Weight Gain and Cardiometabolic Disease on Modern Antiretroviral Therapy

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Disclosures

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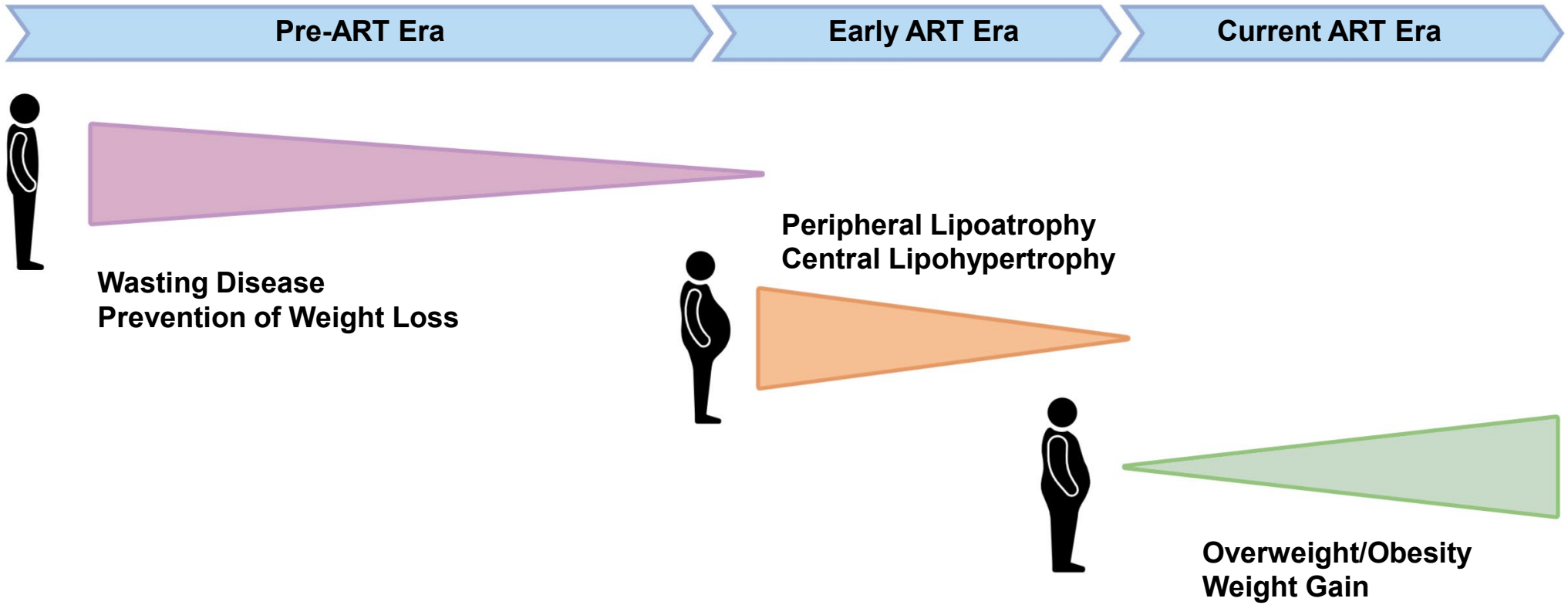
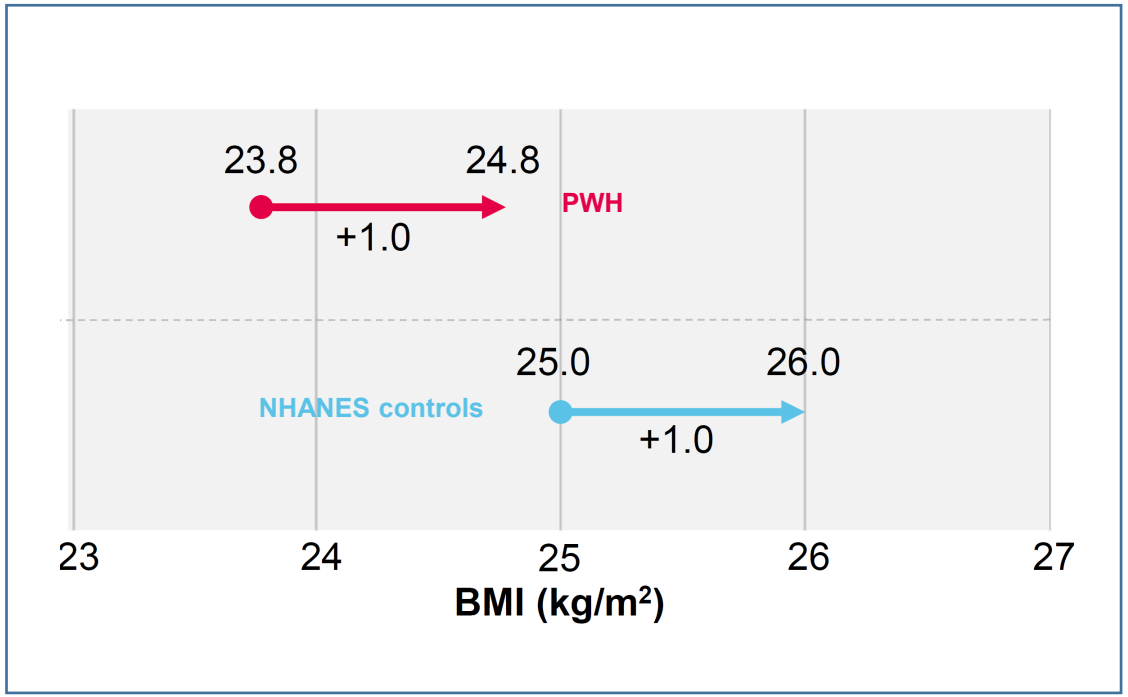
Nutrition and Weight Concerns in PWH Over Time

1981 to Today

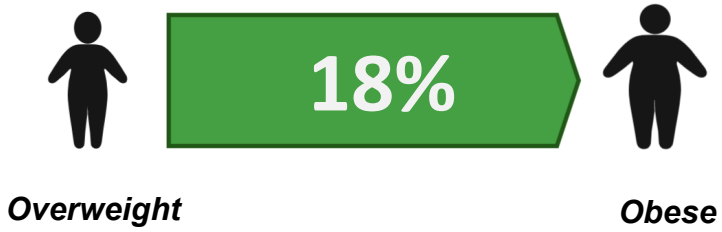


Body Mass Index at HIV Treatment Initiation Has Increased Over Time and PWH Gain Weight on ART

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



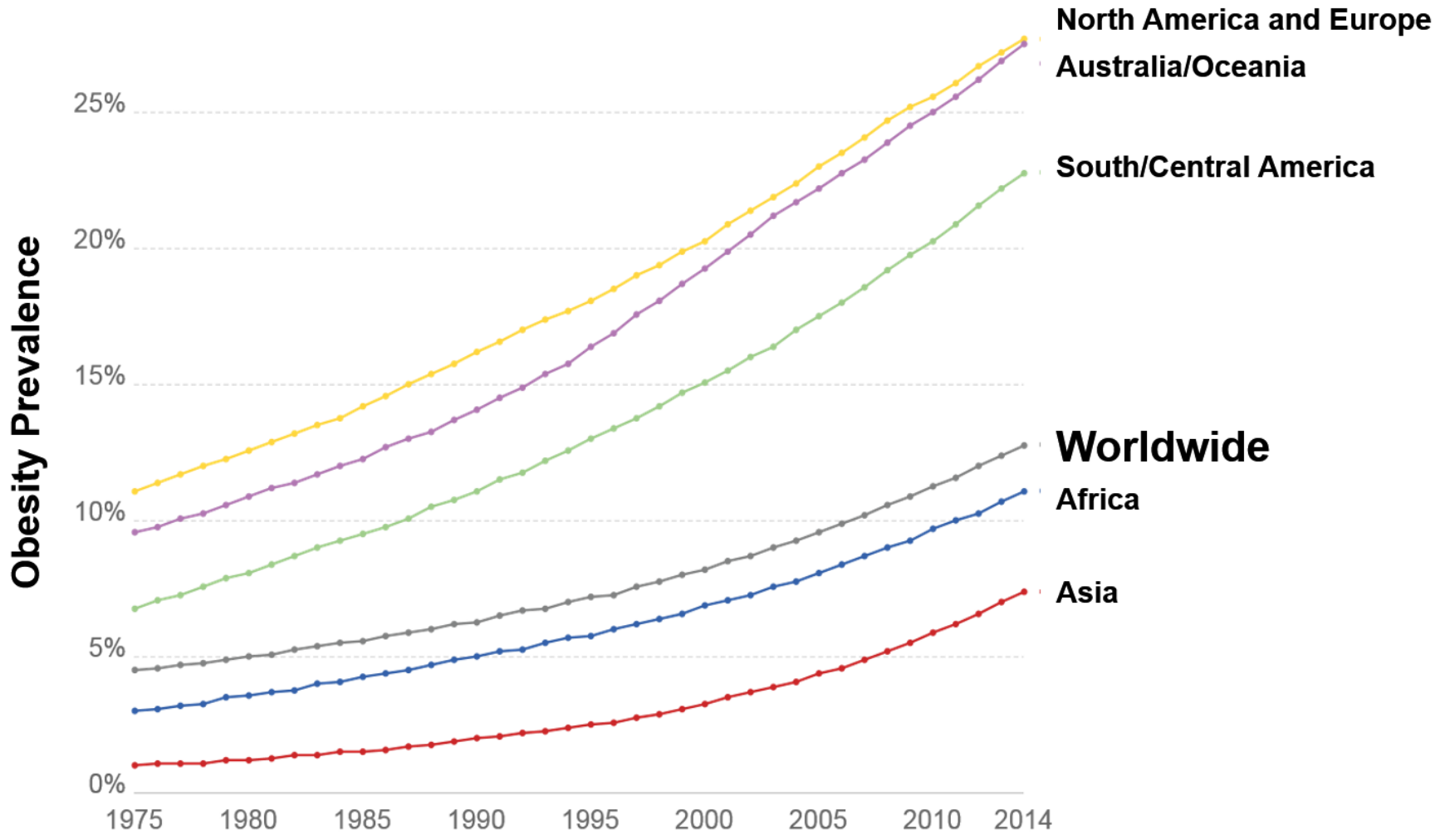
Shifts in BMI categories in the 3 years after ART initiation



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

NA-ACCORD, ARHR 2016

Worldwide Prevalence of Obesity

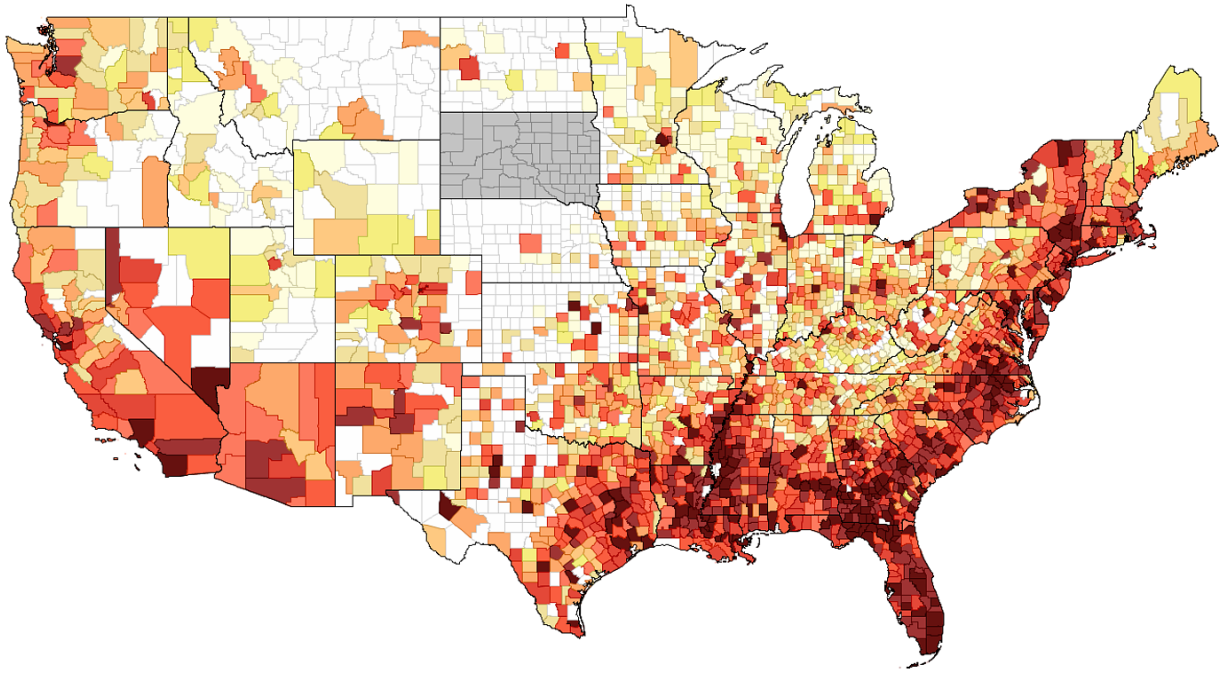


WHO Fact Sheets 2018 & UN Food and Agricultural Organization

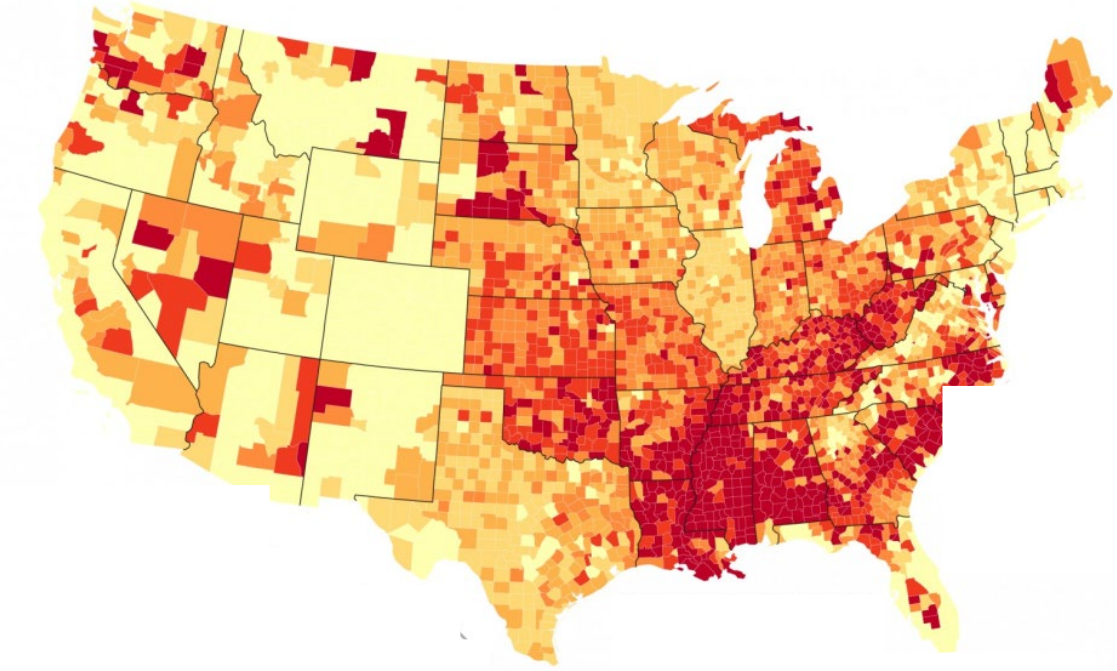
Overlapping Epidemics

HIV and Obesity in the United States

HIV prevalence



Obesity prevalence



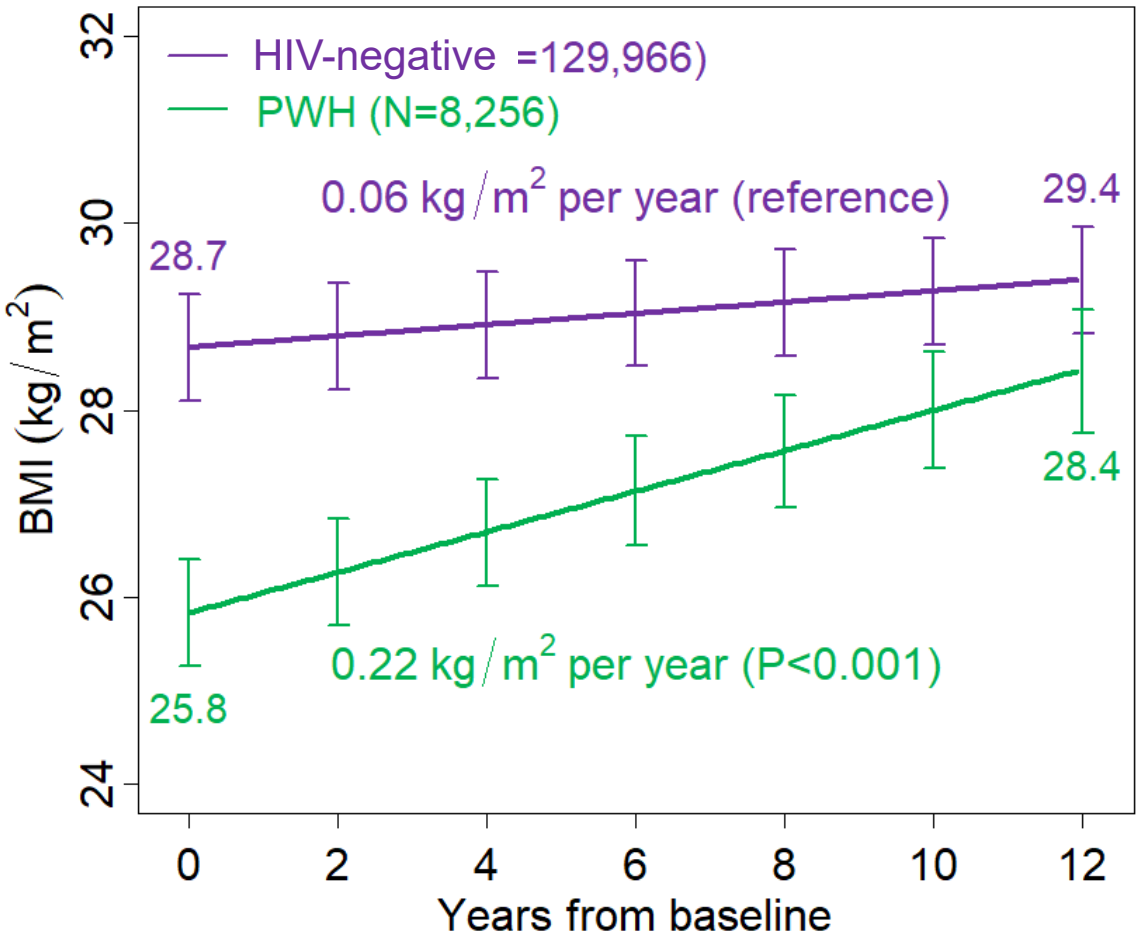
Sources: AIDSVu.com, National Center for Health Statistics (https://www.cdc.gov/dhdsp/maps)

Rising Obesity Prevalence in PWH Reflects Broader Trends

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

Weight Gain on ART: 'Return to Health' or Something Different?

