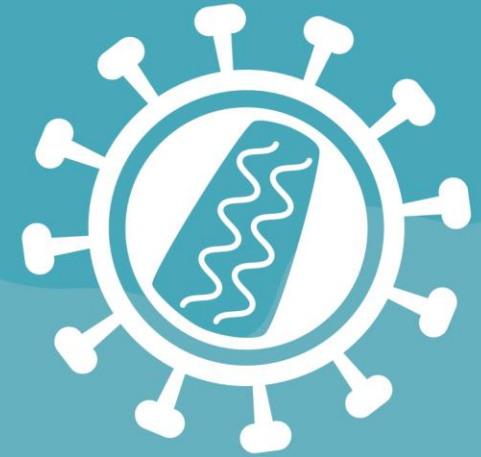


BHIVA



British HIV Association

2023 Spring Conference

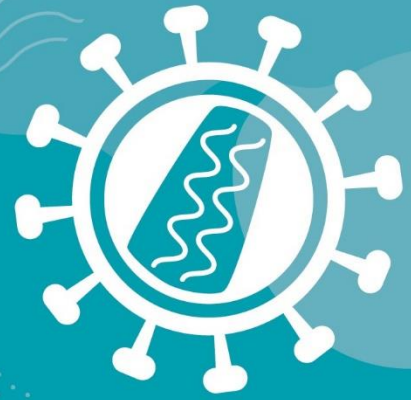


Mon 24th - Wed 26th April
Gateshead, UK

www.bhiva.org

#BHIVA23 Follow us on social media





Longer-term safety of integrase inhibitors

Chair:

Jonathan Underwood

This educational event is supported by



Longer-term safety of integrase inhibitors

Andrew Carr

St Vincent's Hospital, Sydney, Australia



Integrase Inhibitors, Weight Gain, and Cardiovascular Disease

Andrew Carr DSc MD MBBS FRACP FRCPA

HIV and Immunology Unit

St Vincent's Hospital, Sydney

Professor of Medicine, University of New South Wales

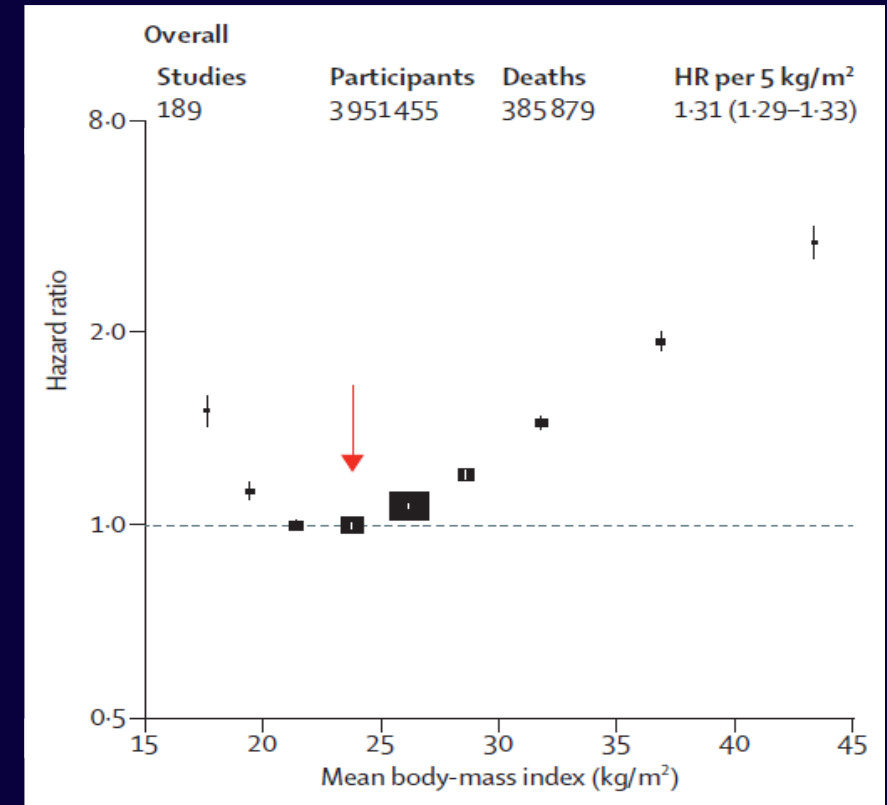
Disclosures

- **Research funding / support: MSD, ViiV**
- **Advisory boards: Gilead, MSD, ViiV**

