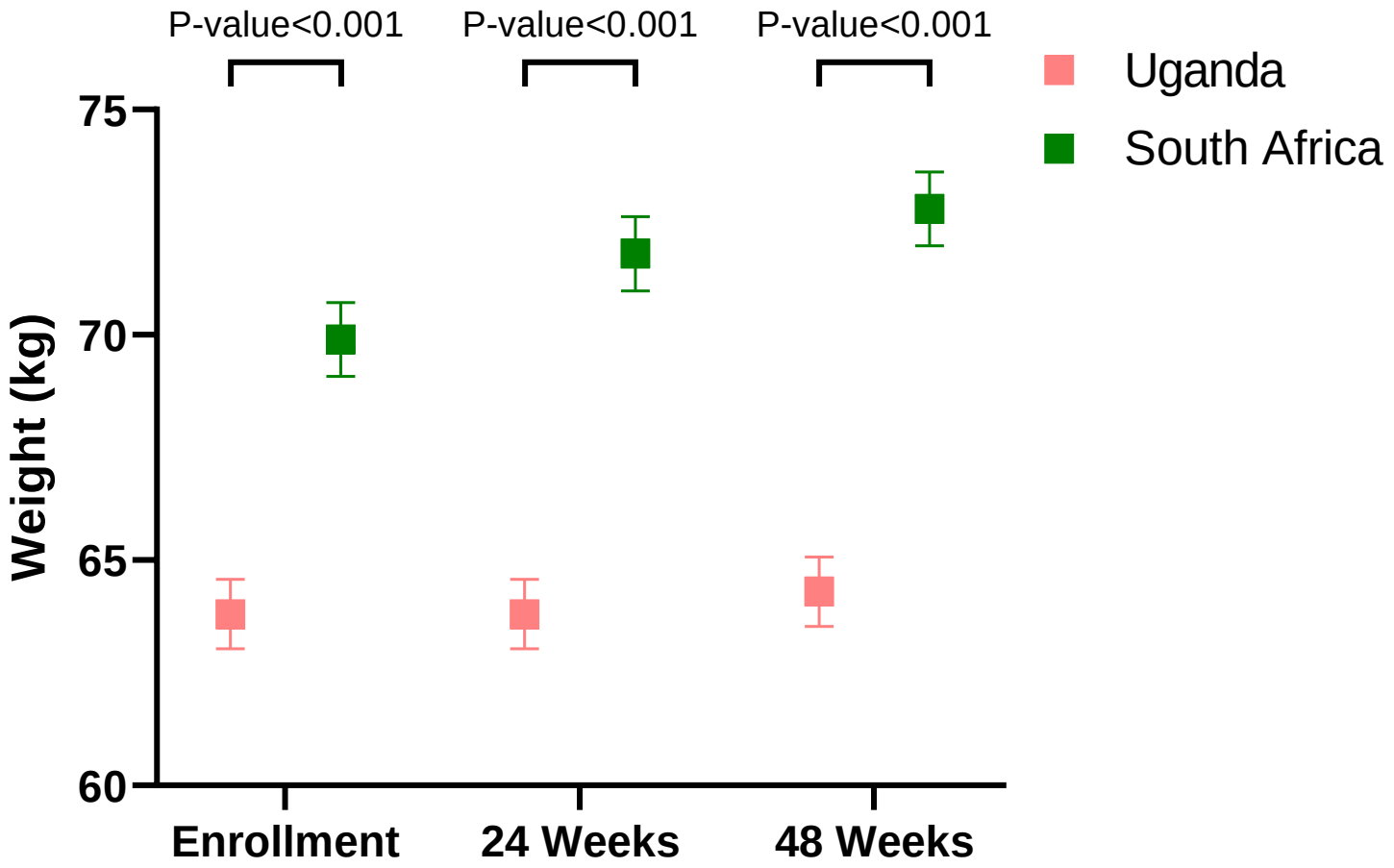
Study Aims

- To assess implementation of TLD in rural clinics
- To quantify viral suppression rates following the transition to TLD
- To assess TLD tolerability and discontinuation



Source: The DISCO Study Team

Predicted body weight over 48 weeks in Uganda and South Africa



In South Africa, 18% of participants gained ≥*10% of their body weight* compared to 9% in Uganda

Source: Migisha and Manne-Goehler et al, in preparation

Managing obesity and preventing diabetes in PLWH

Case #1 (Part II)…

Within 1-2 years of starting TLD:

- BMI increased from 26.0 kg/m^2 to 33.9 kg/m^2

- Random glucose = 8.9 mmol/L

Next visit, checked HbA1c & found to be 9.0%

Blood pressure increases from 118-128/75-80 to 140-145/80-85

Poll

Current guidelines would recommend switching this patient back to efavirenz to avoid further weight gain.