Over 8000 PWH starting ART matched 1:10 to HIV-negative persons by age, sex, race/ethnicity, clinic, and year



PWH had lower BMI at the start but weight increased at 3-times the rate of the HIV-negative.

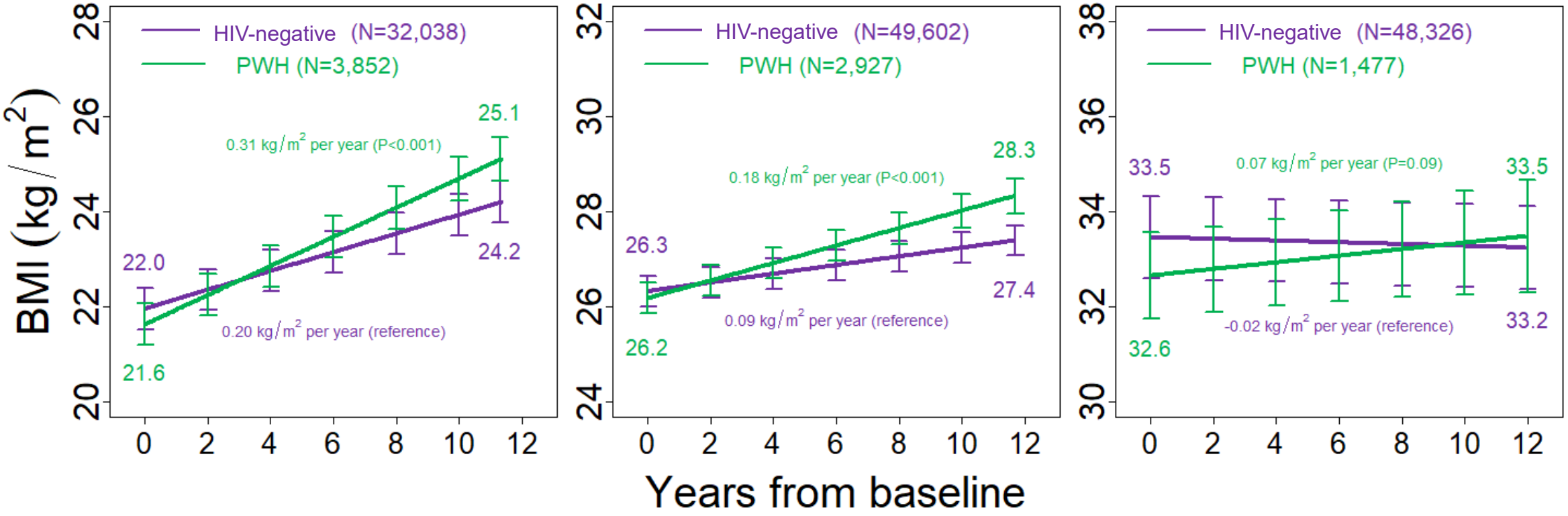
Silverberg M, et al. AIDS 2020 Abstract OAB0603

Weight Gain on ART: 'Return to Health' or Something Different?

Normal/underweight
(<25.0 kg/m2)

Overweight
(25.0-29.9 kg/m^2)

Obese
(≥30 kg/m2)

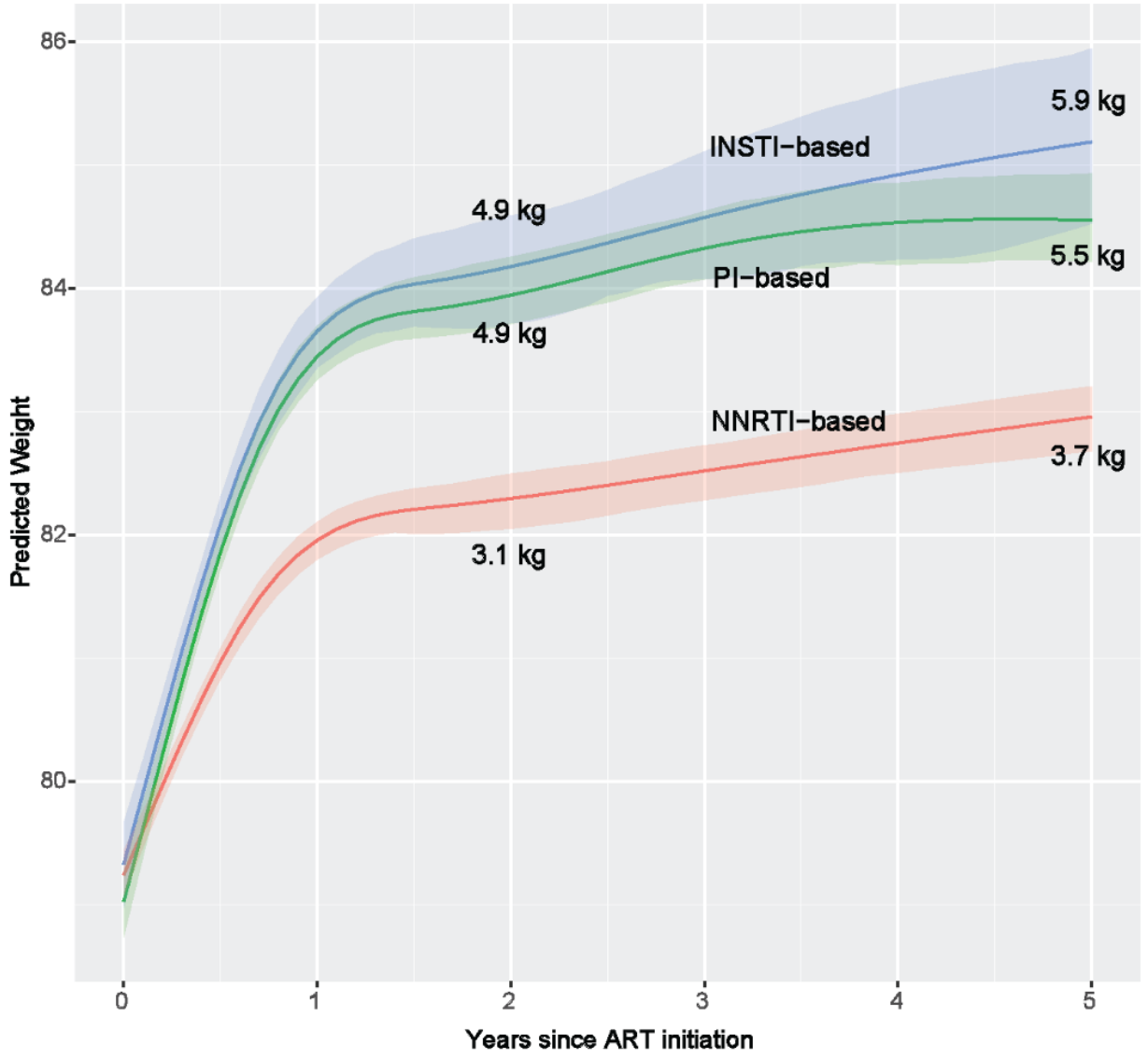


Silverberg M, et al. AIDS 2020 Abstract OAB0603

Weight Gain in ART-naïve Persons

NA-ACCORD Cohort

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

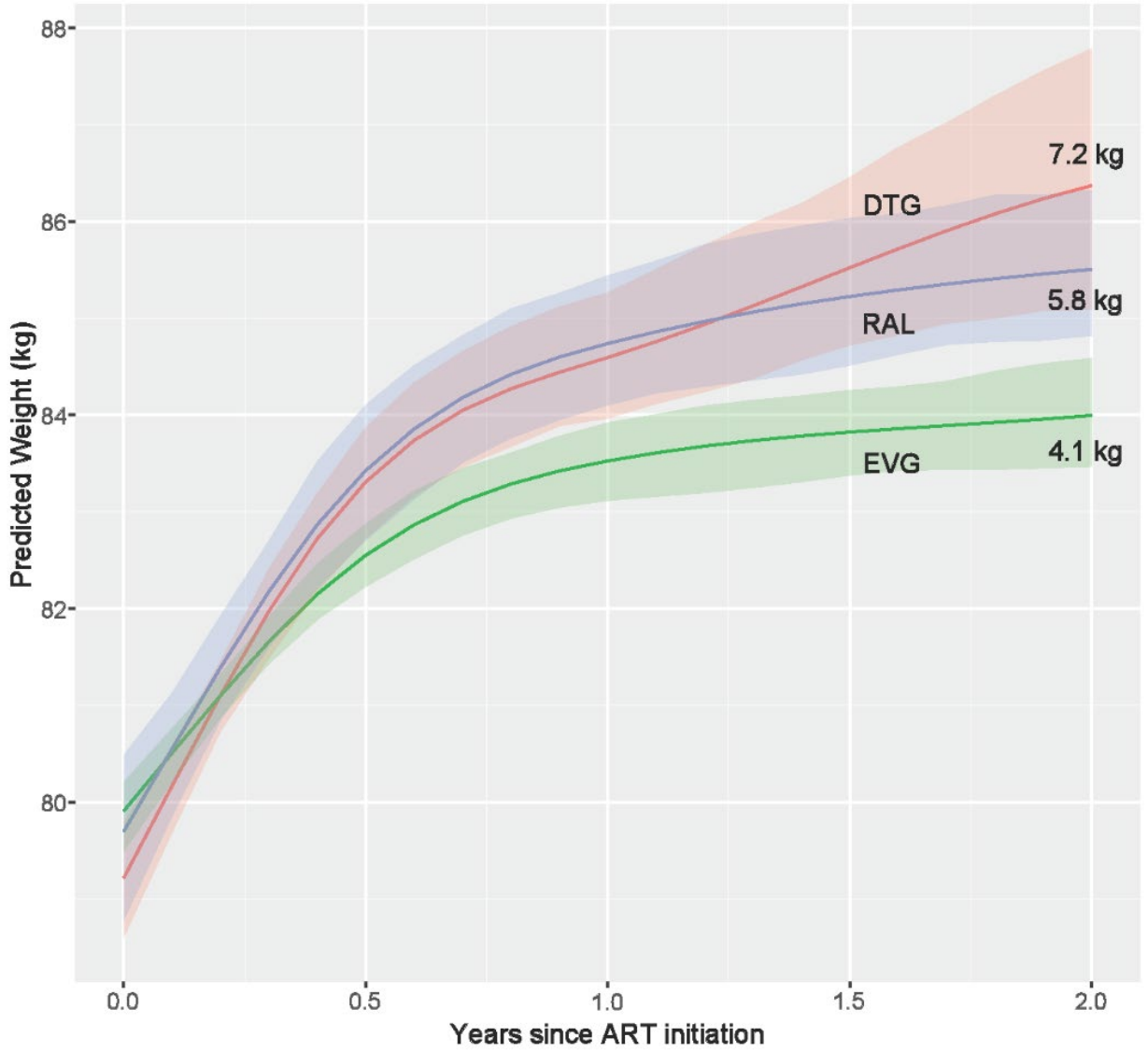


NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design

Bourgi K, et al. JIAS 2020

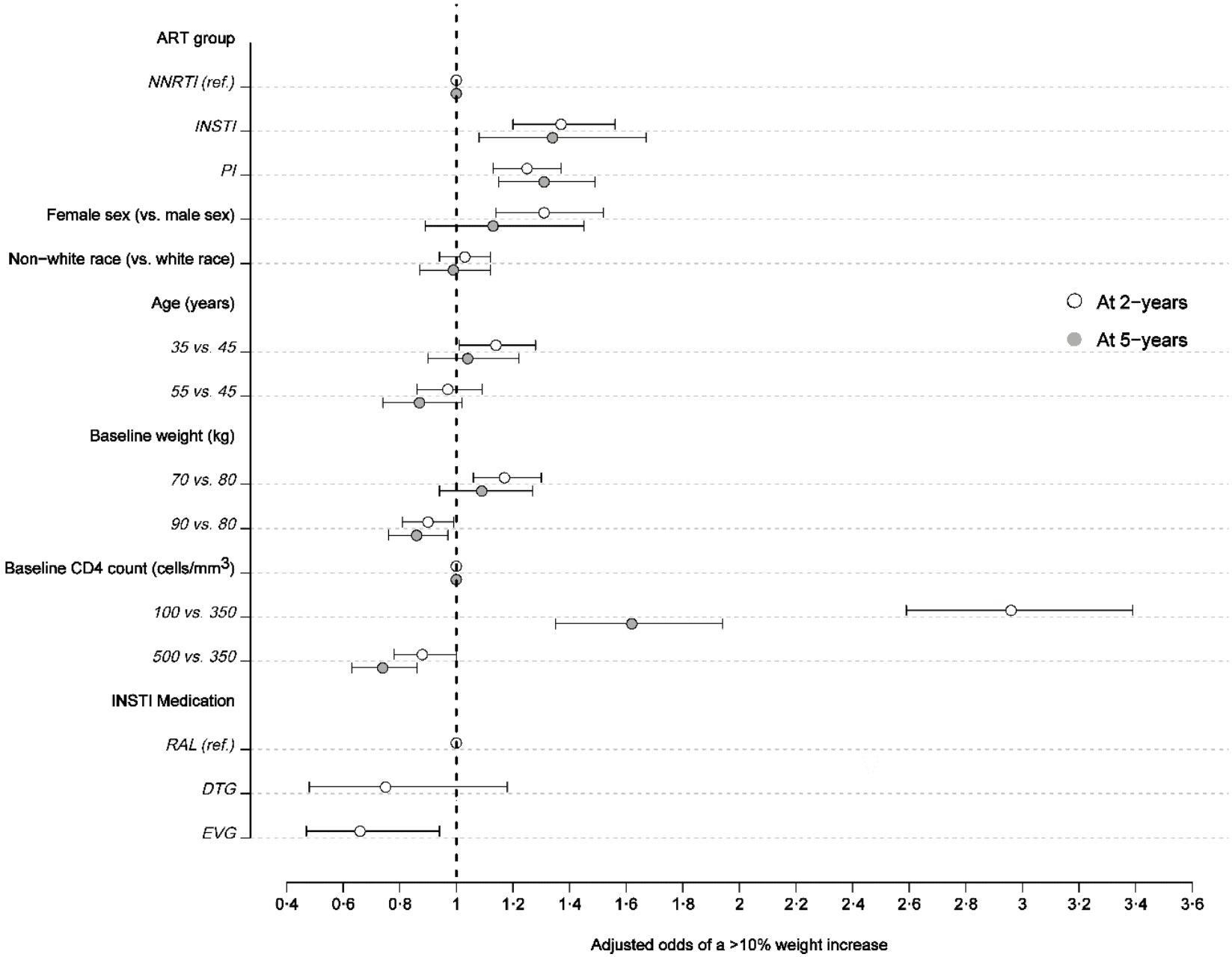
NA-ACCORD Cohort

4,190 patients starting INSTI drugs from 2007-2016 in the US and Canada



Bourgi K, et al. JIAS 2020

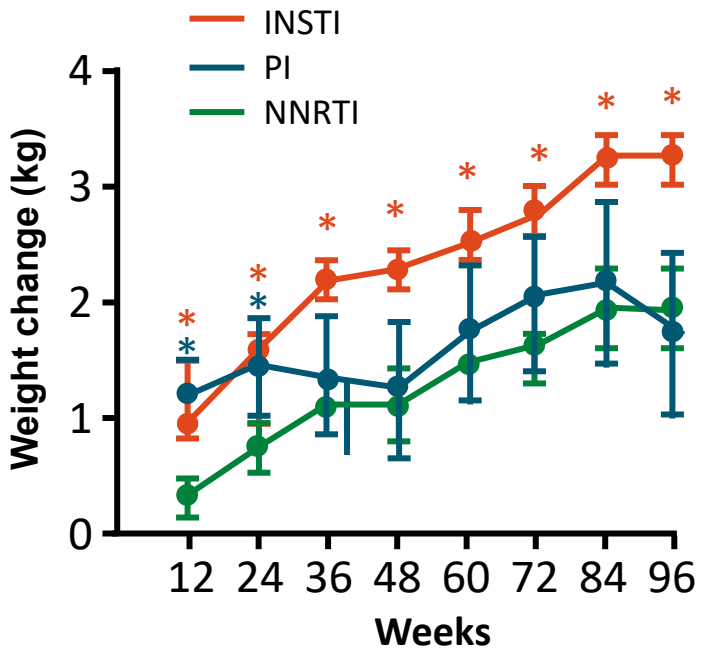
Risk Factors for a >10% Weight Gain on ART