INSTIs, weight gain and CVD

Epidemiology of overweight

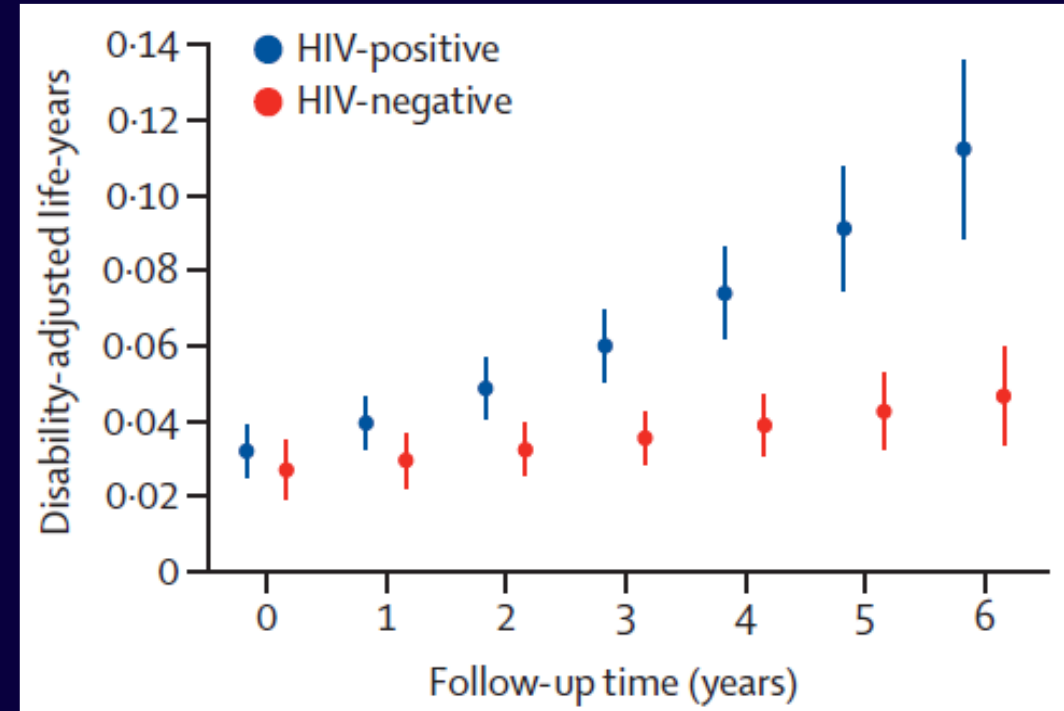
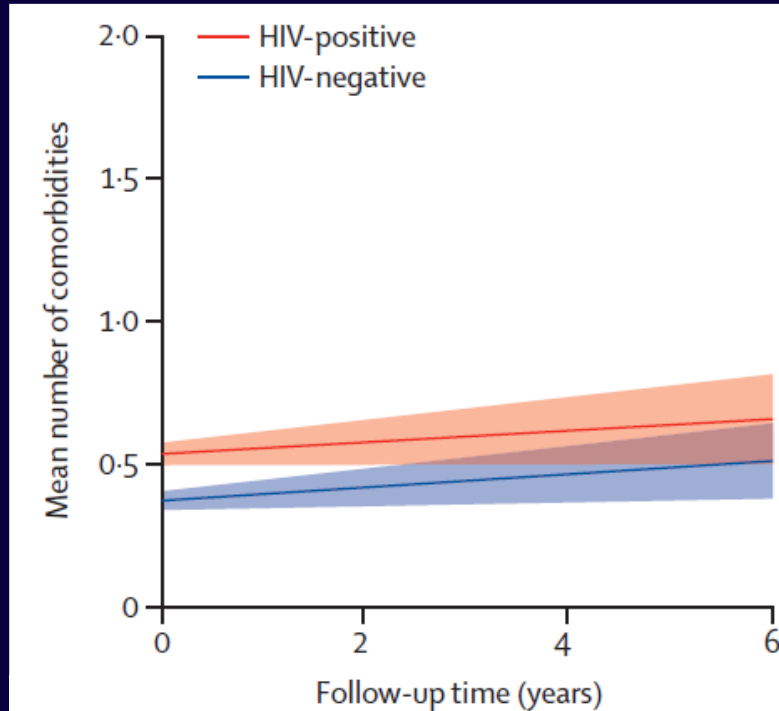
- **Obesity = BMI >30 kg/m²**
- **Global prevalence (2016) = 13%**
 - nearly tripled since 1975
 - >30% in 7 countries (USA 36.2%)
 - Australia-Europe 20-30%
- **HIV+ adults (15% to 39%)**
- **Complications**
 - Hypertension – cardiovascular disease
 - Type-2 diabetes – CVD, kidney disease, retinopathy, peripheral neuropathy
 - Other – osteoarthritis, cancers, sleep apnoea, fatty liver disease
 - 4 million deaths a year (70% from CVD; 85% in LMIC)
 - 5 kg/m² BMI increment increases risk of death by ~30% (HIV no different?)



https://gamapserver.who.int/gho/interactive_ch/INSTIs/ncd/risk_factors/obesity/atlas.html; Yitbarek et al, Diabetes Metab Syndr Obes 2020
Khatri et al, BMC Nutr 2020; Bourgi et al, J Int AIDS Soc 2020; Savinelli S et al, HIV Med 2020; Global Burden of Disease 2017 Disease and Injury Incidence and Prevalence Collaborators, Lancet 2018; Global Burden of Disease Diet Collaborators, New Engl J Med 2017 and Lancet 2019
<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>

INSTIs, weight gain and CVD

Epidemiology of comorbidities (AGE_hIV cohort)