1. True

2. False

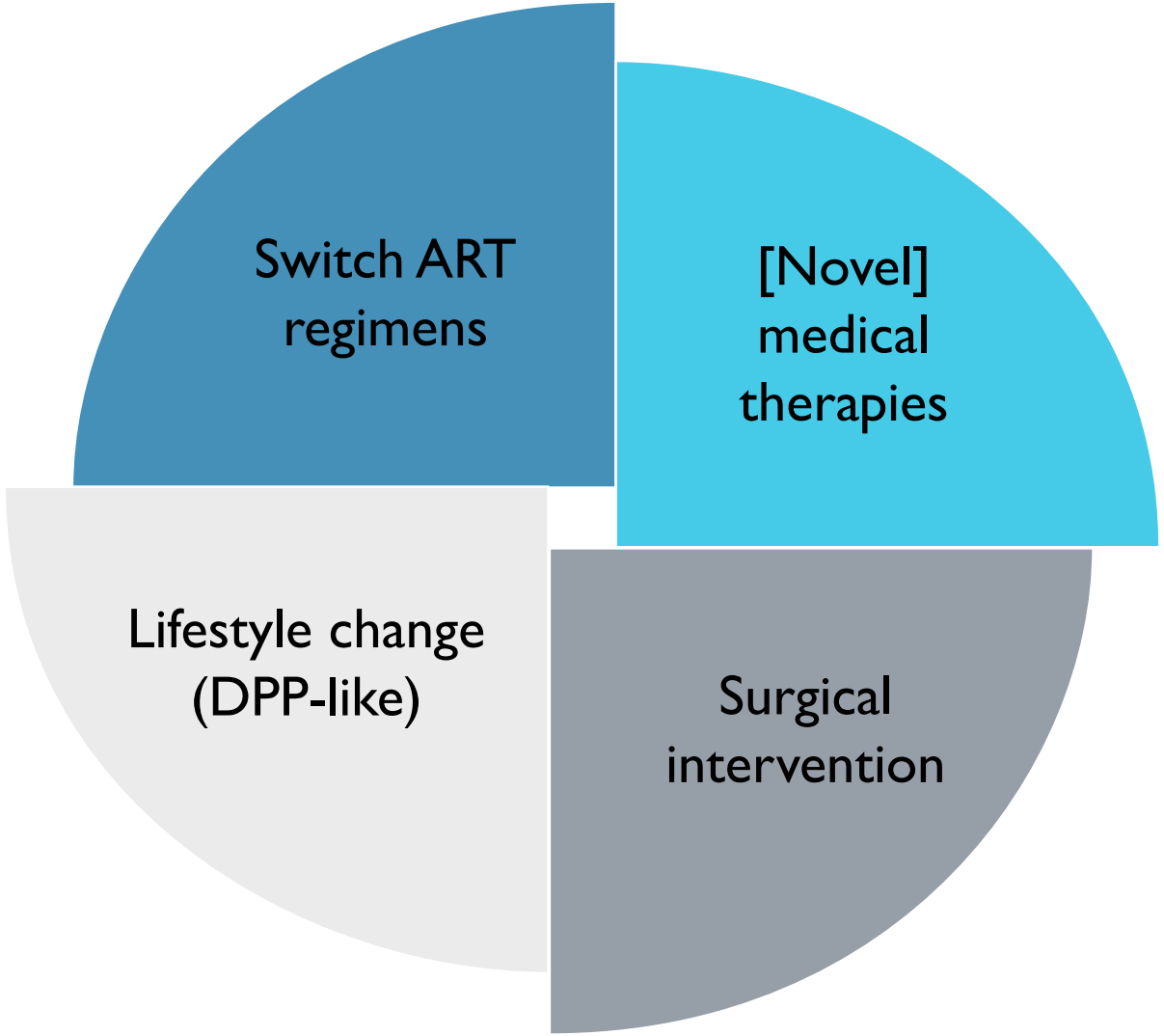
Poll

Current guidelines would recommend switching this patient back to efavirenz to avoid further weight gain.