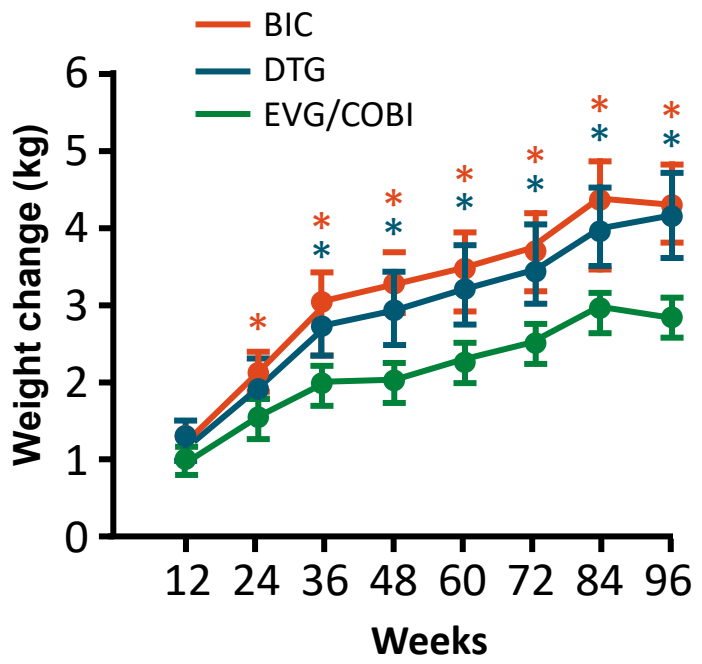


Bourgi K, et al. JIAS 2020

Pooled Analysis of Weight Gain in 8 RCTs

5680 treatment-naïve PWH initiating ART between 2003-2015





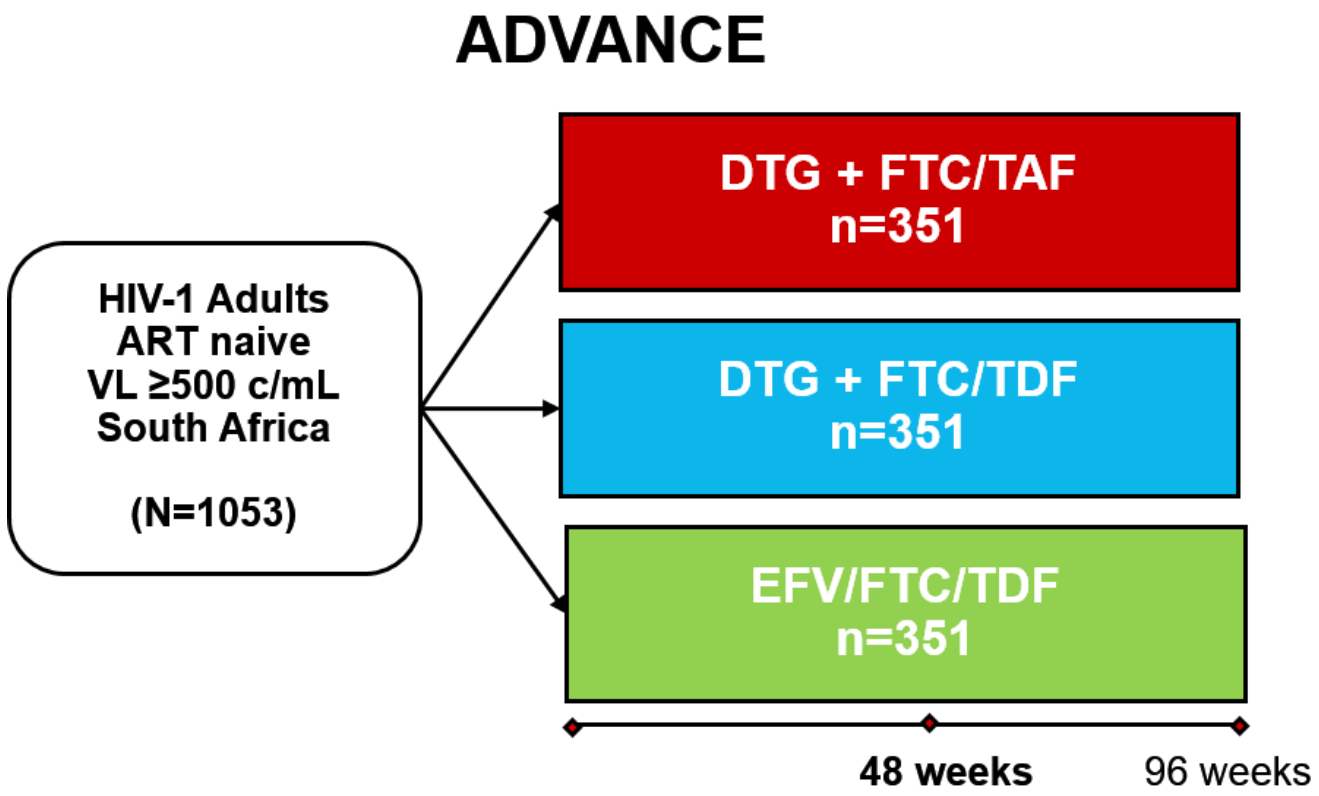
Sax. Clin Infect Dis. 2020;71:1379.

Risk Factors for a >10% Weight Gain in 8 RCTs

Variable	Odds Ratio	95% CI	p-value
CD4 count (<200 vs ≥200)	4.36	(3.6–5.27)	<0.001
HIV RNA (>100K vs ≤100K)	1.98	(1.65–2.37)	<0.001
BMI			
Normal vs overweight	1.54	(1.27–1.87)	<0.001
Normal vs obese	1.66	(1.29–2.15)	<0.001
Sex (female vs male)	1.54	(1.21–1.96)	<0.001
Race (black vs non-black)	1.32	(1.10–1.59)	<0.01
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	<0.01
EVG/c vs EFV	1.36	(1.04–1.78)	0.03
ATV/r vs EFV	0.92	(0.59–1.45)	0.73

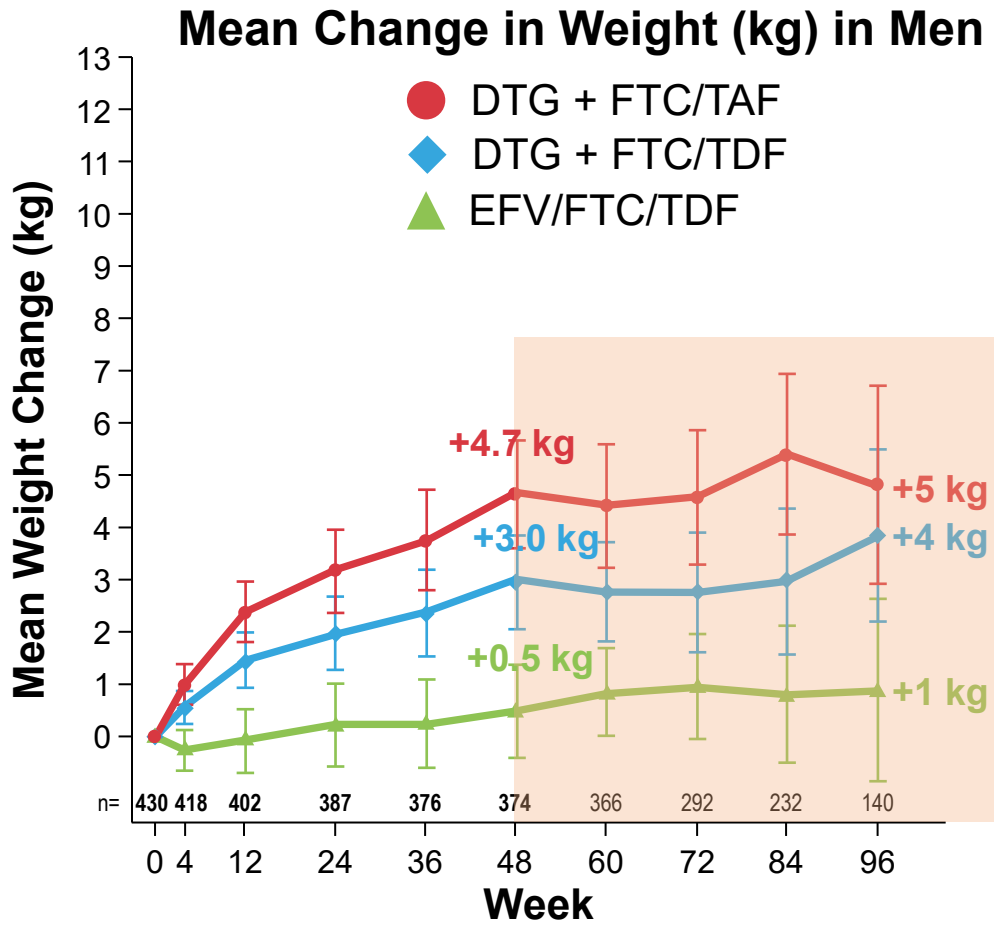
Sax. Clin Infect Dis. 2020;71:1379.

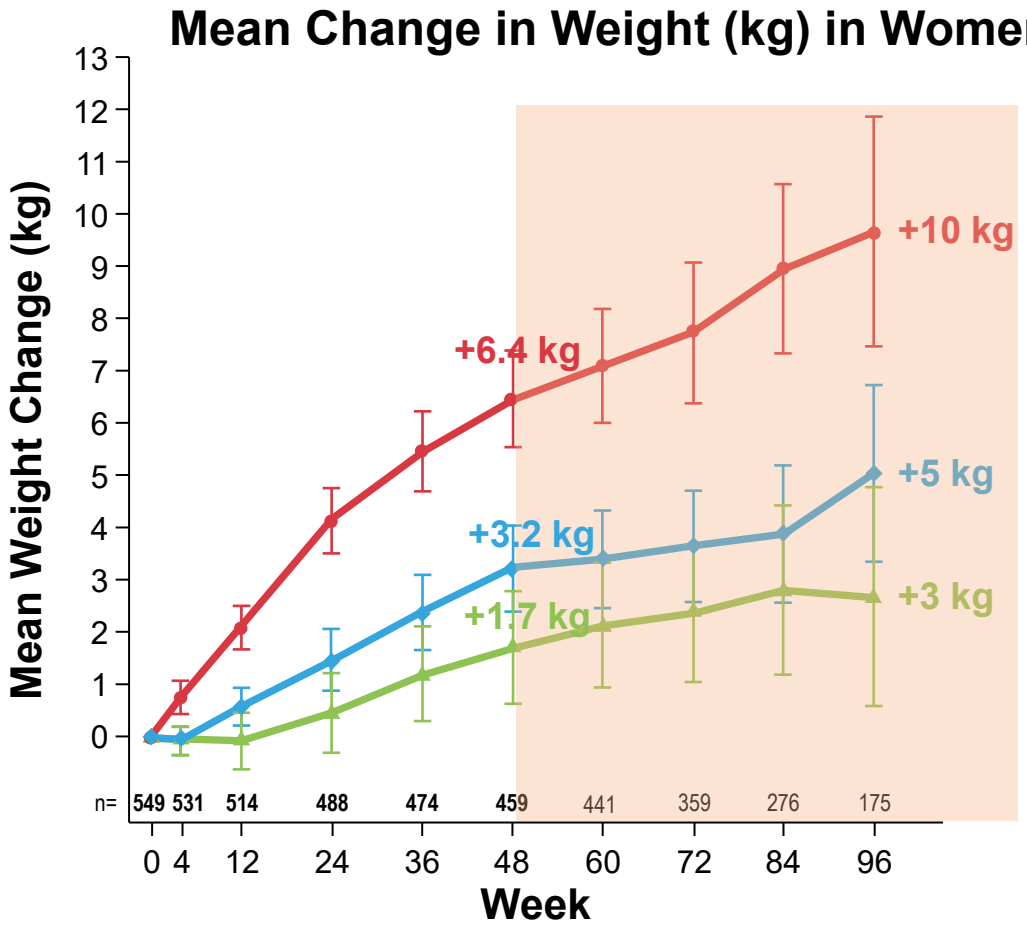
ADVANCE Study: South Africa



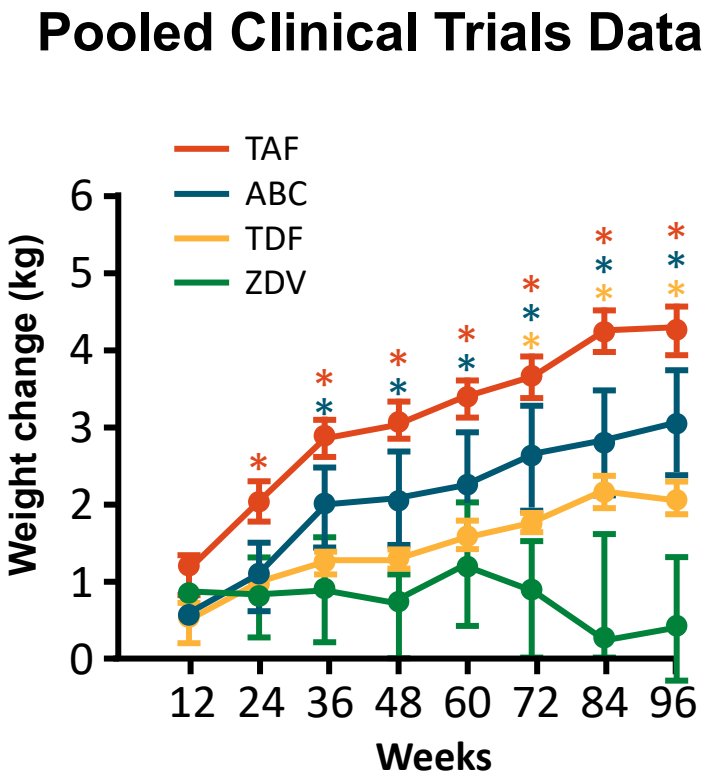
Hill A, et al. IAS 2019, Oral MOAX0102LB
Venter W, et al. N Engl J Med 2019 and supplementary appendix

ADVANCE Study: South Africa



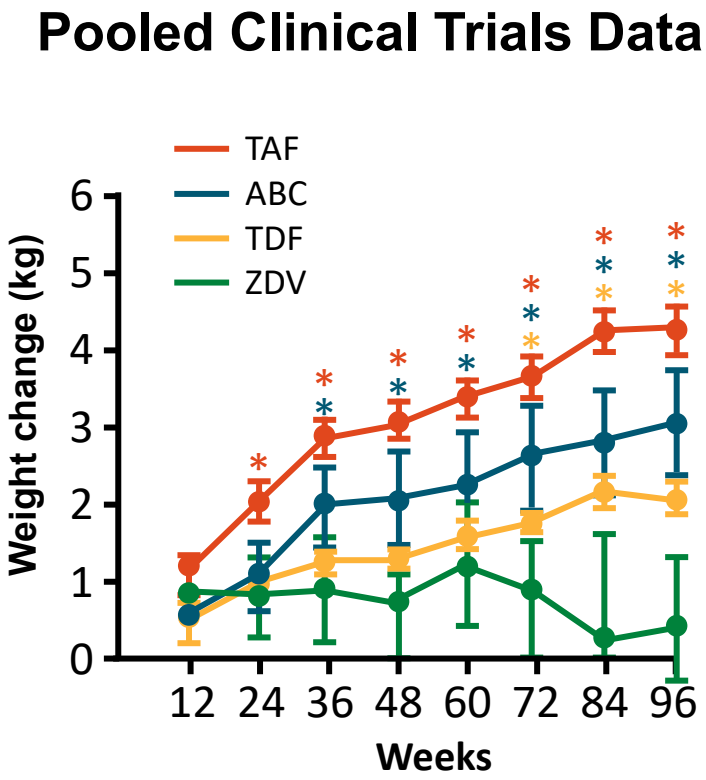


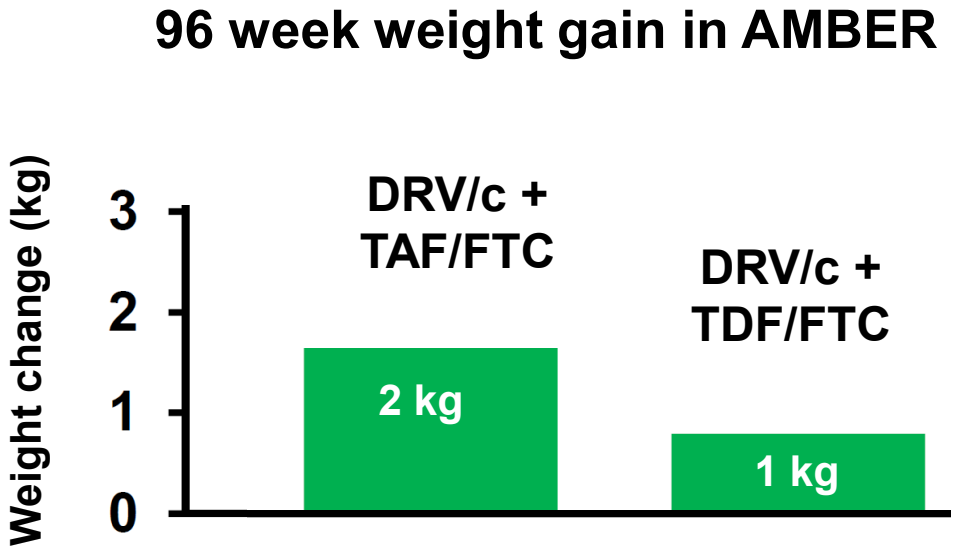
Tenofovir Alafenamide Fumarate and Weight Gain in the ART-naive



Sax. Clin Infect Dis. 2020;71:1379

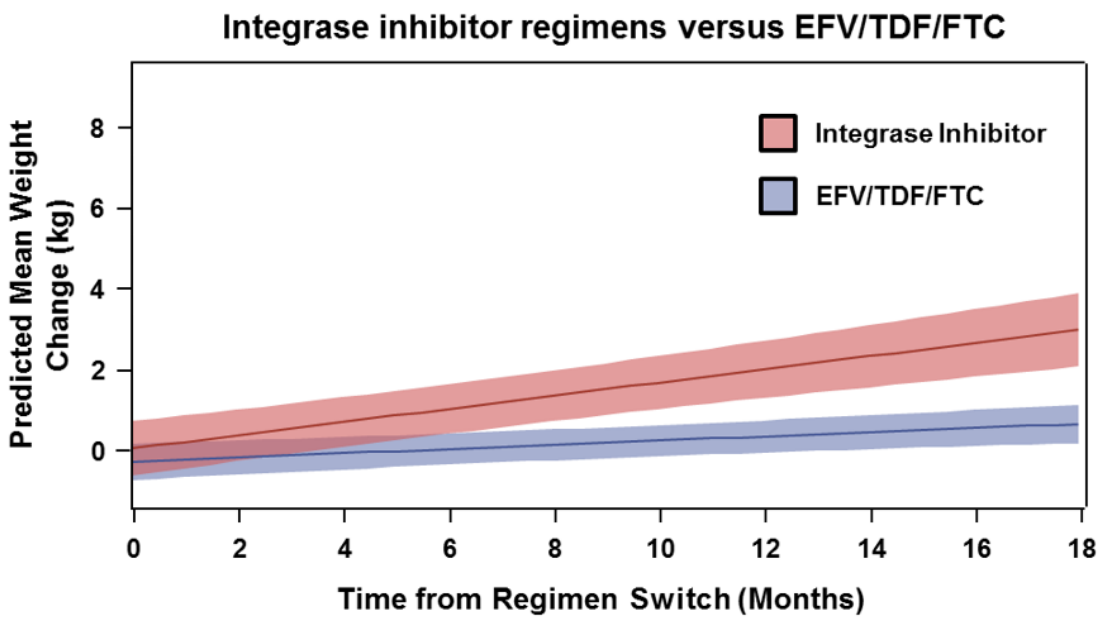
Tenofovir Alafenamide Fumarate and Weight Gain in the ART-naive