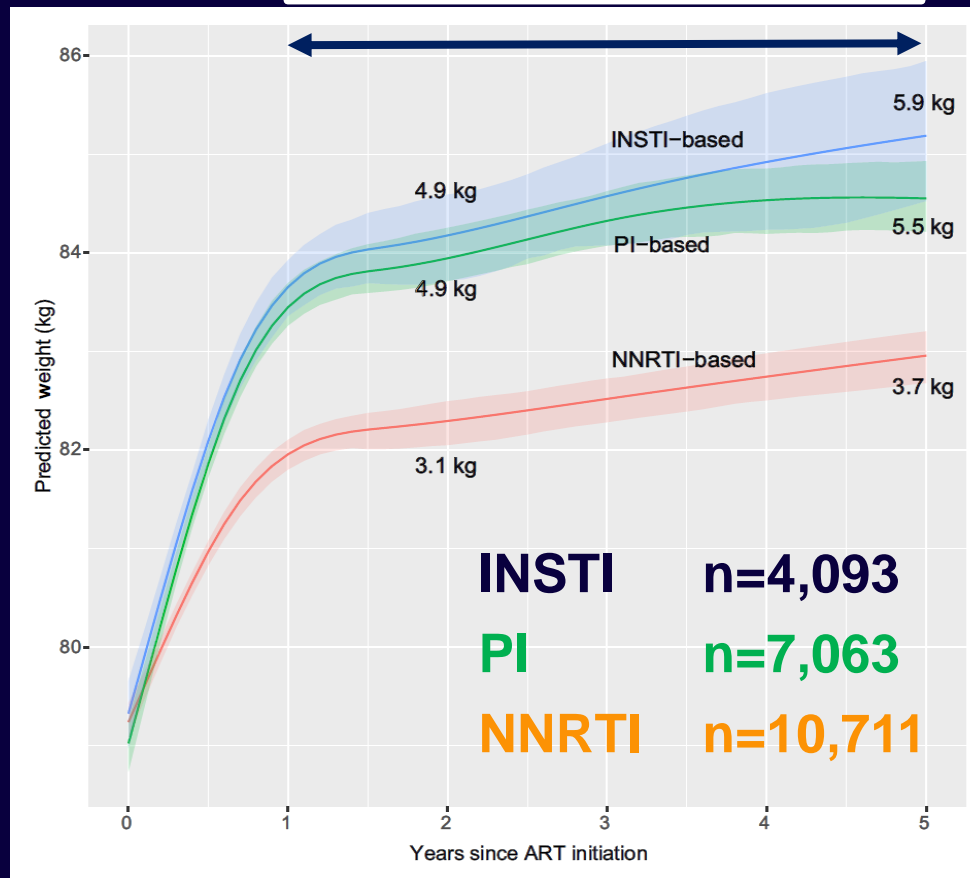
- Comorbidities more common in HIV
- Incidence of new comorbidities similar for HIV+ vs HIV-
- Each comorbidity was associated with a 3-fold greater risk of death
- HIV+ patients had greater loss of DALYs

INSTIs, weight gain and CVD

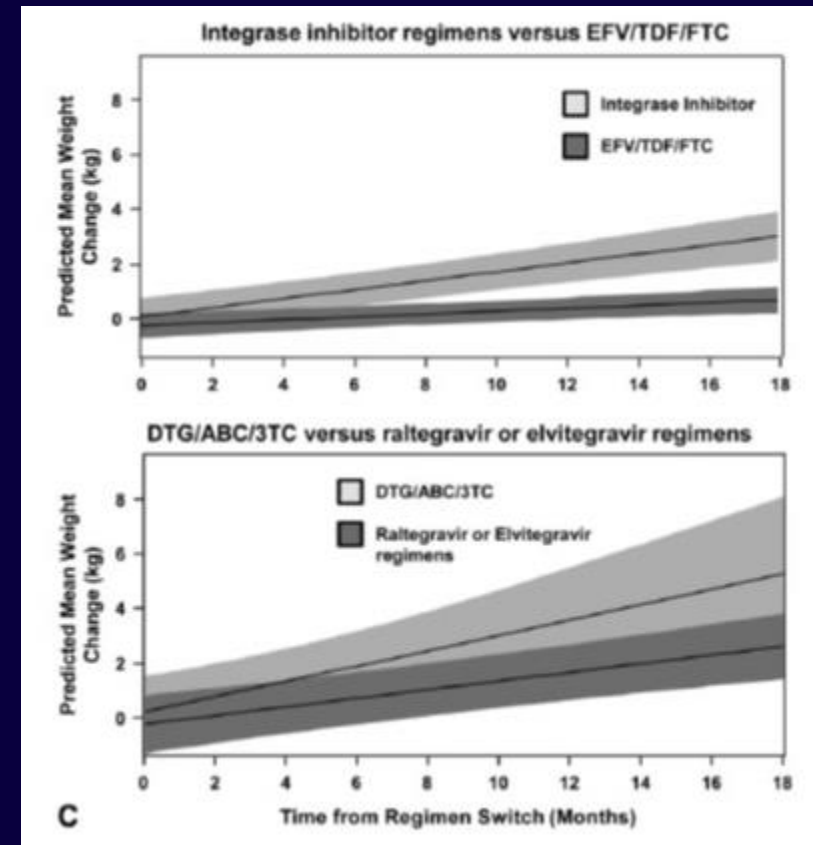
INSTIs: Associations with weight gain in cohorts