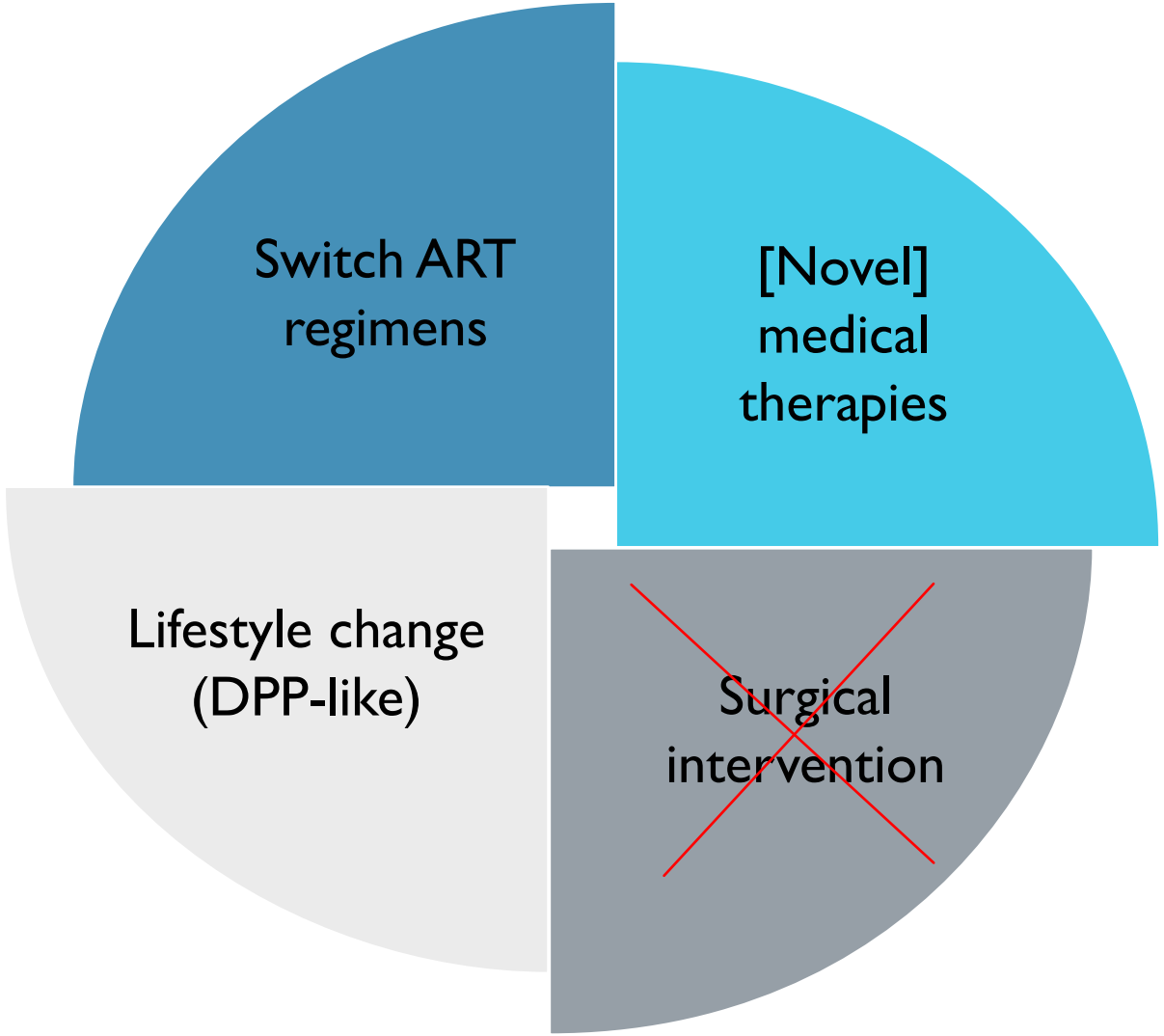
1. True

2. False

Four strategies to manage obesity + prevent T2DM in PLWH



Four strategies to manage obesity + prevent T2DM in PLWH



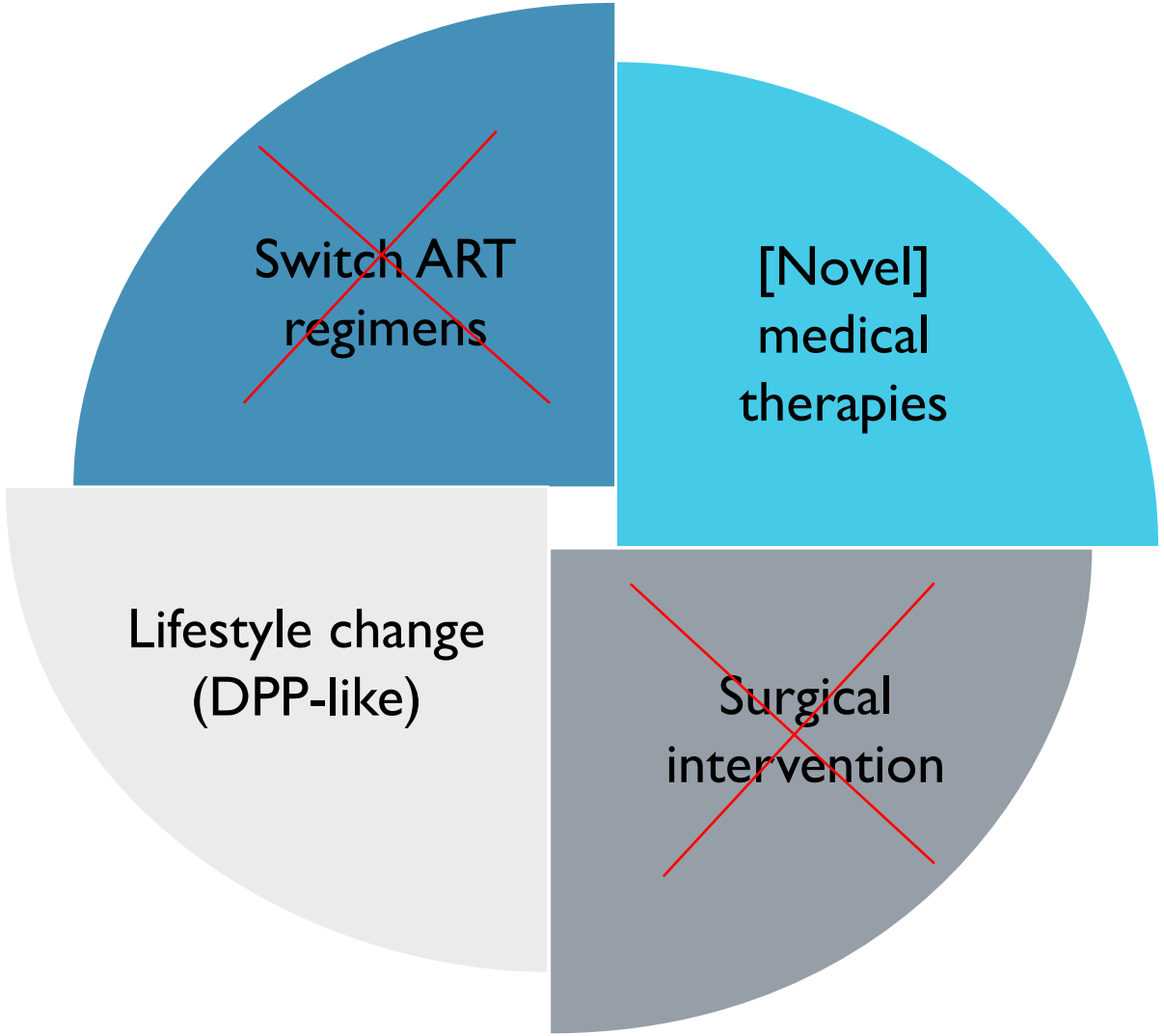
Strategy #1: Switching regimens is *not* recommended…

Key management principles:

- Clinicians initiating or switching patient to DTG should take care not to unnecessarily imply that DTG "causes" weight gain, as this may lead to suboptimal treatment adherence in patients who do subsequently gain significant weight.
- The possibility of weight gain should be discussed by clinicians when starting all ART regimens, as obesity is an increasing problem in HIV care, particularly but not exclusively amongst women.
- Proactive advice for preventing weight gain through diet and exercise should be given to all patients starting or switching ART. Evidence is accumulating for specific weight loss therapies such as GLP-1 agonists, but these are likely to be unaffordable and out of reach of the vast majority of patients currently.
- Since the failure to gain weight in EFV-containing regimens is frequently mediated by toxic levels of EFV because of genetically slower drug metabolism, there is no current role for switching from DTG-containing regimens in patients gaining weight. In addition, drugs such as EFV are associated with inferior viral suppression rates compared to DTG.

Source: SAHCS Guidelines: 2023 Update

Four strategies to manage obesity + prevent T2DM in PLWH



Strategy #2: lifestyle change…is complicated

DIET and EXERCISE important for health but do not often lead to sustained weight loss!

Obesity driven by modern food environment, social determinants of health, genetics, etc.

Obesity is a highly stigmatized condition by both public and health workers…

Source: The Guardian

Strategy #2: lifestyle change…is complicated

10 years after the Diabetes Prevention Program (DPP):

#1 – Participants in lifestyle change program had an average delay in diabetes onset of 4 years