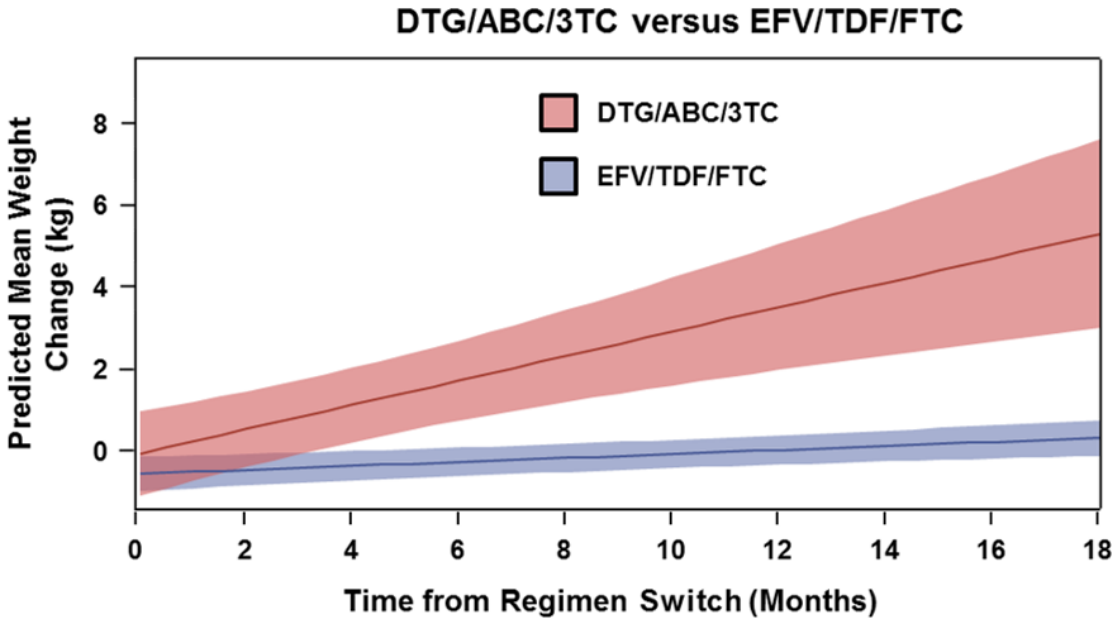




Sax. Clin Infect Dis. 2020;71:1379; Orkin C, et al. AIDS 2020

Weight Change After ART Switch





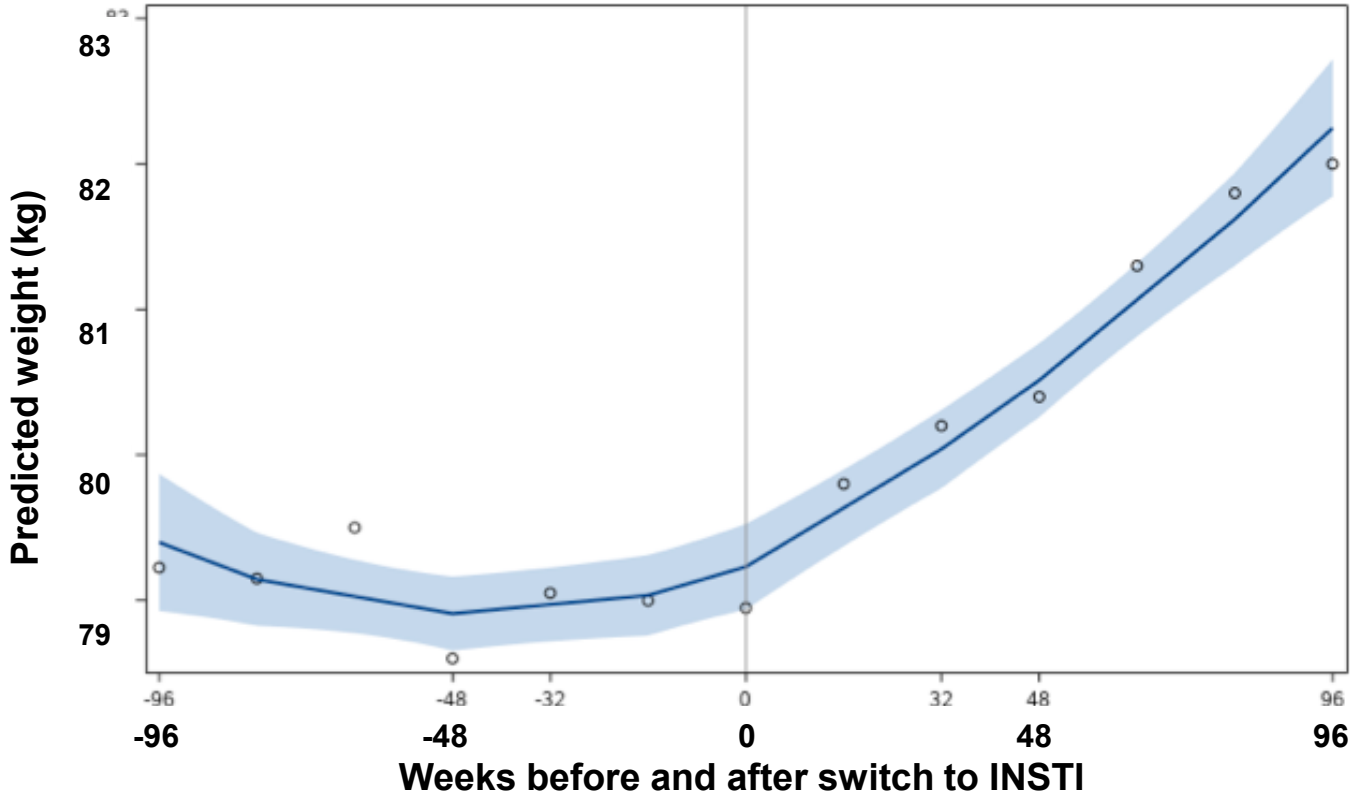
Weight gain in PWH switched from Efavirenz to INSTI-based regimens

- Retrospective, single-site study (n=495)
- Adults on EFV/TDF/FTC with viral suppression for 2 years switched to an INSTI vs. continued on EFV/TDF/FTC
- Weight gain highest among those switching to Doultegravir with ABC/3TC

Norwood J. *et al. JAIDS*, 2017

AIDS Clinical Trials Group: Excess Weight Gain Following Switch to INSTI-based Regimens

- **972 adults switched to INST-based regimens in ACTG A5001 and A5322**
- **Median 7.8 years of prior treatment**
- **Women, blacks and persons age ≥60 experienced the largest increases**
- **Dolutegravir associated with greatest weight gain**

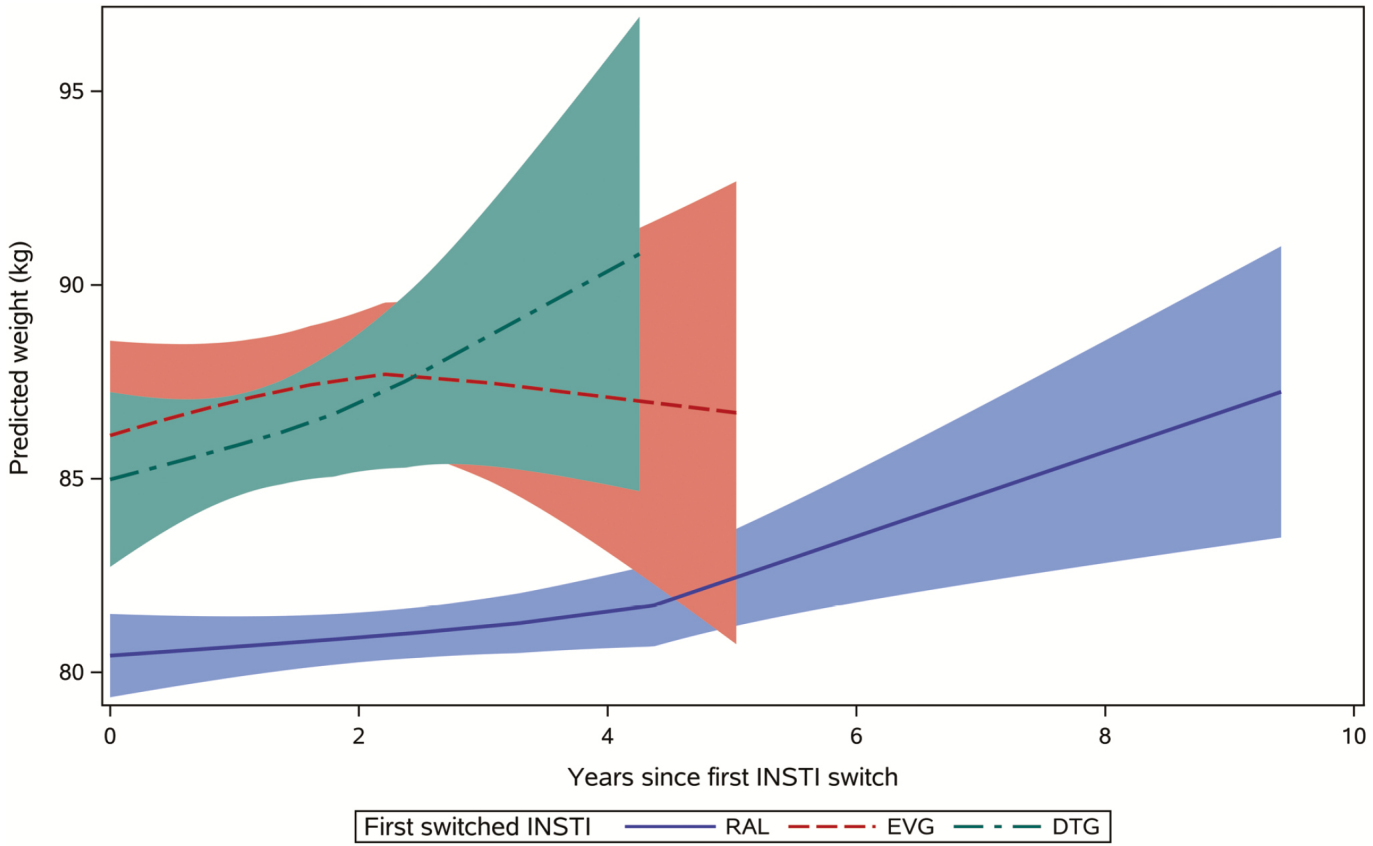


Lake, JE. et al. *CID*, 2020

Estimated Weight After Switch to an INSTI

ACTG A5001 & A5322

DTG (green)
EVG (red)
RAL (blue)

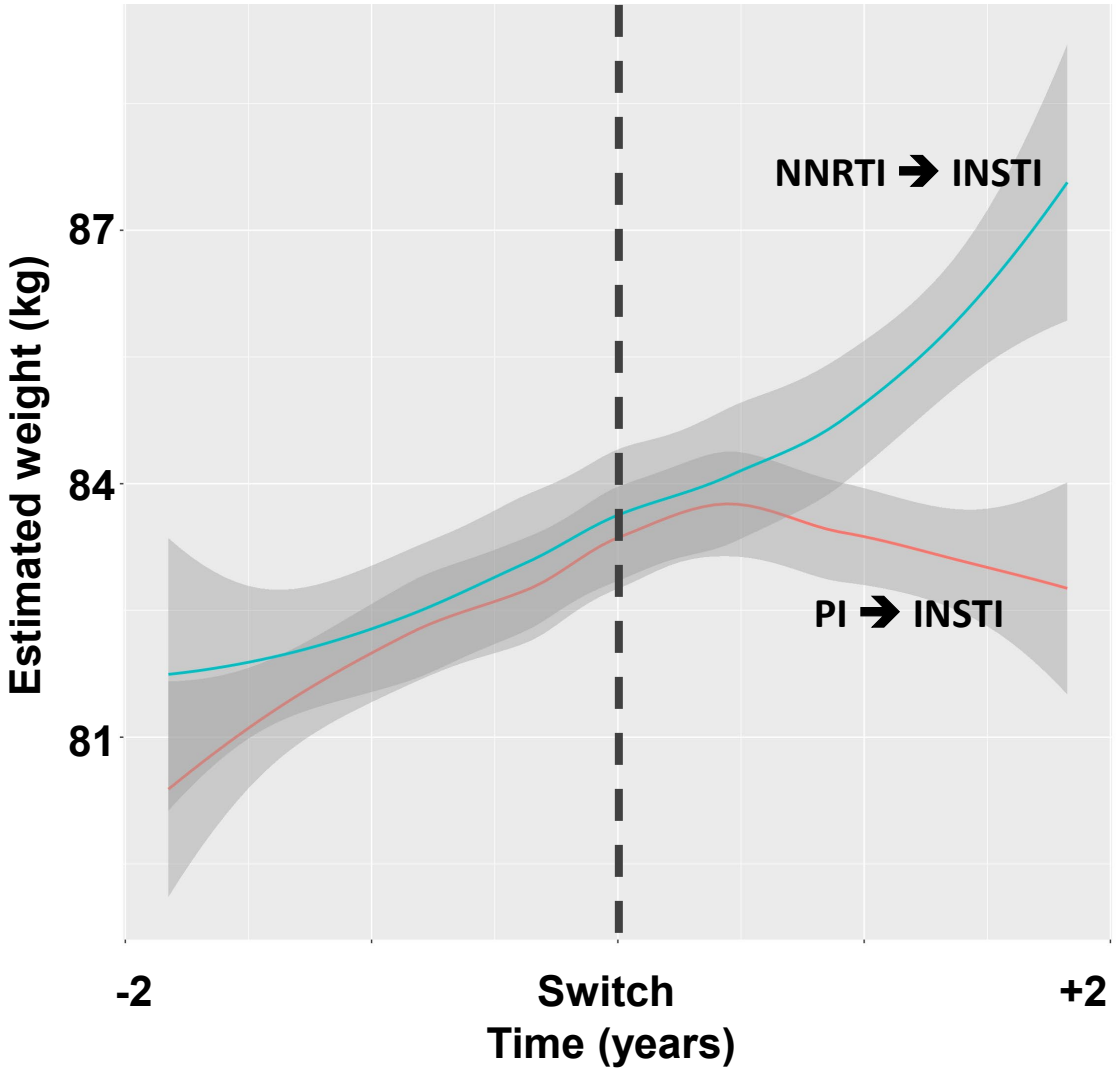


	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2 (0.1)	0.5 (0.008)	0.5 (<0.001)
Post-INSTI	1.3 (<0.001)	0.9 (<0.001)	0.3 (0.05)
Pre-post difference	1.0 (<0.001)	0.5 (0.1)	-0.2 (0.4)

kg/year (p value); DTG=dolutegravir, EVG=elvitegravir, RAL=raltegravir

Lake, JE. et al. *CID*, 2020

NA-ACCORD: Weight Change after Switch from NNRTI or PI to an INSTI-based Regimen

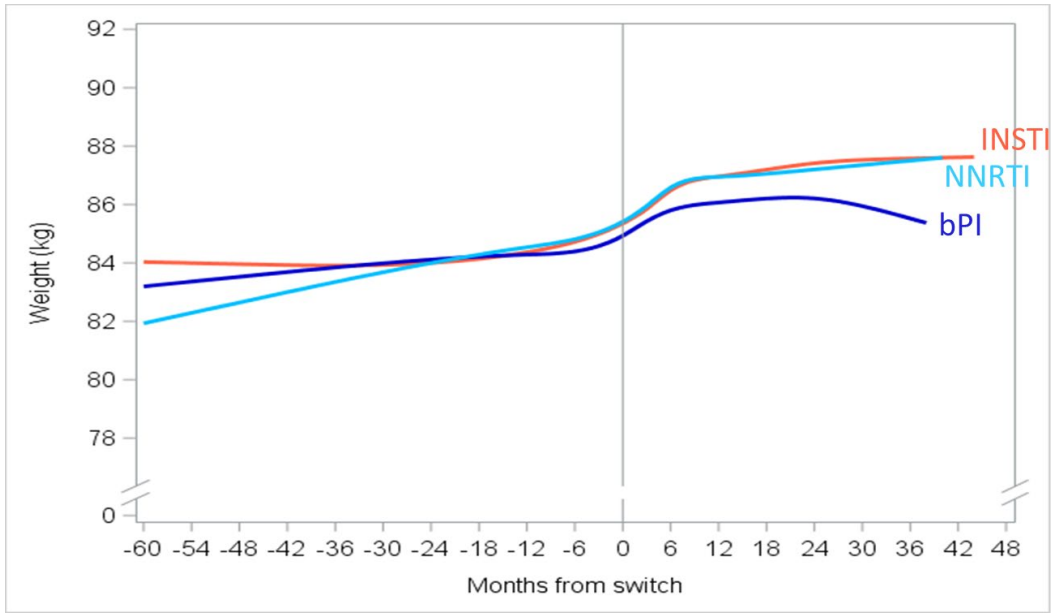


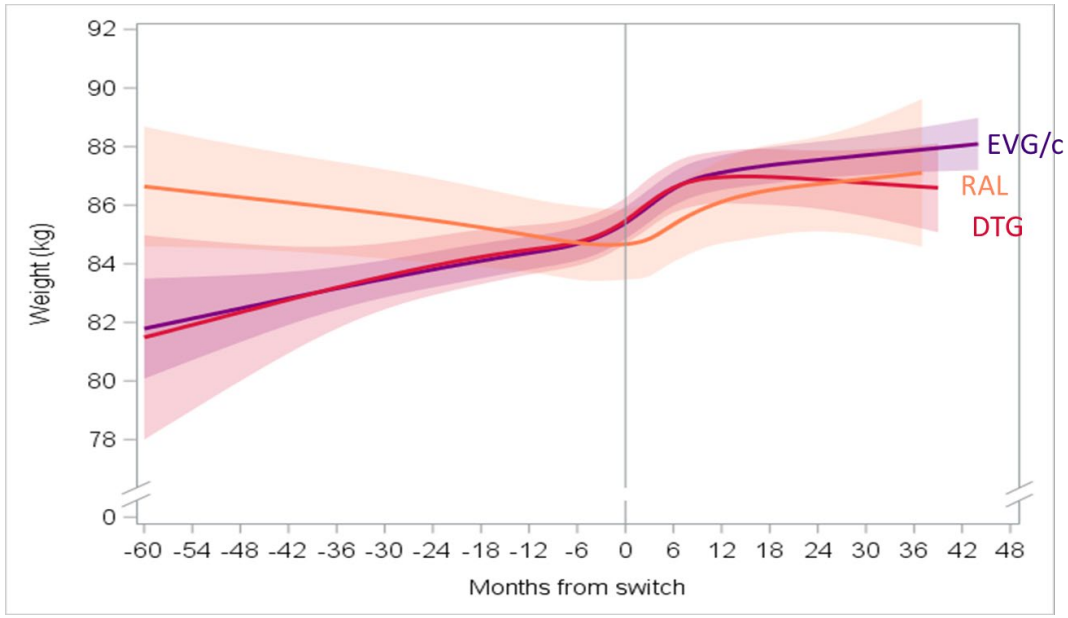
Regimen switch	Pre-switch weight slope (kg/year)	Post-switch weight slope (kg/year)	P-value for slope change
NNRTI → INSTI	**0.63**	**1.13**	**<0.001**
NNRTI → DTG	0.84	1.73	<0.001
NNRTI → RAL	0.74	0.97	0.21
NNRTI → EVG	0.56	1.00	0.07
PI → INSTI	**0.80**	**0.34**	**<0.001**
PI → DTG	0.84	-0.04	<0.001
PI → RAL	0.74	0.17	<0.001
PI → EVG	0.56	0.89	0.11