**Initial
ART**

Average US adult gains
0.5-1.0 kg / yr from early
to middle adulthood



ART switching



Bourgi et al, J Int AIDS Soc 2020
<https://jamanetwork.com/journals/jama/fullarticle/2643761>

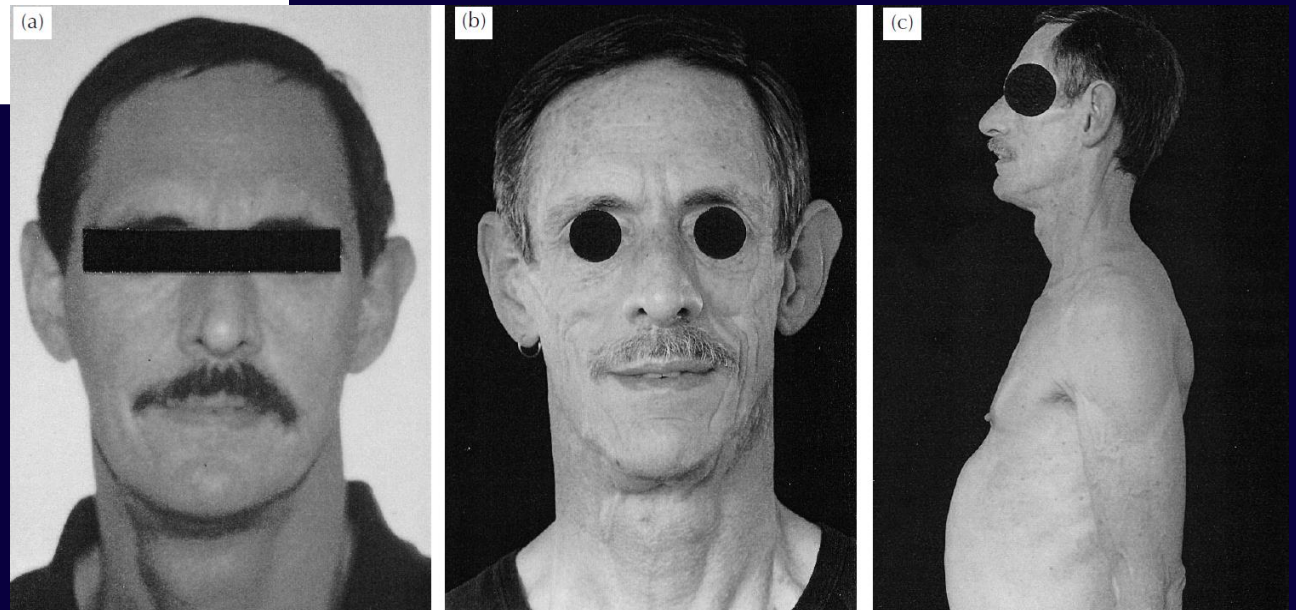
Norwood et al, JAIDS 2017; Zheng et al. JAMA 2017

INSTIs, weight gain and CVD

Association does not always mean causality

A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors

Andrew Carr*, Katherine Samaras[†], Samantha Burton*,
Matthew Law[‡], Judith Freund[§], Donald J. Chisholm[†]
and David A. Cooper^{*‡}



INSTIs, weight gain and CVD

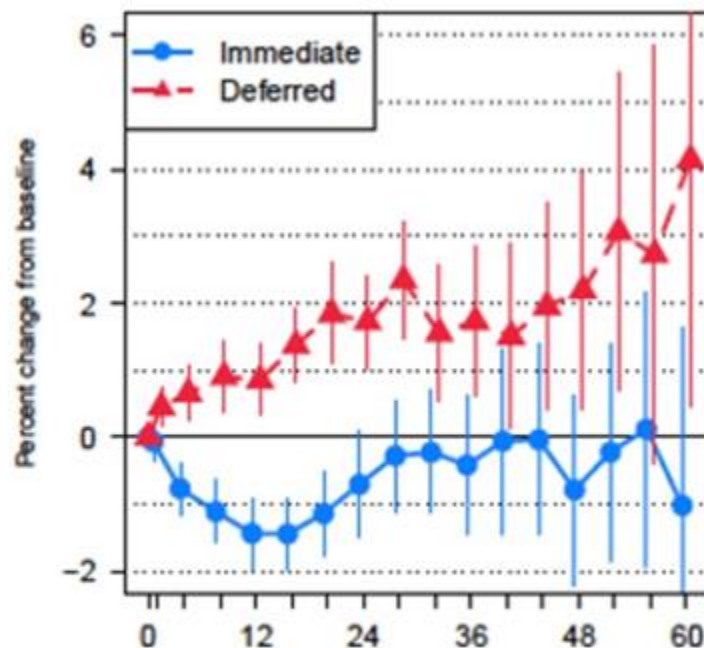
Comorbidities: Delayed recognition

Drug / class	FDA approval	Toxicity	Strong signal	Delay (years)
Zidovudine	1987	lipoatrophy	1999	12
Stavudine	1994	lipoatrophy	1999	5
Nevirapine	1996	hepatitis/rash at high CD4	2005	9
Protease inhibitors	1996	myocardial infarction	2003	7
Efavirenz	1998	suicidality	2013	15
Abacavir	1998	myocardial infarction	2008	10
Tenofovir	2001	kidney disease	2006	5
		fracture	2012	11
Atazanavir	2003	kidney stones	2007	4
Raltegravir	2007	myopathy	2012	5