#2 – People who took metformin had a delay of about 2 years

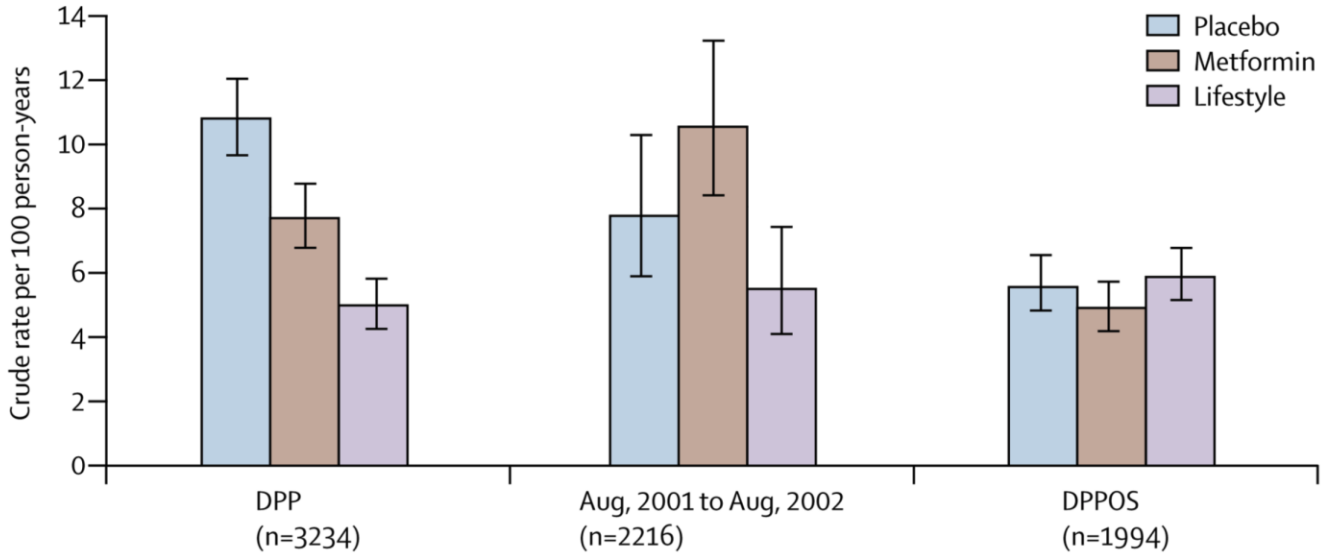


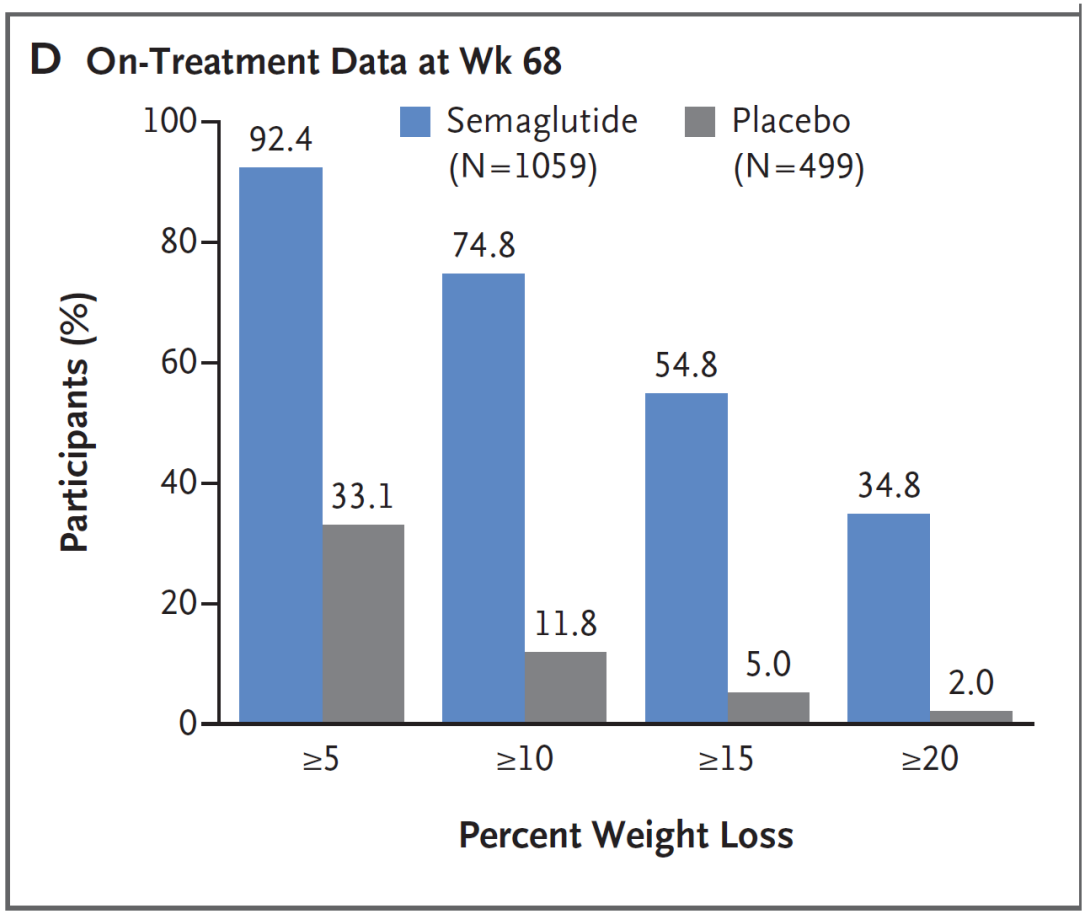
Figure 4. Incidence rates of diabetes during the three study phases of DPP, bridge, and DPPOS
The bars show diabetes incidence rates and the error bars 95% CIs. DPP=Diabetes Prevention Program.

DPP objective: to prevent or delay the onset of T2DM with proven, achievable interventions including lifestyle change – especially in people at greatest risk

Source: NIDDK, DPP Research Group 2009

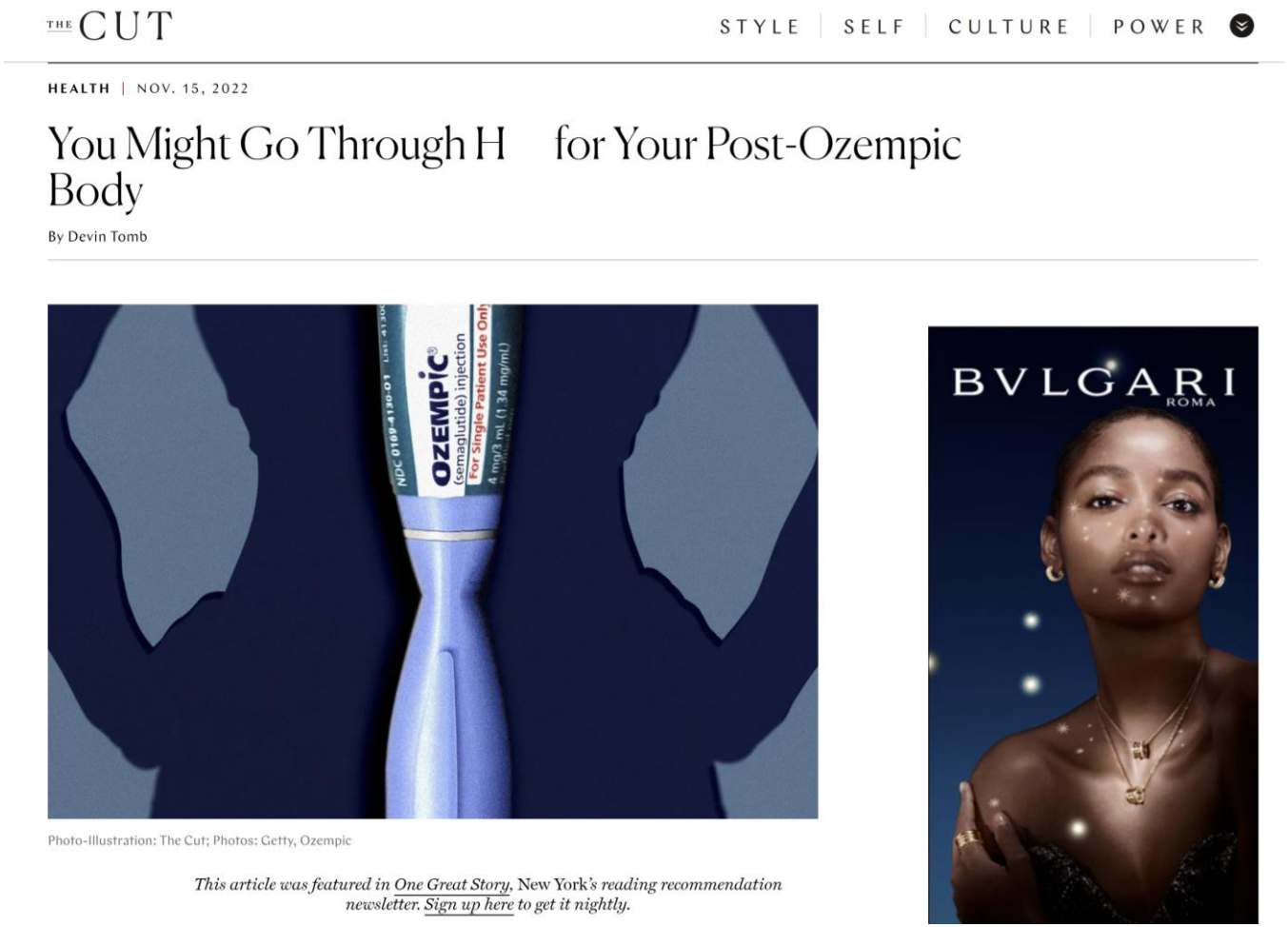
Strategy #3: new medical therapies for obesity are exciting…

- The Semaglutide Treatment Effect in People with Obesity (STEP) Trial
- Semglutide is a GLP-1 analogue
- 1961 adults with BMI ≥30 or ≥27 if ≥1 weight-related comorbidity
- Randomized 2:1 to weekly SC semaglutide 2.4 mg v. placebo for 68 weeks
- Nausea in 44% and diarrhea in 32%



Source: Wilder JPH et al, *NEJM* 2021

Strategy #3…but will this approach "work" in PLWH?