NA-ACCORD, CROI 2020 Abstract 668

OPERA: Weight Gain Before and After Switch from TDF to TAF

OPERA Cohort: Prospectively captured, routine clinical data from electronic health records

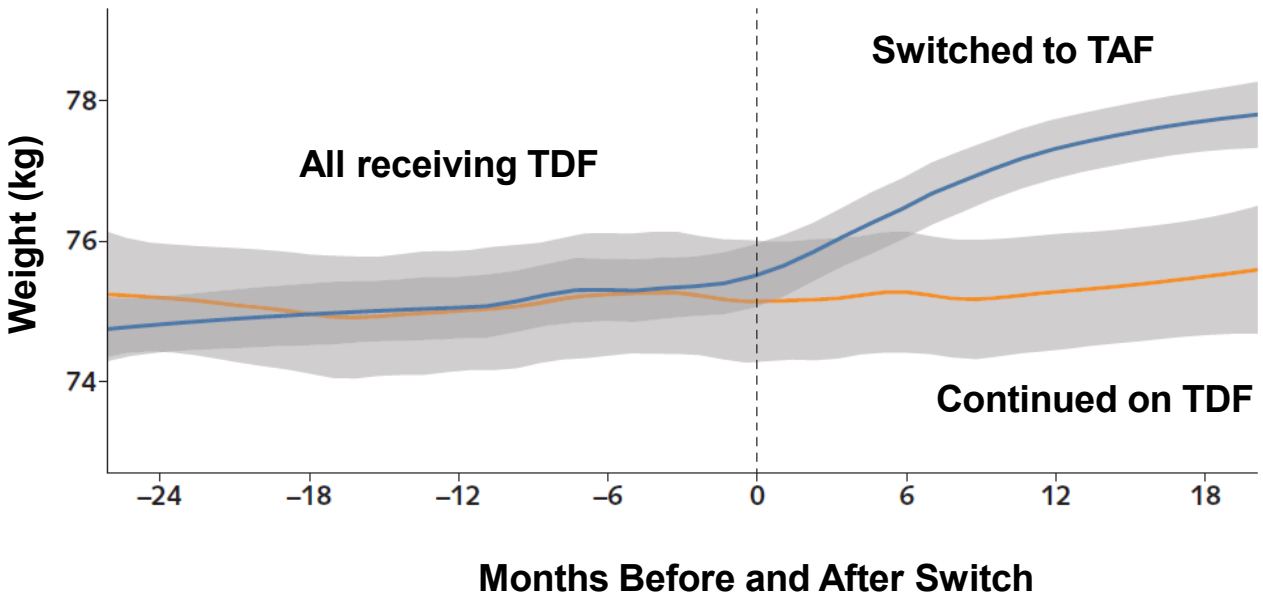


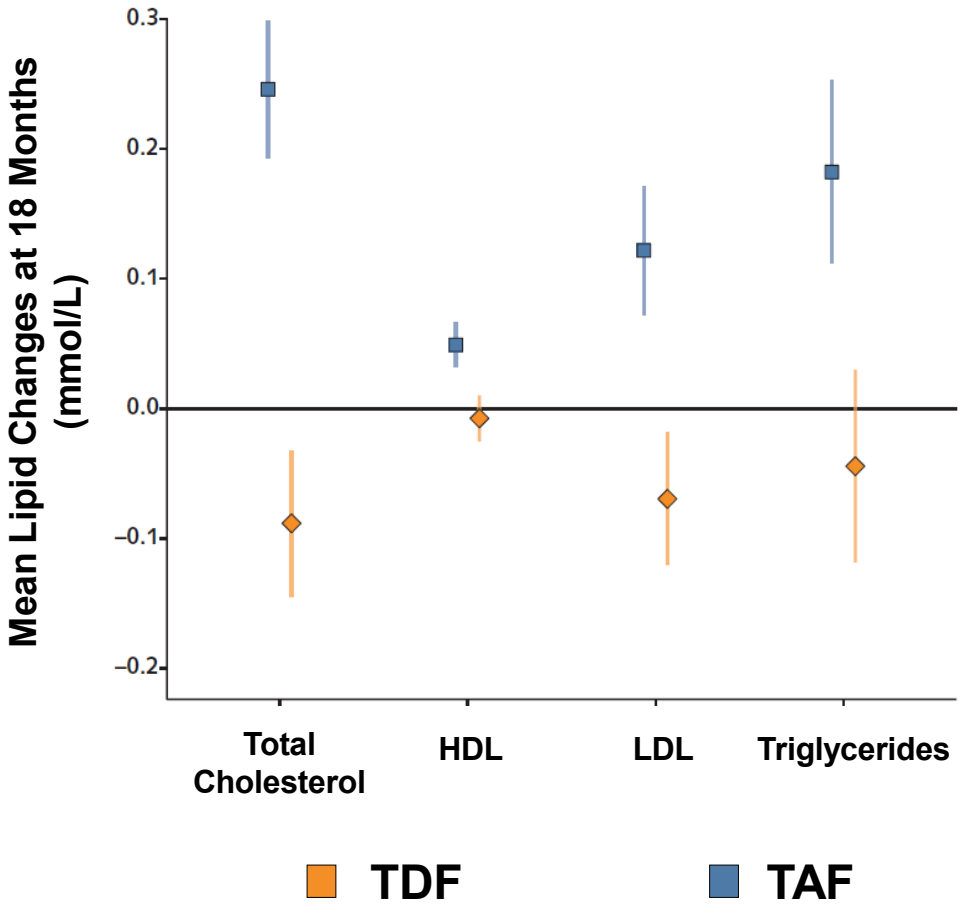


	-60 to 0 months	0 to 9 months	9+ months
INSTI (n=3,281), kg/year (95% CI)	0.42 (0.26, 0.59)	2.64 (2.26, 3.01)	0.29 (0.08, 0.51)
Boosted PI (n=746), kg/year (95% CI)	0.31 (-0.02, 0.64)	1.98 (1.13, 2.83)	-0.11 (-0.57, -0.35)
NNRTI (n=1,452), kg/year (95% CI)	0.66 (0.51, 0.81)	2.25 (1.78, 2.71)	0.20 (-0.14, 0.54)

Brunet L, et al. AIDS 2020.

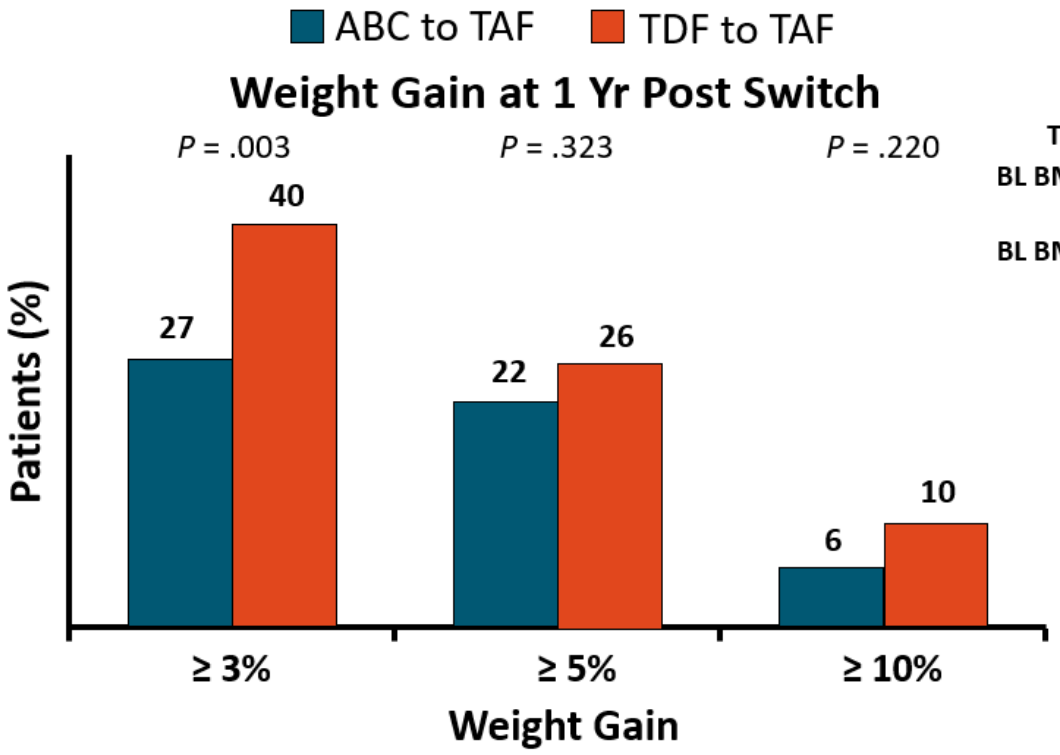
Swiss HIV Cohort Study: Weight and Lipid Changes after Switch from TDF to TAF

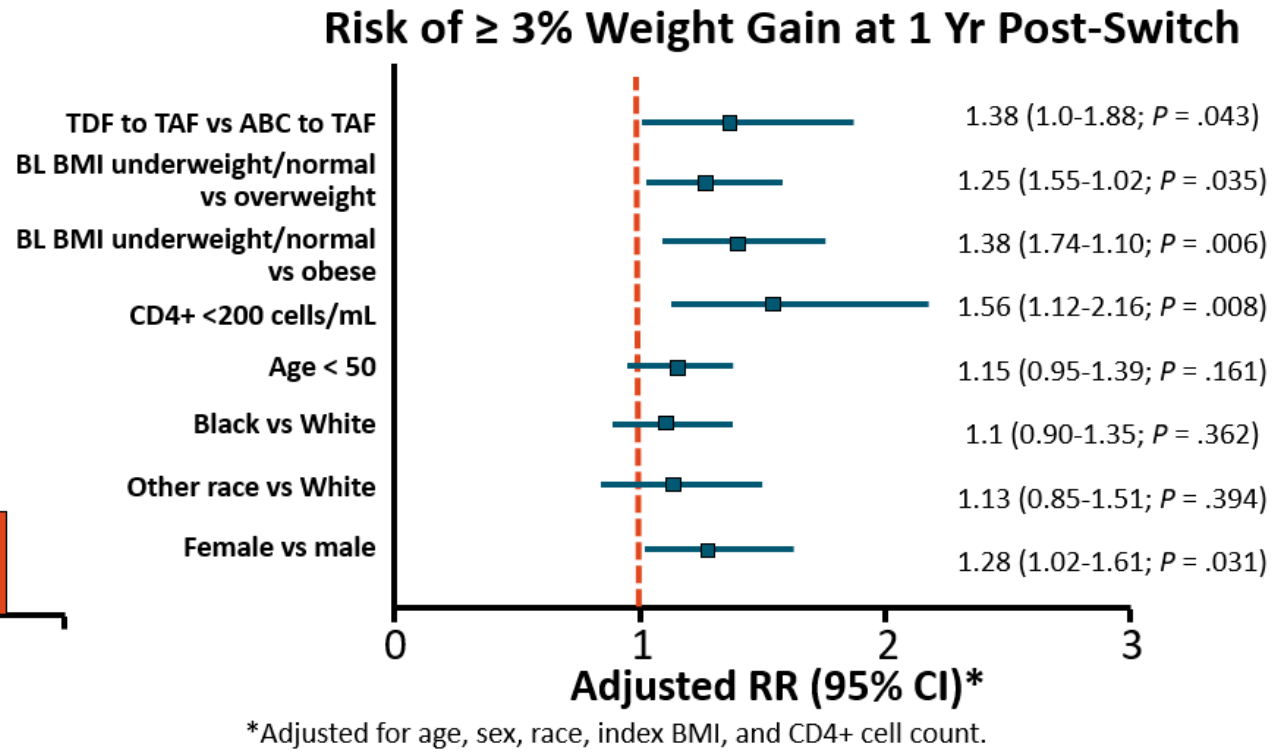




Surial B. et al. Annals of Internal Medicine, 2021

TRIO: Greater Weight Gain After TDF to TAF vs. ABC to TAF Switch





While TDF to TAF had a higher proportion of persons gaining ≥3% weight compared to ABC to TAF, differences in ≥5% and ≥10% not significant

McComsey, G. ID WEEK 2020

graph credit: clinicaloptions.com

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

Demographics and Comorbidities


Female Sex


Non-white race


Age

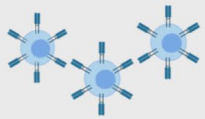

Psychiatric comorbidities


AST <30


Hypogonadism

HIV and Antiretroviral Therapy


INSTIs, bPIs, TAF


CD4+ count <100-200 cells/ul


HIV RNA >100,000 copies/ml


CYP2B6 & resistin alleles

Lifestyle


BMI at treatment start


IVDU

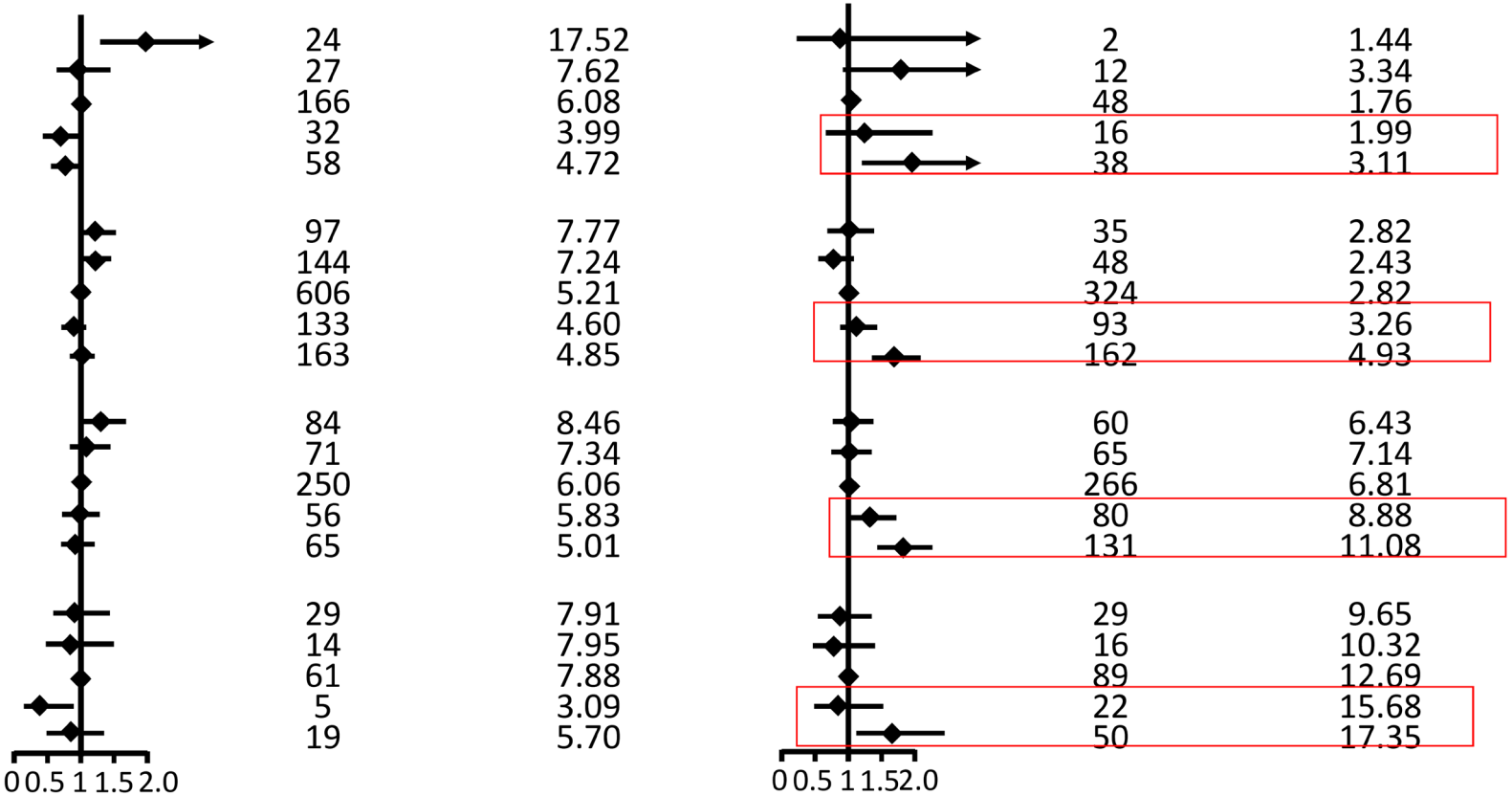

Caloric intake and dietary composition


Physical activity

Metabolic Consequences of Weight Gain on ART

D:A:D Study – Higher Risk of Diabetes, but not CVD, after BMI Increase on ART

	CVD	CVD Events	Rate/1000 Yrs	DM	DM events	Rate/1000 Yrs
Baseline BMI < 20						
BMI decrease > 2		24	17.52		2	1.44
BMI decrease 1-2		27	7.62		12	3.34
BMI stable ± 1		166	6.08		48	1.76
BMI increase 1-2		32	3.99		16	1.99
BMI increase > 2		58	4.72		38	3.11
Baseline BMI 20-25						
BMI decrease > 2		97	7.77		35	2.82
BMI decrease 1-2		144	7.24		48	2.43
BMI stable ± 1		606	5.21		324	2.82
BMI increase 1-2		133	4.60		93	3.26
BMI increase > 2		163	4.85		162	4.93
Baseline BMI 25-30						
BMI decrease > 2		84	8.46		60	6.43
BMI decrease 1-2		71	7.34		65	7.14
BMI stable ± 1		250	6.06		266	6.81
BMI increase 1-2		56	5.83		80	8.88
BMI increase > 2		65	5.01		131	11.08
Baseline BMI 30+						
BMI decrease > 2		29	7.91		29	9.65
BMI decrease 1-2		14	7.95		16	10.32
BMI stable ± 1		61	7.88		89	12.69
BMI increase 1-2		5	3.09		22	15.68
BMI increase > 2		19	5.70		50	17.35