INSTIs, weight gain and CVD

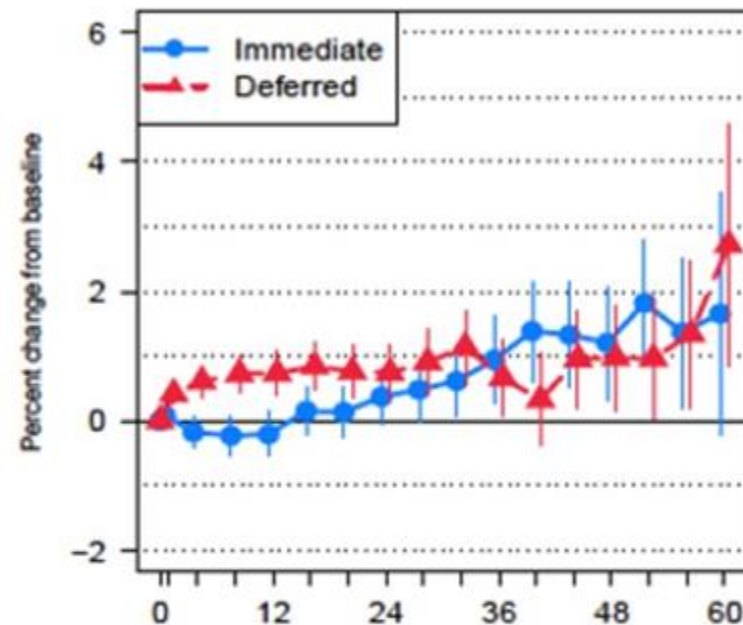
Initial ART: Pre-INSTI era (START trial)

Initial ART suppressed weight gain in pre-INSTI era (mostly TDF-EFV)



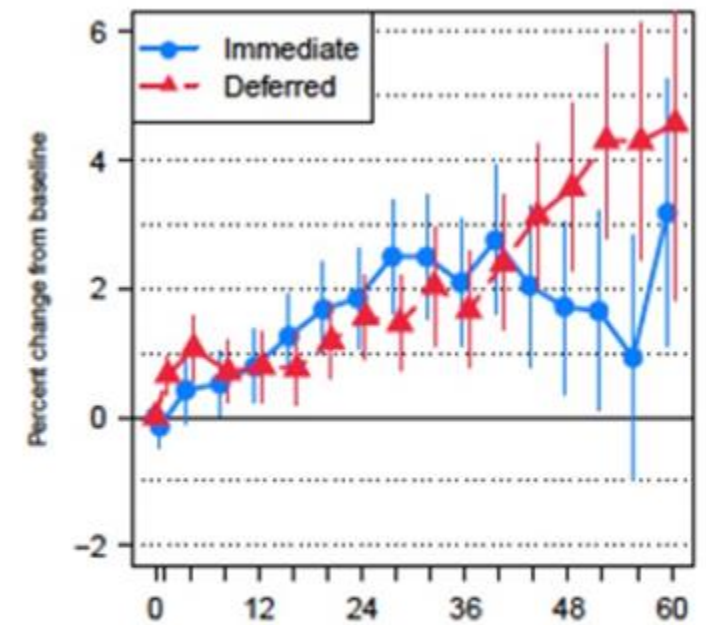
Months from randomization					
No. of participants:					
I: 568	526	440	241	129	38
D: 591	549	443	247	124	38

Baseline VL <3000



Months from randomization					
No. of participants:					
I: 1235	1165	998	606	319	82
D: 1260	1172	998	590	313	92