THE CUT

STYLE | SELF | CULTURE | POWER

HEALTH | NOV. 15, 2022

You Might Go Through H for Your Post-Ozempic Body

By Devin Tomb

Photo-Illustration: The Cut; Photos: Getty, Ozempic

This article was featured in One Great Story, New York's reading recommendation newsletter. Sign up here to get it nightly.

Rates of GI side effects

Semaglutide (SC): 45% with nausea, 1/3 with diarrhea

Tirzepatide (SC): 1/3 had nausea, 1/5 had diarrhea

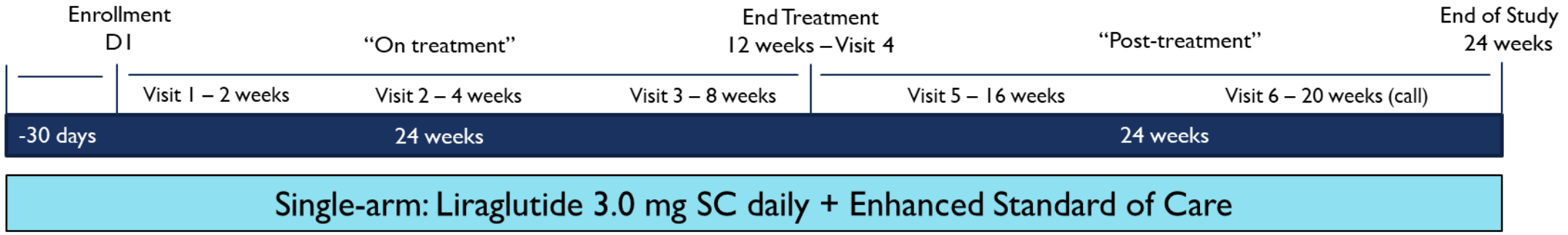
Source: Devin Tomb at NYMagazine, Nov 2022 and Dani Blum at NYTimes, Nov 2022

…qualitative interviews with 26 PLWH in KZN…

Theme	Quotation
Above-average body size is viewed as "normal" and preferable to being thin	*"**A small body size means you are sick**. If you are weighing a higher weight scale that means you are healthy." (Female, 32)*
TLD transition believed to contribute to weight gain	*"I think I have **gained more weight due to the treatment** I am using because I never had a heavy body." (Female 28)*
Interest in weight management exercise program but prefer to workout in groups	*"I can't [workout] by myself; it would be **better I [exercise] with a group…** [exercising alone] I would keep on postponing…and feeling lazy." (Female, 34)*
Interest in pharmacologic option for weight loss	*"**I am interested in losing weight**…I can take it [weight loss pill] if it has fewer side effects." (Female 28)*

Source: The DISCO Study Team

Liraglutide for management of obesity in PLWH: a pilot study



- PLWH on TLD with BMI≥30 kg/m2
- Single-arm, open-label design with approved GLP-1 RA (liraglutide SC daily)

Diabetes care in PLWH – a few pearls…

Poll

What drug and dose would you start FIRST for diabetes management in this patient on TLD with HbA1c of 9.0%:

1. Metformin (immediate release) 500mg daily

2. Metformin (immediate release) 2,000mg daily

3. Gliclazide 80mg daily

4. Insulin Glargine –10 units daily in the morning

Poll

What drug and dose would you start FIRST for diabetes management in this patient on TLD with HbA1c of 9.0%:

1. **Metformin (immediate release) 500mg daily**

2. Metformin (immediate release) 2,000mg daily

3. Gliclazide 80mg daily

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Case #1 (Part III)…

Started on metformin 500mg daily

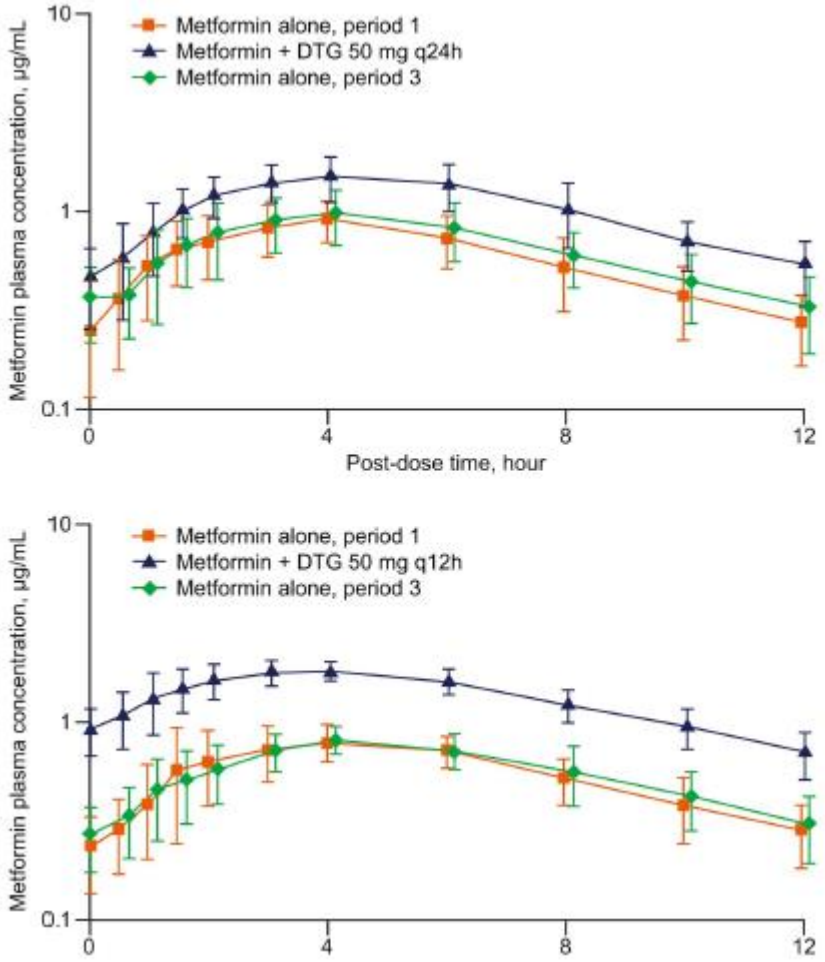
Titrated up to 1000mg daily

Added atorvastatin 10mg daily + amlodipine 10mg daily

Discussing if semaglutide would be of interest/possible…

Metformin use in PWH on DTG

DTG	
Study Design	Open-label, parallel-group, multi-dose, 3-period crossover study in healthy adults
Mechanism	Partly explained by OCT2 inhibition
Pharmacokinetics (metformin)	DTG 50 mg Q12H • ↑AUC 145% & Cmax 111%
Management	Consider metformin dose adjustment if starting/stopping DTG Avoid metformin >1000mg per day