CVD: Adjusted for age, race, transmission mode, sex, recent ABC and other NRTI use, cumulative protease inhibitor use, CD4+ count, family history of CVD, smoking status
DM: Adjusted for age, race, mode of transmission, sex, stavudine use, triglycerides, CD4+ count, smoking status, and HDL

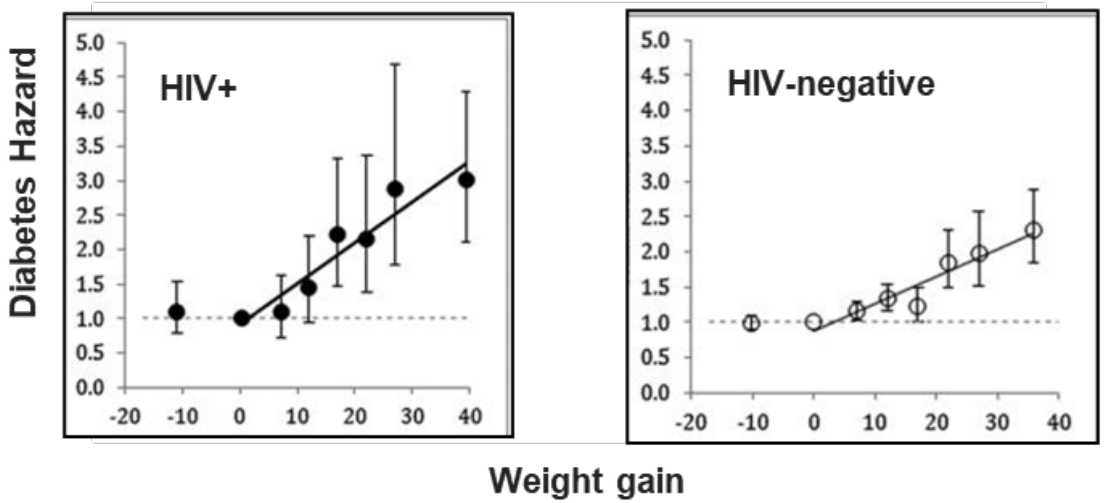
Petoumenos, et al. CROI 2020 Abstract 83

Obesity Disproportionately Increases Diabetes Risk in PWH Compared to HIV-negative Controls

Diabetes prevalence is higher in obese PWH….

BMI category	Diabetes Odds PLWH	Diabetes Odds HIV-negative
20-24.9	1.0	1.0
25-29.9	1.4	1.4
≥ 30	**3.2**	**2.7**

…and incidence rises more steeply with weight gain

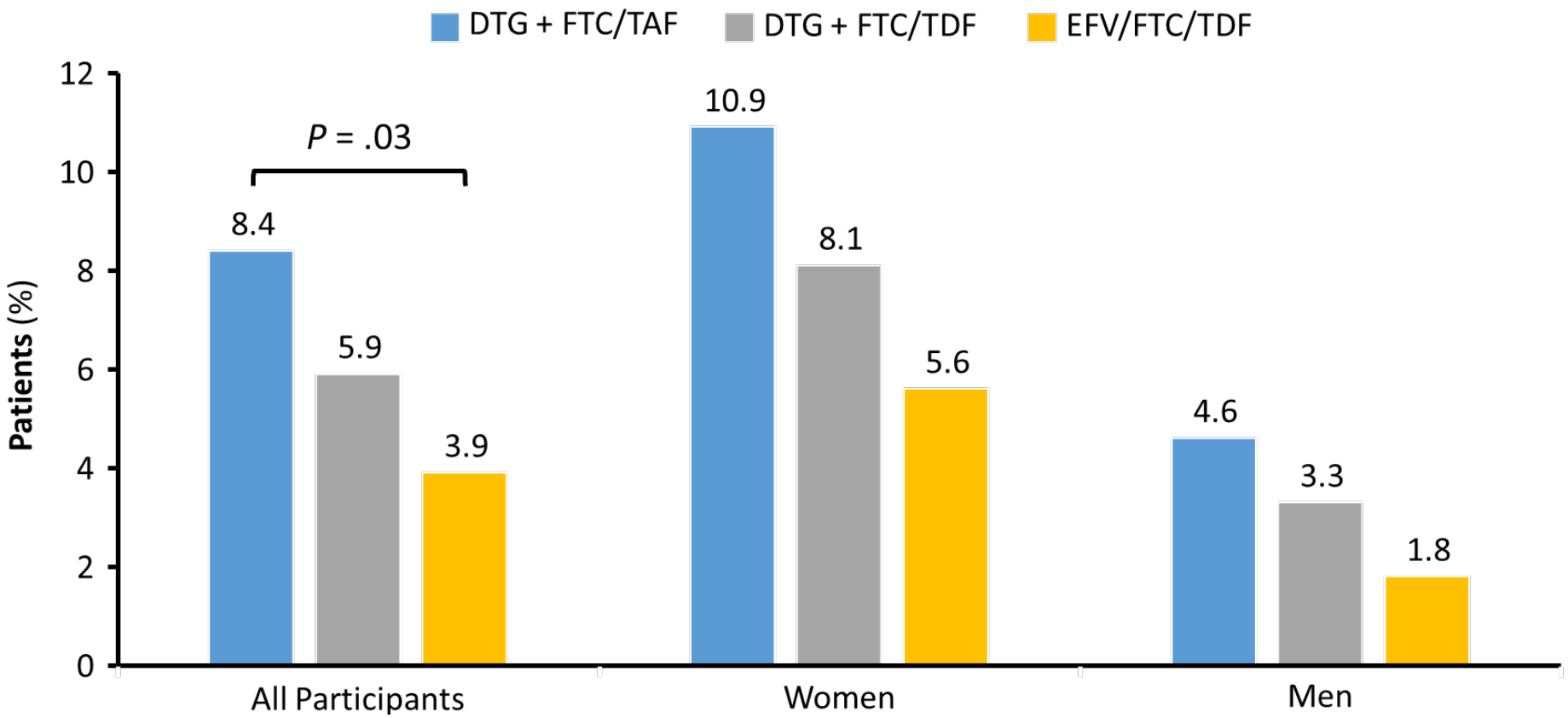


Higher BMI and central obesity are associated with neurocognitive decline, fatty liver disease, cardiovascular events, and multimorbidity in PLWH

Butt AA, *et al. AIDS*. 2009, Kim DJ, *et al. JAIDS*. 2012, Herrin M, *et al. JAIDS* 2016, Womack JA *et al. JAHA* 2014, Freiberg M *et al. JAMA Int Med* 2013, Sattler F, *et al. JAIDS* 2015, Rubin LH, et al. CROI 2019 Poster #1069.

ADVANCE Study: South Africa

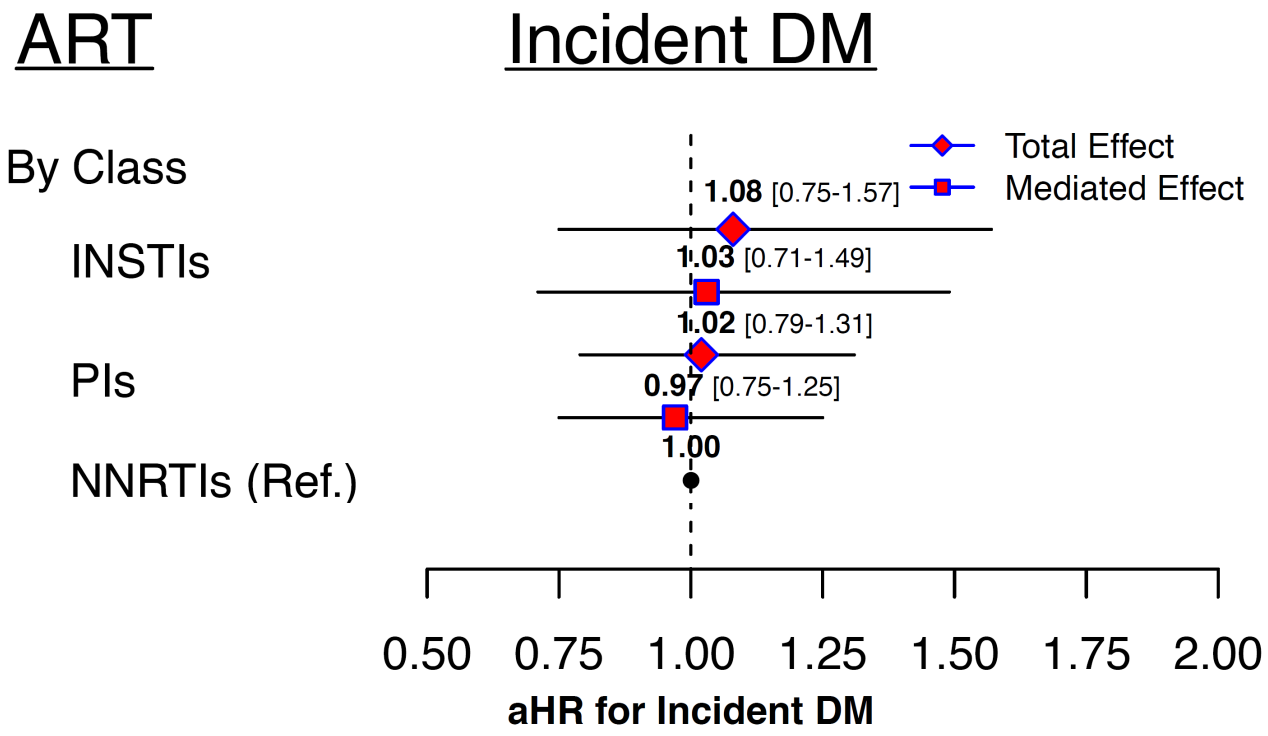
Treatment-Emergent Metabolic Syndrome at Week 96



Sokhela S, et al. AIDS 2020.

NA-ACCORD: Risk of Incident Diabetes Mellitus after Initiation of ART

- 22,884 PWH starting ART in NA-ACCORD
- Higher risk of developing diabetes (Total Effect) after starting INSTI and PI compared to NNRTI-based regimens, but 95% CI crossed 1.0
- Diabetes risk attenuated (Direct Effect) when models further adjusted for 12 month weight



Rebeiro P, et al. CID 2020

Metabolic Disease Risk Is Affected by *Where* Weight is Regained on ART

ART initiation

Weight Gain

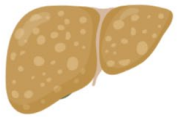
- Reduced resting energy requirements
- Improved appetite and nutrient absorption
- Impaired energy storage in subcutaneous fat & altered lipid kinetics
- Access to nutrition and smoking cessation services
- Specific ART regimens

Stable ART

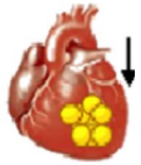
Response spectrum

Visceral fat

Hepatic steatosis



Peri/epicardial fat



Muscle fat / sarcopenia

<u>Comorbid conditions:</u>

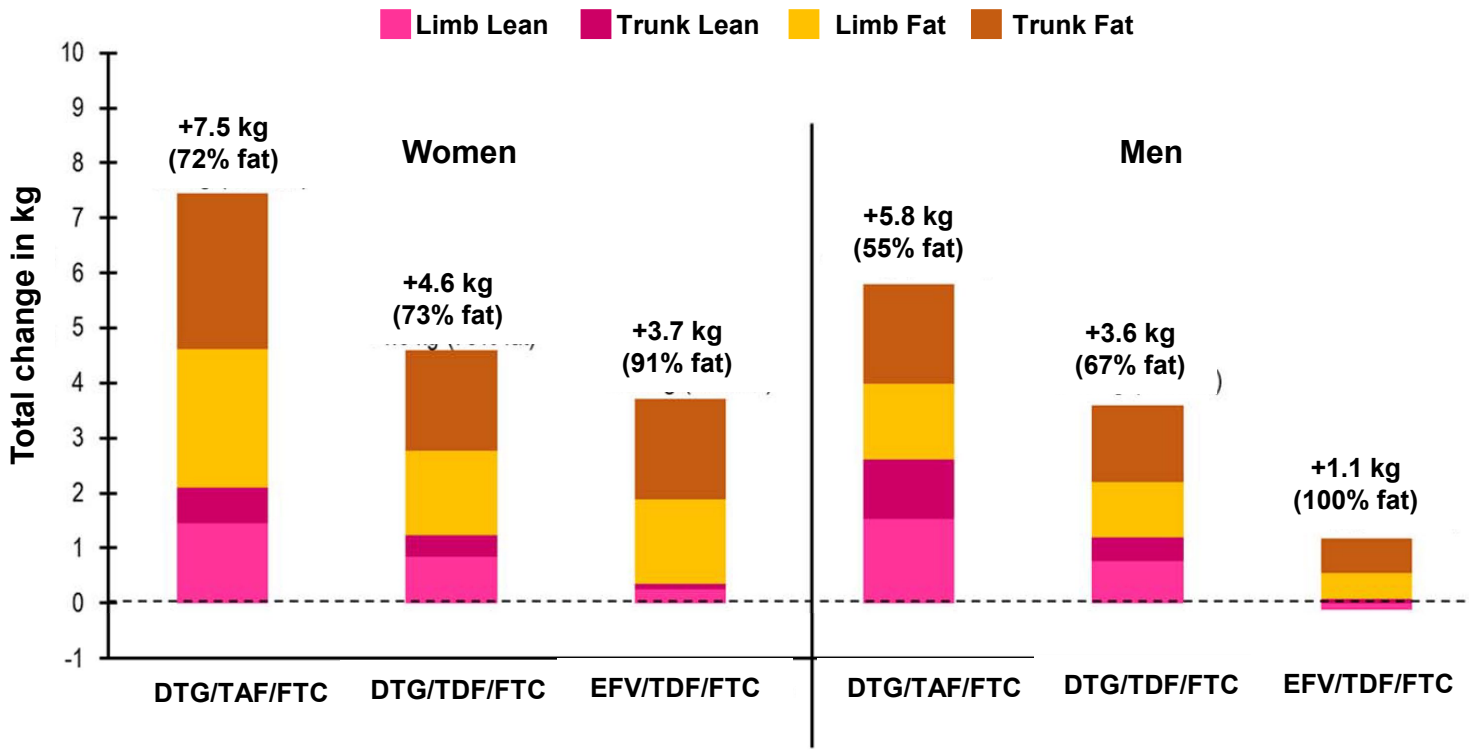
- **Insulin resistance / diabetes**
- **Hypertriglyceremia and mixed hyperlipidemia**
- **Liver fibrosis**
- **Hypertension**
- **Coronary and peripheral artery atherosclerosis**
- **Frailty (including sarcopenic obesity)**
- **Neurocognitive decline**

<u>Other consequences:</u>

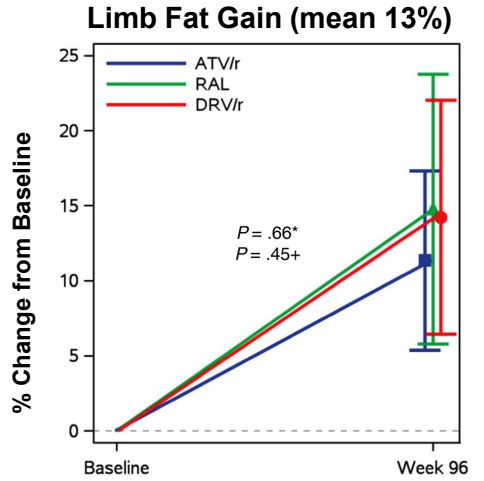
- **Impaired mobility**
- **Body shape changes: peripheral lipoatrophy & central lipohypertrophy**
- **Reduced quality of life**
- **Depression & anxiety**

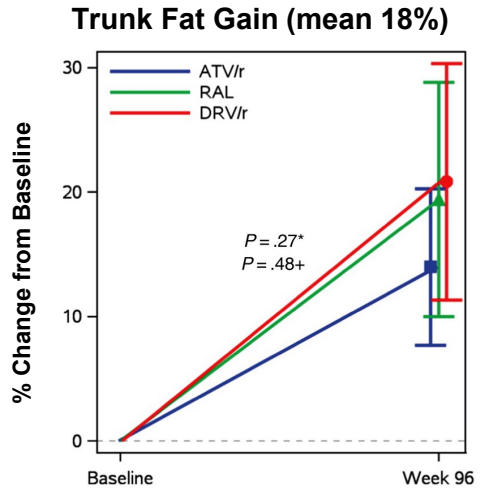
Weight Gain on ART Differs by Anatomic Depot and Is Highly Variable