Baseline VL 3000-50000

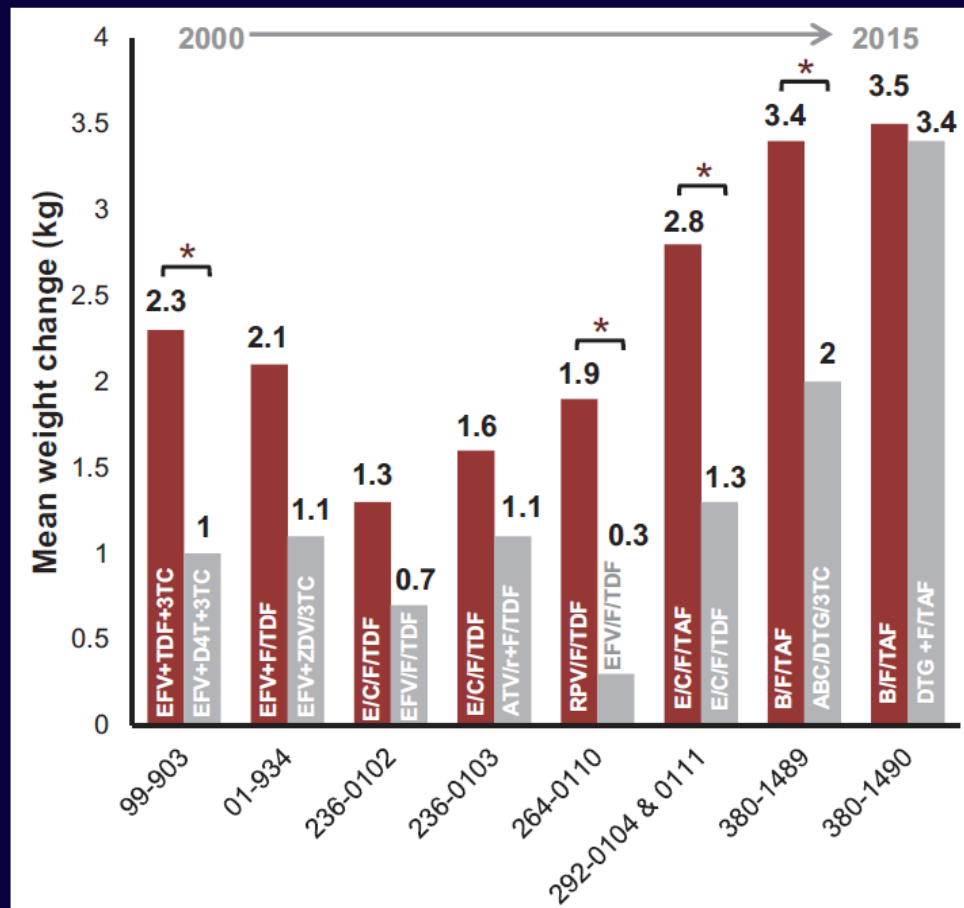


Months from randomization					
No. of participants:					
I: 517	496	420	241	135	41
D: 504	464	395	241	118	39

Baseline VL >50000

INSTIs, weight gain and CVD

Initial ART: Gilead RCTs



Risk factor	Odds ratio
Patient	

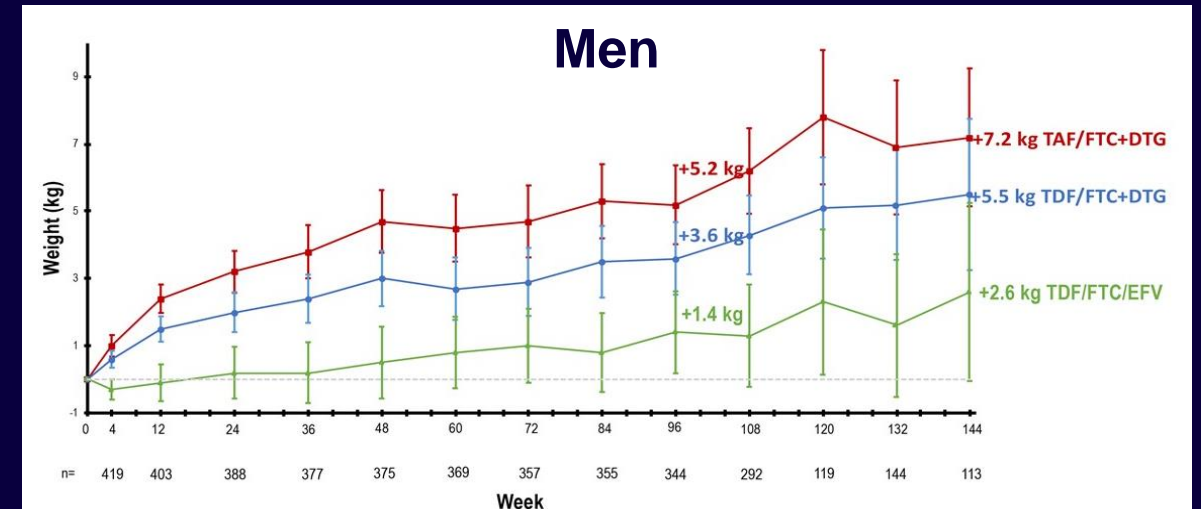
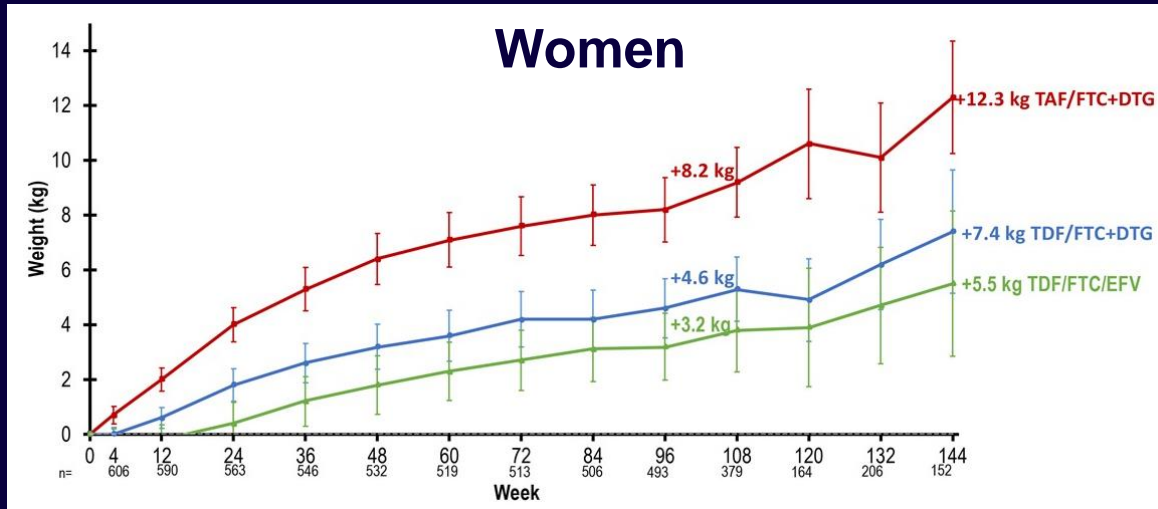
CD4 <200 vs. >200	4.36
RNA >100,000 vs. <100,000	1.98
BMI >25, >30 vs. <25	1.54, 1.66
Women vs. men	1.54
Black race vs. other races	1.32