Source: Song et al, JAIDS 2016

Clinical pearl regarding the diagnosis of diabetes in PWH…

HbA1c may underestimate glucose intolerance in PWH

Plasma fasting blood glucose is the preferred test for diabetes in people with HIV

Harder to obtain in clinical practice

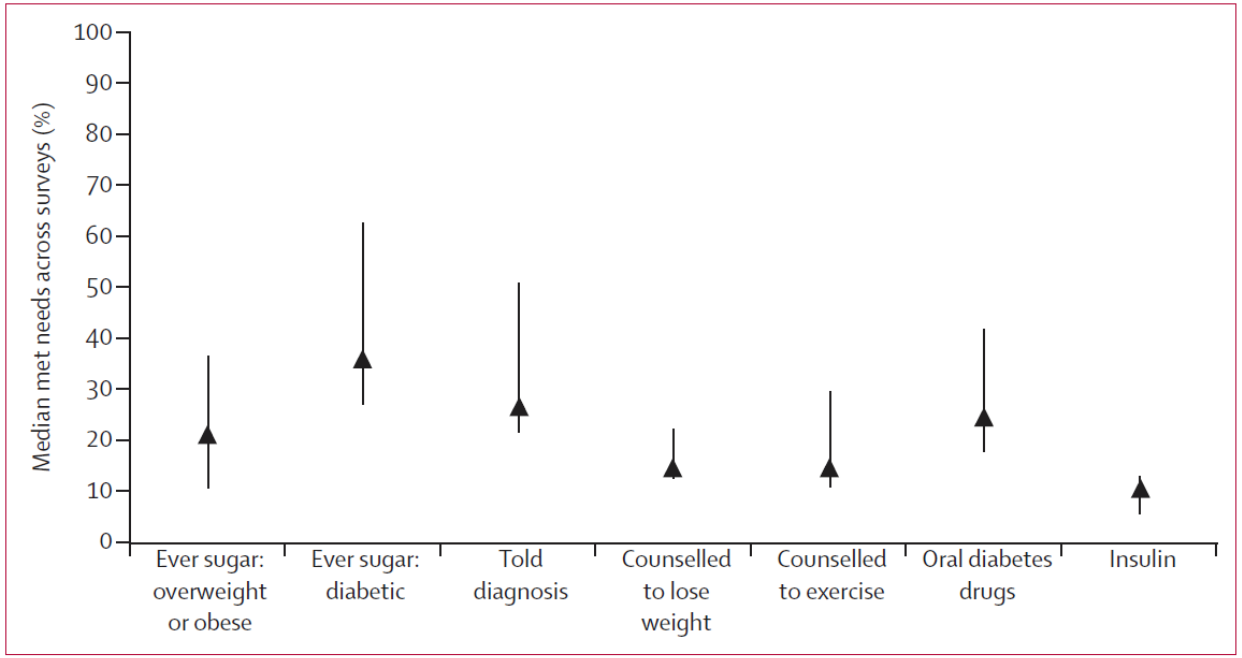
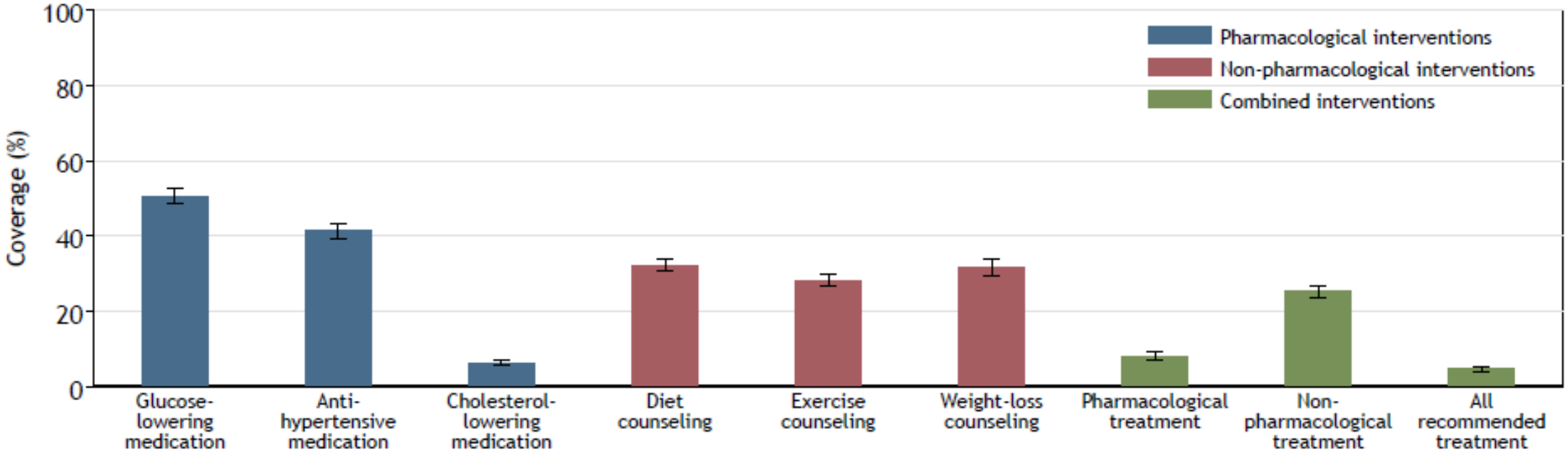


Figure 3: **Met need for diabetes diagnosis and care**
This figure displays the median and IQR for met need for diabetes diagnosis and care across surveys. The denominator for Ever sugar: overweight or obese is the overweight or obese population; the denominator for all of the other indicators of met need is the diabetic population.

Source: Bailin and Koethe, *Current HIV/AIDS Reports* 2022 and Manne-Goehler et al, *The Lancet Diabetes & Endocrinology* 2016

Diabetes care is a challenge and a global priority (in general)

Figure 1: Diabetes treatment coverage in 55 low- and middle-income countries



Source: Flood et al 2022, The Lancet Healthy Longevity

Fundamental clinical goals of diabetes care

1. Glycemic control (HbA1c <8%)
2. Blood Pressure control (BP <140/90 mm Hg)
3. Statin therapy

Source: Gregg et al, 2023 The Lancet

Statins in PLWH with diabetes

People with HIV + T2DM need a statin if:

1. >40 years old
2. They have had T2DM for >10 years
3. They have CKD
4. They have 1+ other CVD risk factor

Module 25 of the 2023 SAHCS Guidelines

Consider pravastatin or low-dose atorvastatin, avoid simvastatin with PIs

	Diagnosed of total diabetes population	People with diagnosed diabetes		
		Attained glycaemic control (HbA_{1c} <8%)	Attained blood pressure control (<140/90 mm Hg)	Statin therapy
All regions				
Mean	61·0%	66·8%	54·0%	23·6%
Median	61·4%	67·6%	55·6%	12·3%
IQR	22·2%	15·3%	20·9%	25·8%
East Asia and Pacific	54·9%	58·9%	54·7%	15·7%
Europe and central Asia	74·0%	77·1%	50·0%	12·1%
Latin America and Caribbean	71·8%	68·2%	65·4%	10·0%
Middle East and north Africa	58·9%	67·6%	50·8%	25·1%
North America	69·7%	75·5%	78·3%	56·8%
South Asia	56·3%	67·3%	52·8%	13·4%
Sub-Saharan Africa	57·6%	54·7%	44·8%	23·0%

Estimates assembled from four primary types of sources: the International Diabetes Federation Diabetes Atlas, the Global Health and Population Project on Access to Care for Cardiometabolic diseases collaborators, literature reviews, and websites containing estimates from national diabetes surveillance systems. References are listed in the appendix (pp 9–11). HbA_{1c}=glycated haemoglobin.