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



Change in limb and trunk fat over 96 weeks in ACTG 5260s

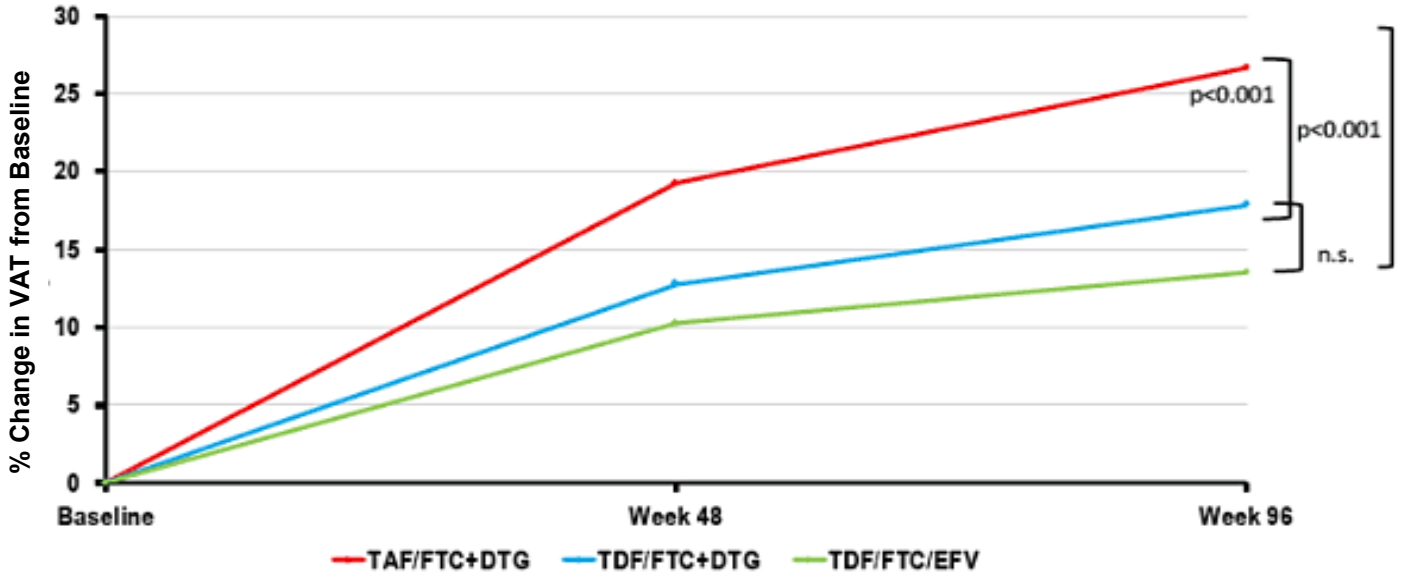




Venter W, et al. Lancet HIV 2020; McComsey G, et al. CID 2016

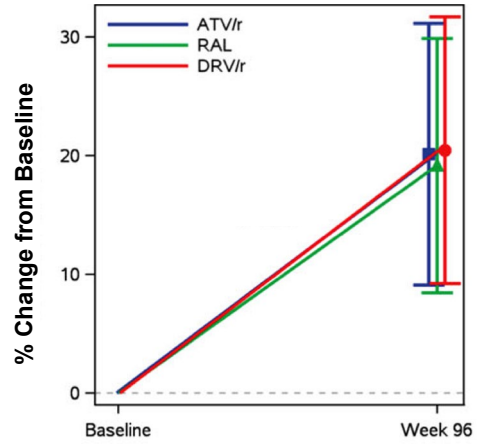
Persons Starting ART May Gain Substantial Visceral Fat

Change in visceral adipose tissue (VAT) by DEXA over 96 weeks in ADVANCE

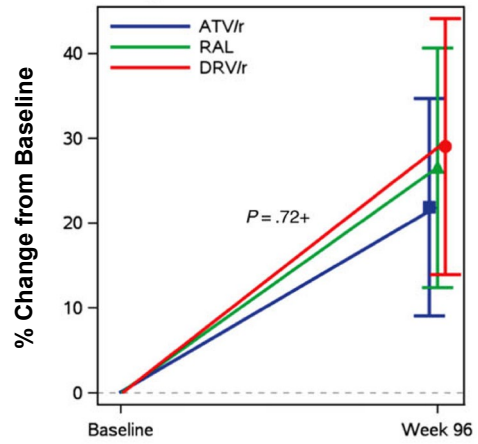


Change in abdominal subcutaneous adipose tissue (SAT) and VAT by CT scan over 96 weeks in ACTG 5260s

SAT Gain (mean 20%)

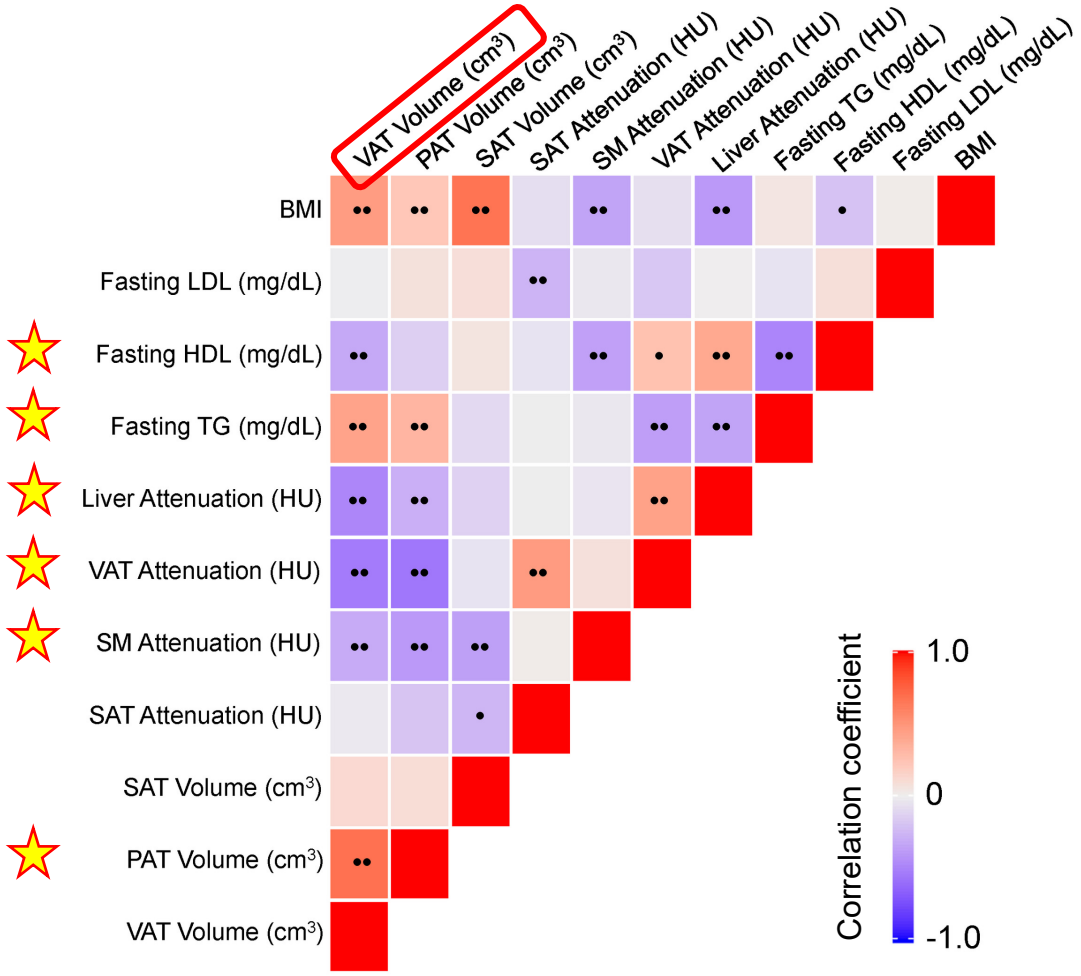


VAT Gain (mean 26%)



Hill, et al. CROI 2020; McComsey G, et al. CID 2016

Increased Visceral Adipose Tissue is Often Accompanied by Other Ectopic Fat Deposits



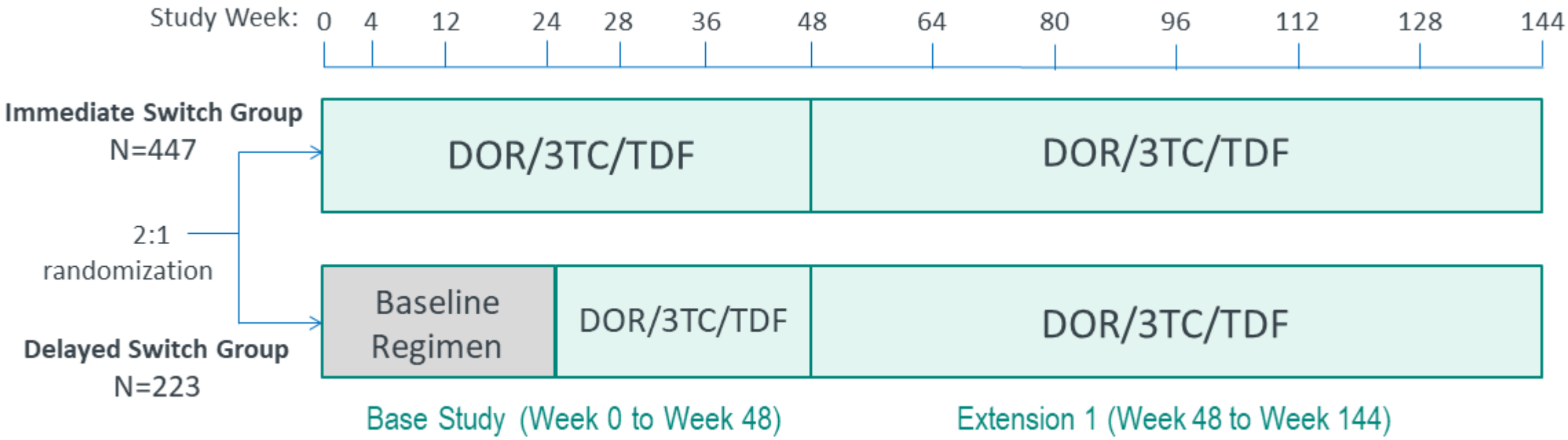
Among 92 PWH on long-term ART, higher visceral adipose tissue (VAT) was correlated with:

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

Gabriel, C et al. Hepatology Comm. 2021

Does Switching from INSTI Regimens Make a Difference in Weight?

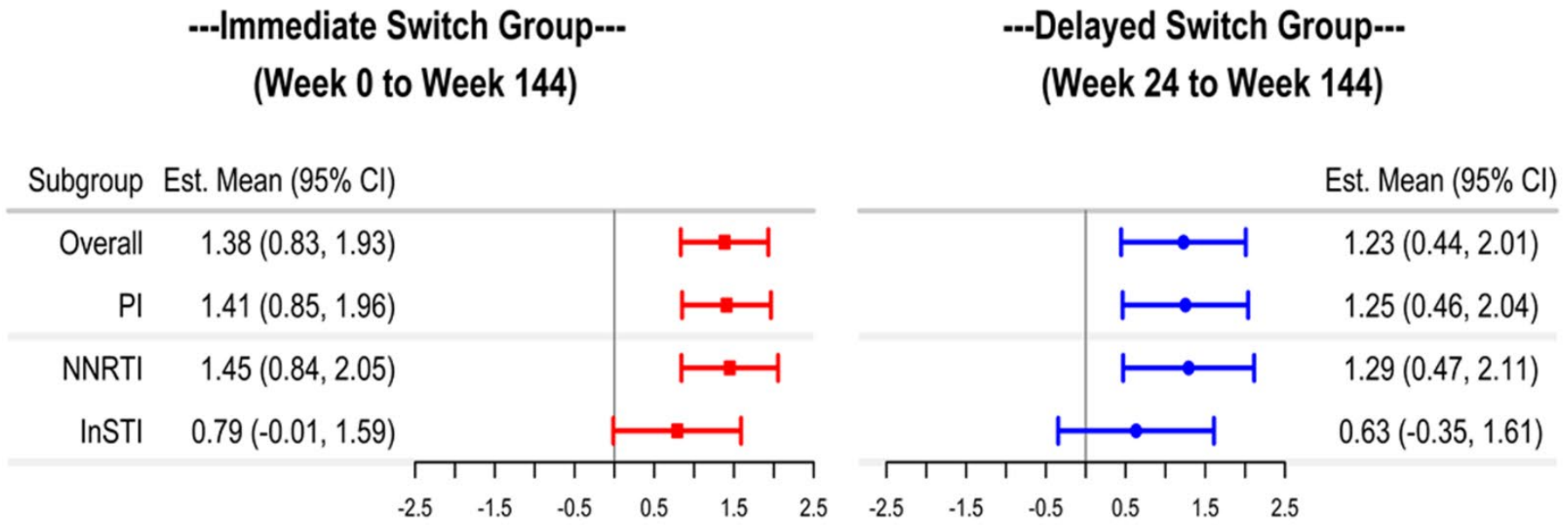
DRIVE-SHIFT: Multicenter study to evaluate a switch from stable ART to Doravirine + 3TC/TDF in virologically suppressed PWH



Kumar P, et al. AIDS 2020

Does Switching from INSTI Regimens Make a Difference in Weight?

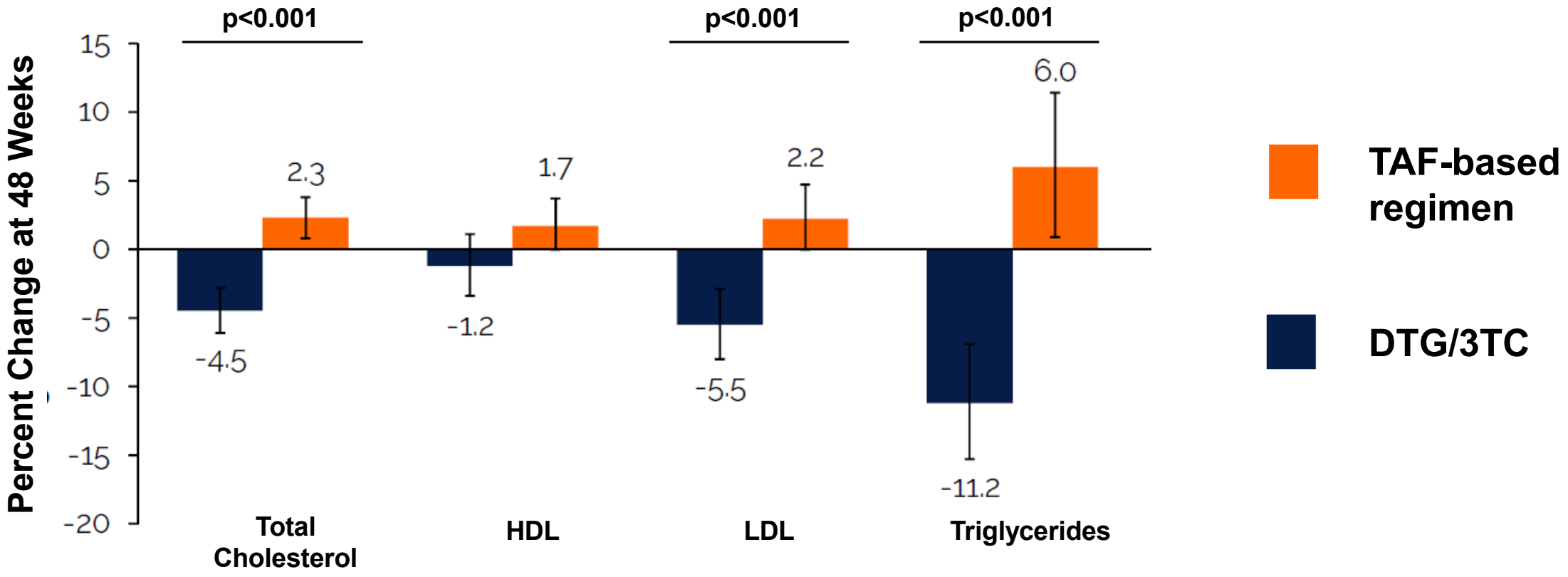
DRIVE-SHIFT: Mean weight change from time of switch to 144 weeks by prior ART regimen



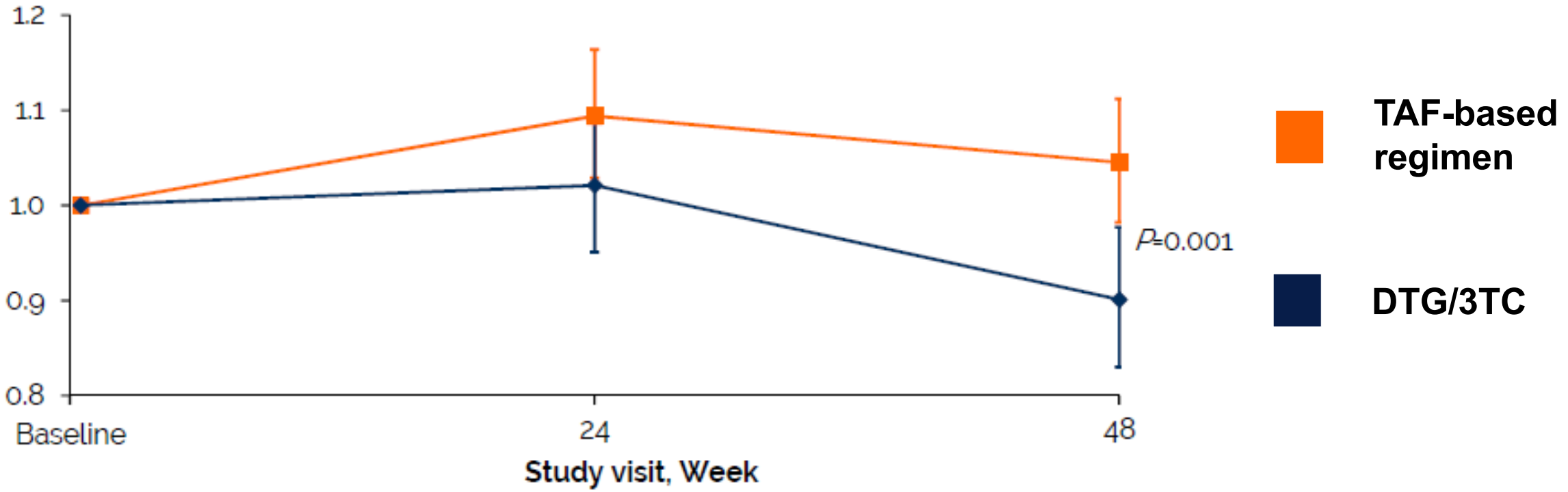
PI = boosted atazanavir, darunavir, or lopinavir. NNRTI = efavirenz, nevirapine, or rilpivirine.
InSTI = boosted elvitegravir and was used with tenofovir alafenamide (TAF) in most cases (17/20 in ISG; 7/9 in DSG).