INSTIs

BIC / DTG vs. EFV	1.82
RPV vs. EFV	1.51
TAF vs. ABC	1.90
TAF vs. TDF	1.47

INSTIs, weight gain and CVD

Initial ART: Dolutegravir, TAF/TDF and efavirenz (ADVANCE)

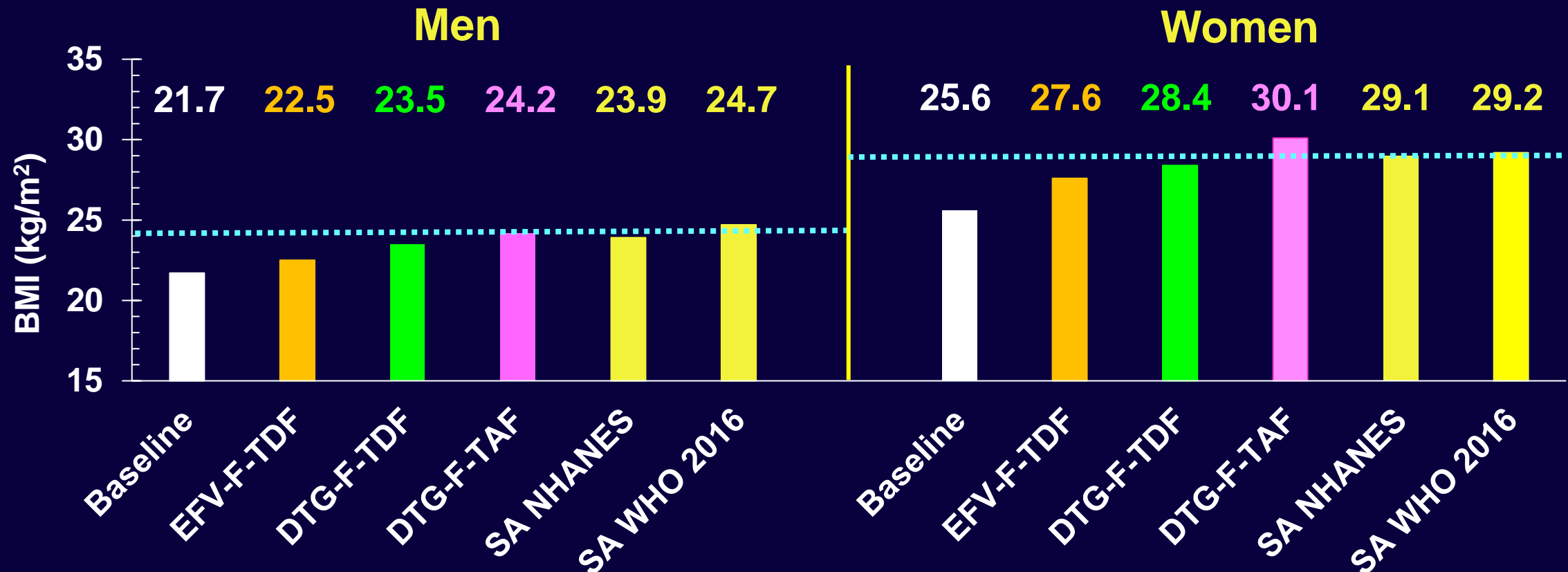


- Fat gain >> muscle gain
- Fat gain peripherally and centrally
- Less fat gain with EFV in slow EFV metabolisers

INSTIs, weight gain and CVD

Initial ART: Dolutegravir, TAF/TDF and efavirenz (ADVANCE)

ADVANCE – Week 144 vs South African general population



■ Similar findings in Kaiser cohort

Sokhela et al, AIDS 2020; Mchiza et al, Int J Environ Res Public Health 2019
Silverberg et al, AIDS 2020; <https://apps.who.int/gho/data/node.main.BMIMEANADULTC?lang=en>

INSTIs, weight gain and CVD

Initial ART: Pregnancy (IMPAACT 2010)