Table 2: **Median percentage of population attaining target outcomes for core metrics by world region**

Conclusions

1. PWH may be at greater risk of developing diabetes in the setting of weight gain and clinical obesity than people without HIV

2. Several strategies to prevent diabetes may be considered, including lifestyle change (not an obesity treatment!) and novel anti-obesity therapies where possible (hopefully access will improve in the future)…

3. When starting metformin in PLWH on TLD, start at a low dose and titrate-up ("start low, go slow")

Thank you to my [awesome] mentors/collaborators:

Paul Sax

Francois Venter

Janet Lo

Mark Siedner

Sylvia Kehlenbrink

Mo Ali

Nomathemba Chandiwana

Selected references

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Appendix

Obesity and diabetes in PLWH

General risk factors

Higher BMI

Older age

Central obesity

Family history

Social inequality

HIV-specific risk factors

Exposure to older ART regimens/lipoatrophy
Stavudine, indinavir, zidovudine, didanosine, ritonavir

Elevated systemic inflammation

Possible persistent adaptive immune activation

Current ART regimens…?

Source: Bailin and Koethe, *Current HIV/AIDS Reports* 2022

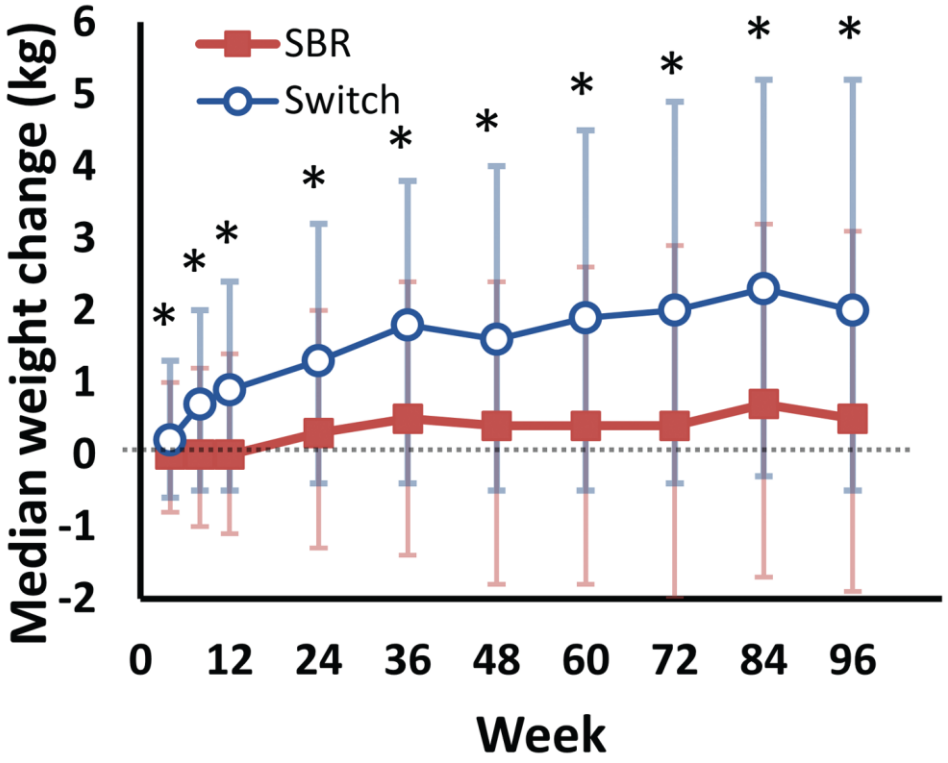
Weight gain after the switch to INSTI therapy, continued…

12 RCTs with 4166 switched, 3150 on stable baseline regimen (SBR) followed for 48+ weeks

<u>SWITCH gained 1.6 kg at 48 weeks</u>
SBR gained 0.4 kg at 48 weeks

<u>SWITCH had 6.4% with ≥10% gain</u>
SBR had 2.2% with ≥10% gain

Switches off EFV and TDF both risk factors for gain



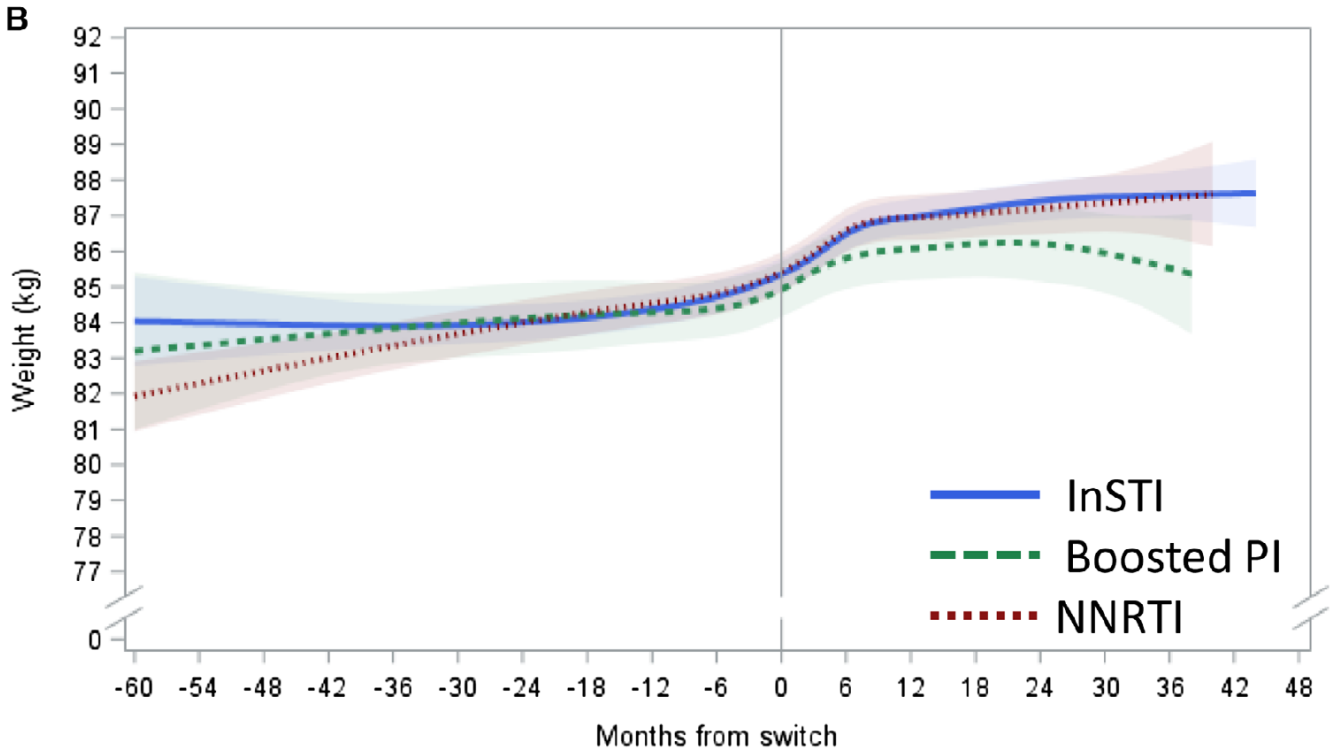
Source: Erlandson et al, *Clinical Infectious Diseases* 2021

Weight gain with switching off TDF?