Kumar P, et al. AIDS 2020

TANGO study: Lipid Changes after a Switch from TAF-based Regimens to Dolutegravir/Lamivudine



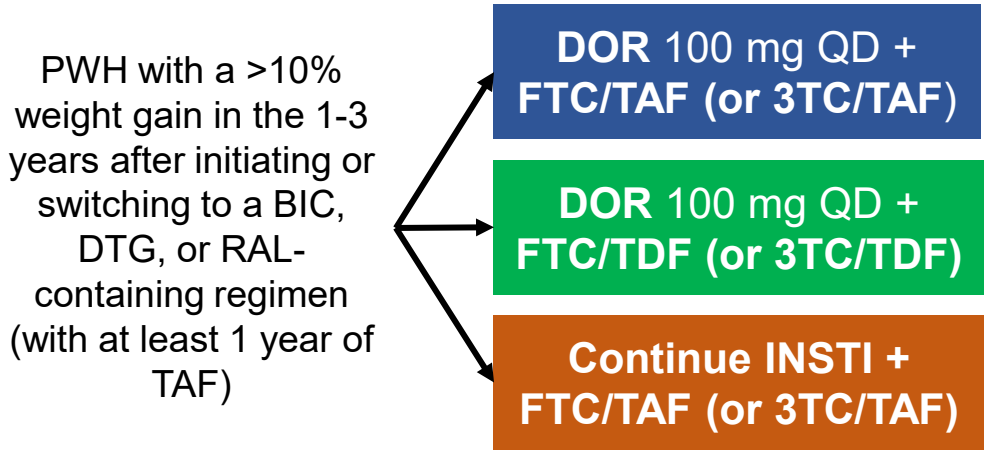
TANGO: Effect of a Switch from TAF-based Regimens to DTG/3TC on Insulin Resistance (HOMA-IR score)



Ongoing ART Switch Studies: ACTG A5391 and DEFINE

ACTG A5391 *Do IT*: Switch from INSTI to Doravirine +/- TDF to TAF

48-week, 3-arm, open label, randomized ART switch study

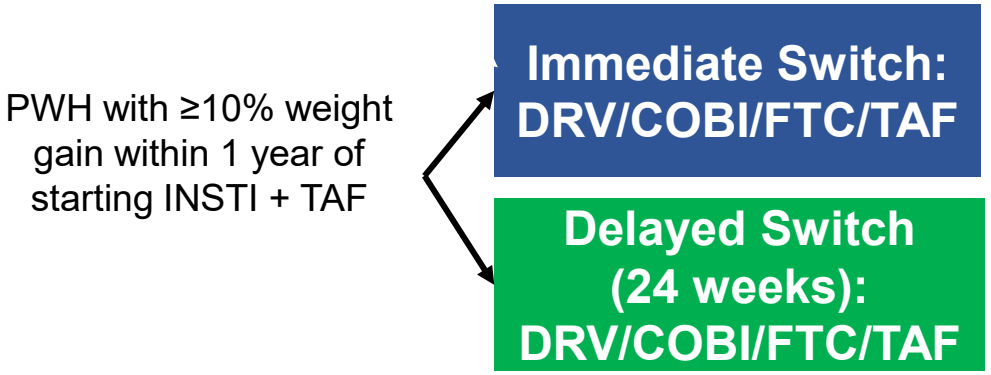


Primary endpoint: Differences in weight change over 48 weeks

Secondary endpoints: viral suppression, safety, body comp., metabolic, bone and renal health

DEFINE: Switch from INSTI + TAF to DRV/c + TAF

24-week, 2-arm, open label, randomized ART switch study



Primary endpoint: Differences in weight change over 24 weeks

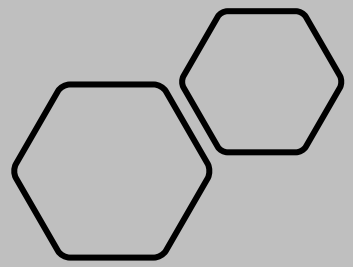
Secondary endpoints: viral suppression, safety, metabolic, liver, bone and renal health

Summary Points

- Weight gain is common after starting ART, and women, persons of African heritage, and those with advanced disease appear more susceptible.
- Observational cohort and pooled trial data suggest weight gain is greater for PWH starting INSTI and TAF-containing regimens, and weight gain can also occur when switching to these agents.
- Weight gain and a higher BMI on ART is accompanied by an increased risk of metabolic syndrome, overt diabetes, and other comorbidities.
- Monitoring weight and metabolic health after ART initiation can identify PWH in need of lifestyle changes or pharmacologic therapy.
- Emerging data suggest some patients with weight gain on ART could benefit from a regimen switch, but additional data from on-going trials is needed.

Thank you

Extra Slides



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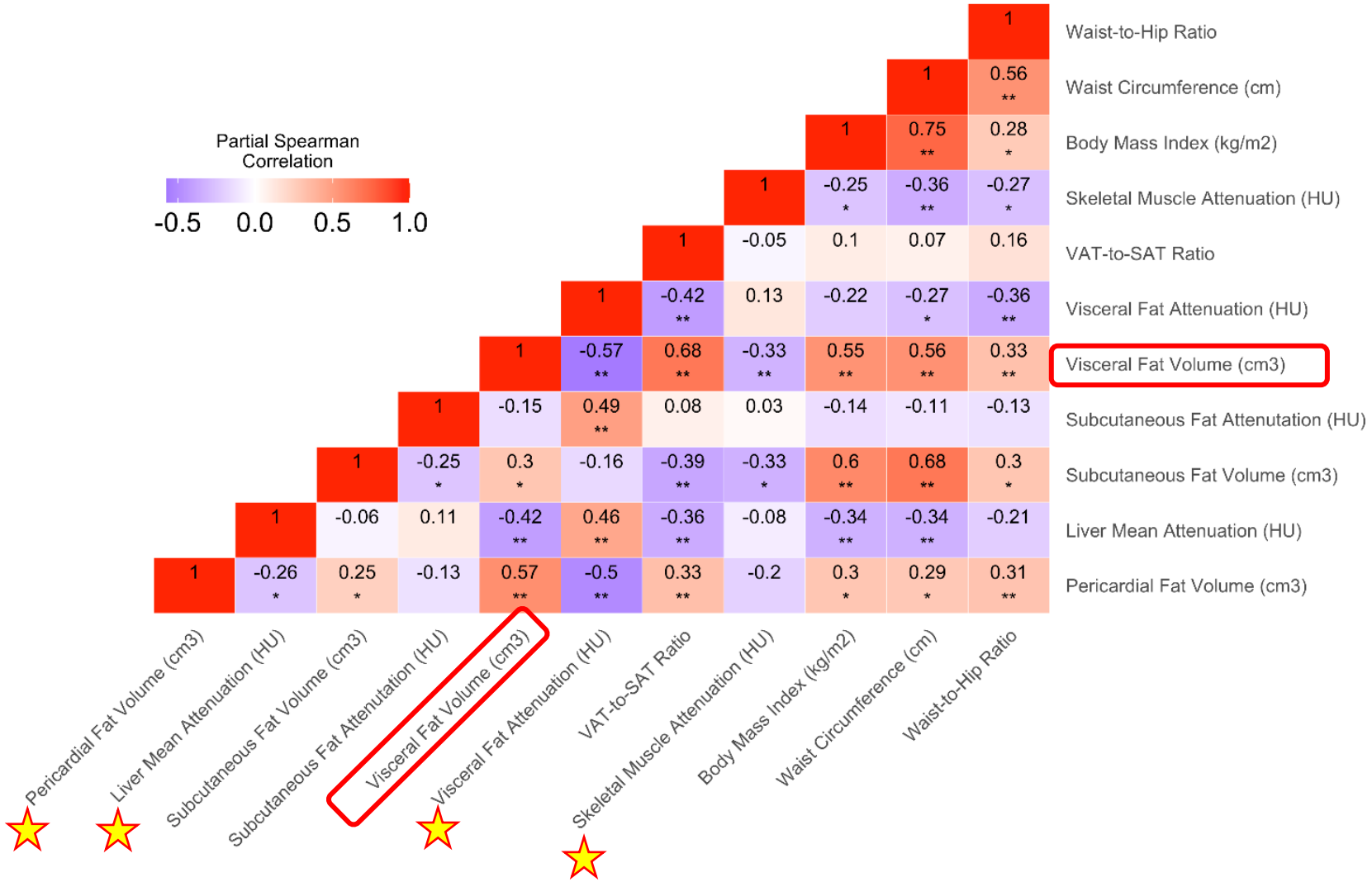


Correlation between anthropometrics, tissue density (Hounsfield Units, HU), and tissue volume (cm^3) in 92 PWH on long-term ART

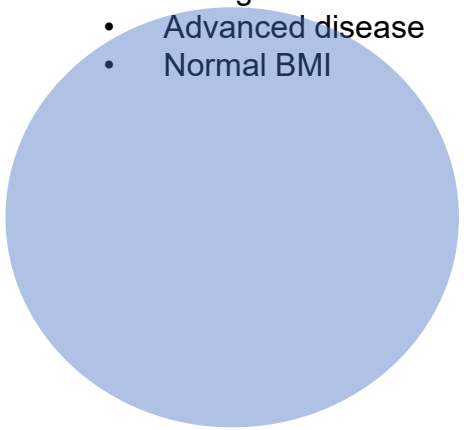
Gabriel, C et al. (manuscript in preparation)

Weight Gain on ART: Where Do We Go From Here?

Risk Stratification

Population level:
- Female
- Non-white
- Younger
- Advanced disease
- Normal BMI

Patient level:
- Genetics
- Diet and exercise
- Health behaviours
- Psychiatric / Psychologic



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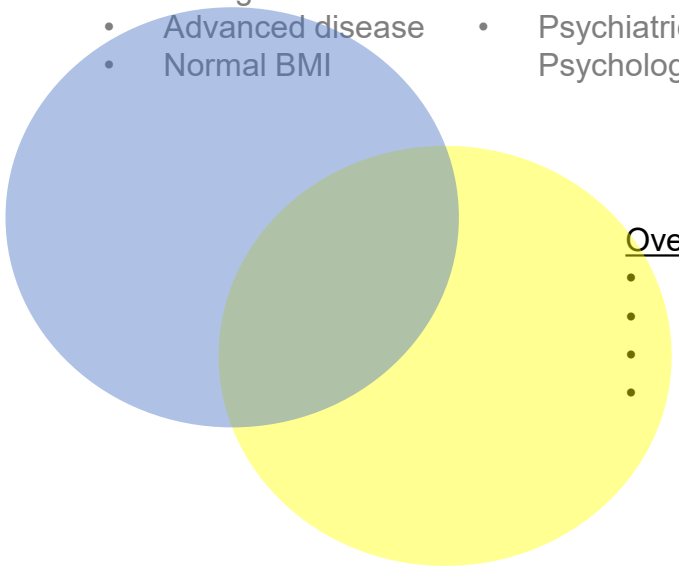

Comorbidities / Consequences

Overt:
- Diabetes
- Fatty liver
- Cardiovascular
- Neurocognitive

Hidden:
- Reduced mobility
- Reduced QoL
- Body shape discomfort
- Meal skipping / supplements
- Adherence issues

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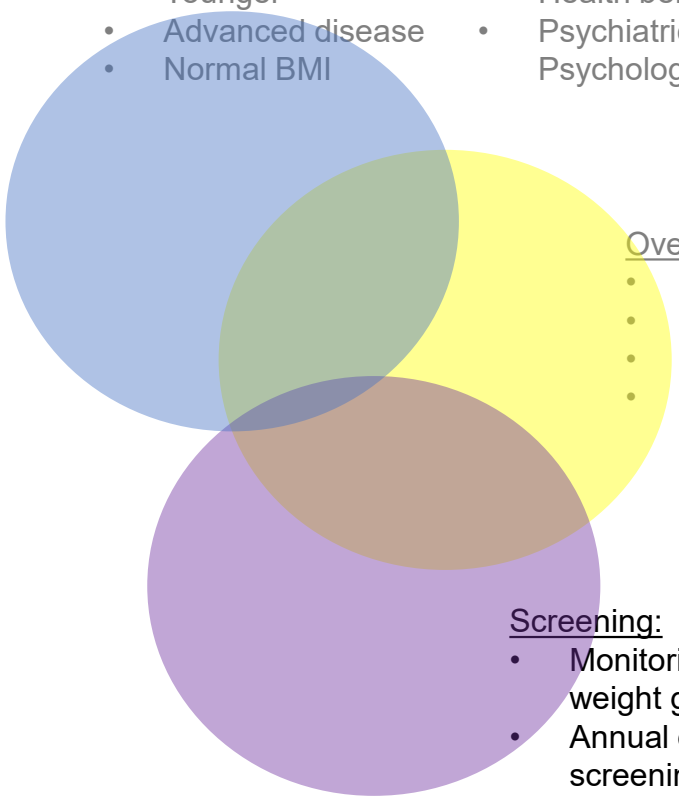

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Mitigation

Screening:
- Monitoring for 5-10% weight gain
- Annual diabetes screening
- Routine fasting lipids
- Coronary angiography
- Liver elastography

Intervention:
- Selection of initial ART
- Potential ART switch
- Maintain lipids and BP at goal
- Early metformin initiation for pre-diabetes
- Risk modification (smoking, alcohol)

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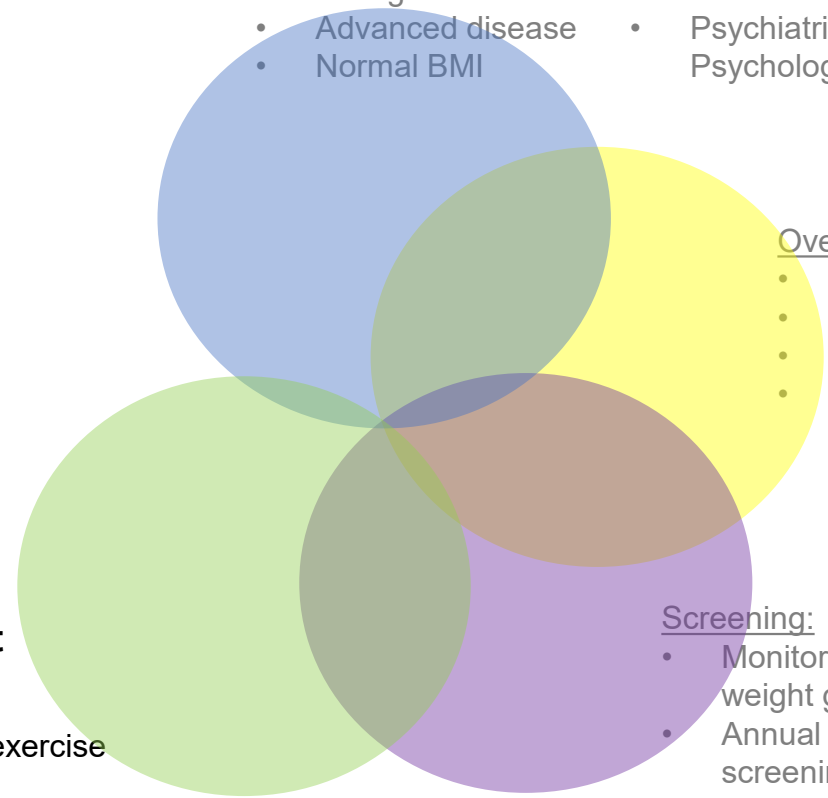

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Long-term Weight Management

Provider:
- Monitoring weight and waist circ.
- Body comp. assessment
- Structured programs
- Addressing weight/nutrition in routine clinical care

Patient:
- Diet and exercise changes
- Calorie tracking apps, food diary
- Discussing concerns

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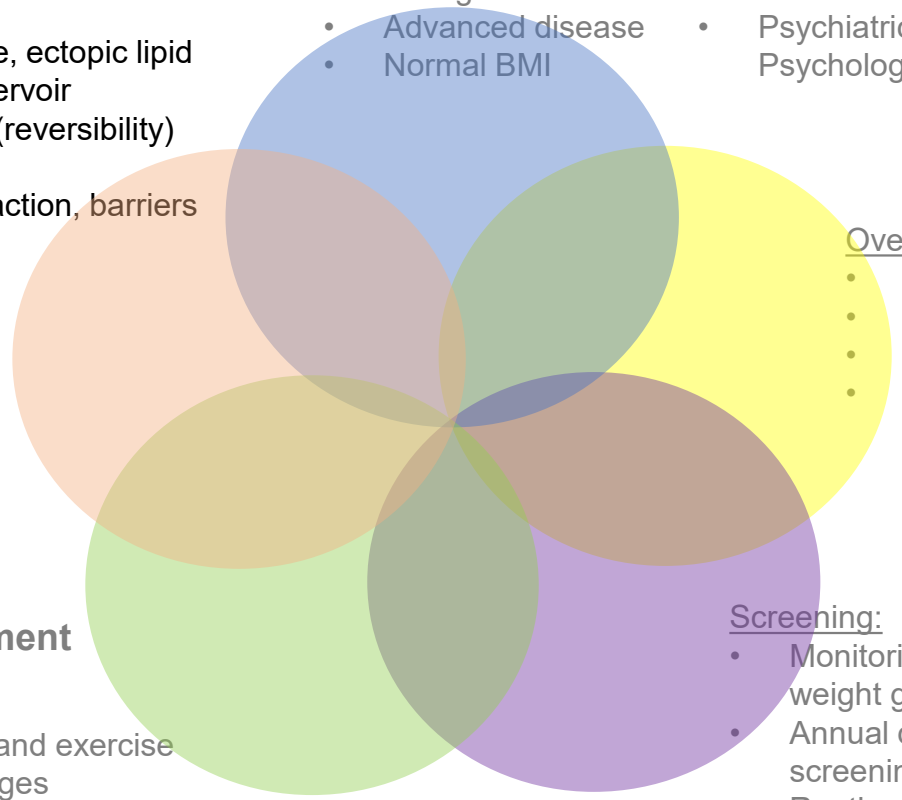
Future Research

- Effects of ART agents on energy expenditure, appetite, ectopic lipid deposition & adipose tissue energy storage / viral reservoir
- Effects of ART regimen change on body composition (reversibility)
- Genetic determinants of weight gain on ART
- Impact of weight gain on patients' QoL & mood/satisfaction, barriers to communication of concerns regarding weight



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