"OPERA" EHR-based database of >107K PWH from 84 clinics in 18 states

PWH >18 years, suppressed + switched from TDF to TAF (2015 – 2019)

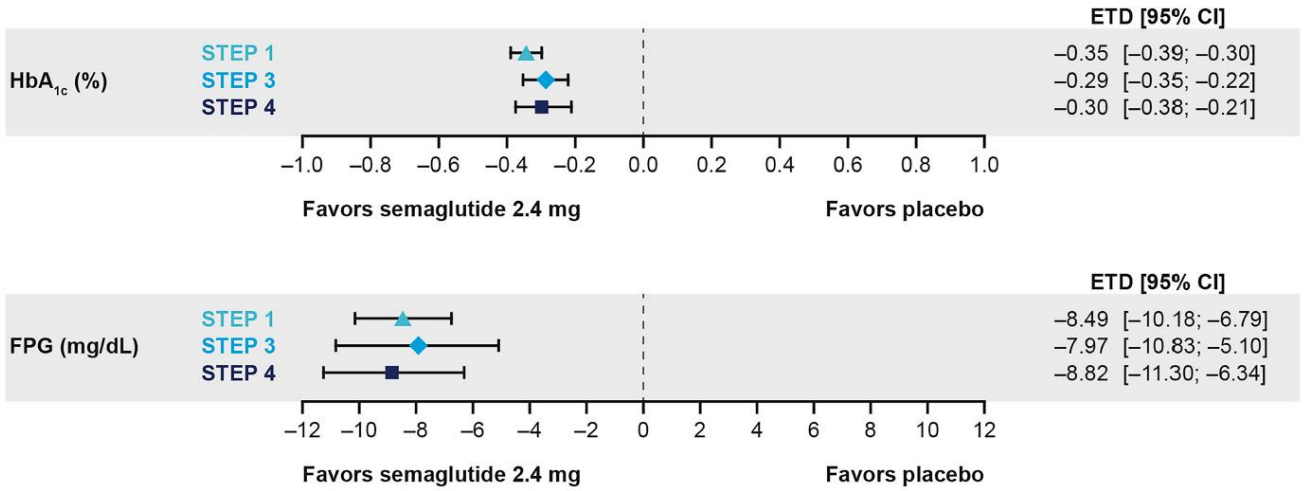
Excess weight gain greatest in first 9 months after switch to TAF (1.80 to 4.47 kg/year)



Source: Mallon et al, *JIAS* 2021

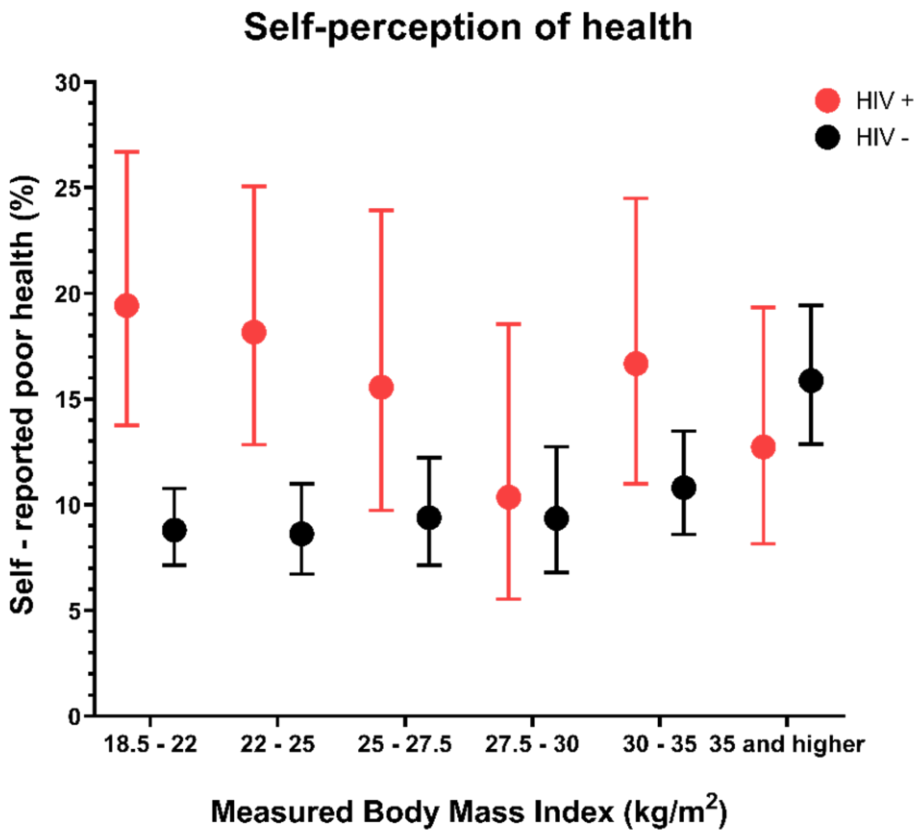
Strategy #3: new anti-obesity therapies to prevent T2DM?

- The Semaglutide Treatment Effect in People with Obesity (STEP) Trial
- 3375 adults with BMI ≥30 or ≥27 if ≥1 weight-related comorbidity
- 2:1 weekly SC semaglutide 2.4 mg v. placebo for 68 weeks
- Participants with baseline pre-DM who had normoglycemia at week 68:
  - 84.1% vs. 47.8% (STEP 1)
  - 89.5% vs. 55.0% (STEP 3)
  - 89.8% vs. 70.4% (STEP 4)



Source: Perreault et al 2022, Diabetes Care

Challenge: self-perception of health may differ in PLWH



- 2016 South Africa Demographic and Health Survey – nationally representative, population-based data
- 1,163 PWH (19.7%) and 4,975 people without HIV (80.3%)
- Greater self-reporting of "poor health status" for PWH with "normal" BMI of 18.5 – 27.5 kg/m^2

Source: Manne-Goehler et al, submitted

Contextual factors influence potential behavioral interventions

	Chips intake		SSB intake	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Infrequent	REF		REF	
Frequent	1.01 (0.9 - 1.14)	0.828	1.13 (1.01 - 1.25)	0.033

SSB = sugar-sweetened beverage

Poisson regression analysis of relationship between nutritional behavior and risk of overweight or obesity in PWH only, adjusted for age, sex, education and wealth

Source: Manne-Goehler et al, submitted