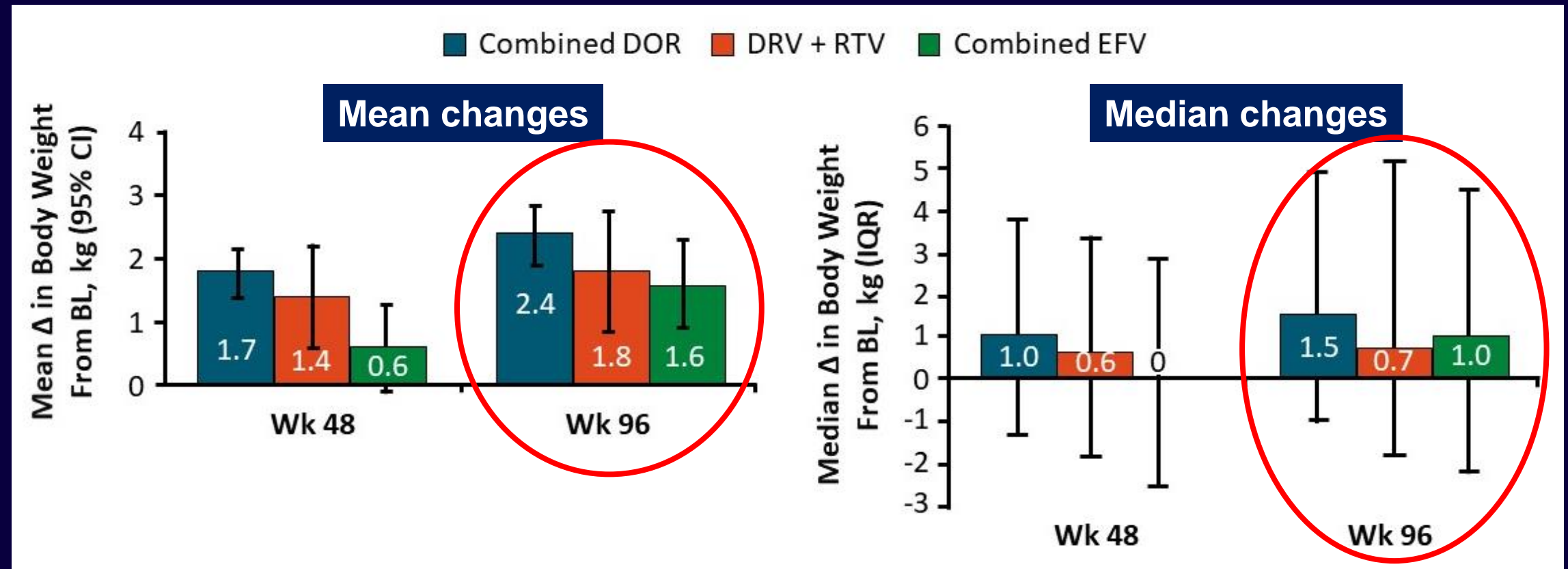
INSTIs regimen	Weight gain / week	Adverse pregnancy outcome	Low weight gain
DTG-F-TAF	0.38 kg	24%	15%
DTG-F-TDF	0.32 kg	33%	24%
EFV/F/TDF	0.29 kg	33%	30%
Recommended	0.42 kg		

- **Less weight gain associated with**
 - more adverse pregnancy outcome (HR 1.4)
 - more small-for-gestational age babies (HR 1.5)

INSTIs, weight gain and CVD

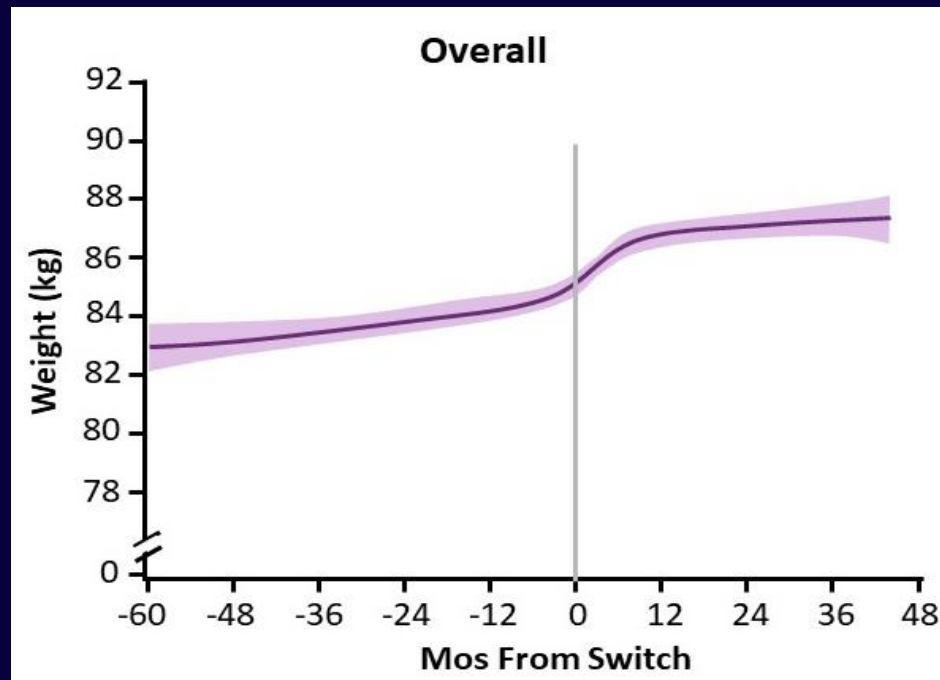
Initial ART: Weight change is not normally distributed

TDF-3TC-DOR vs TDF-3TC-DRVc (DRIVE)



INSTIs, weight gain and CVD

Switch cohort: TDF to TAF (OPERA)



- All patients undetectable
- Switched TDF to TAF only or also switched non-INSTI anchor to INSTI

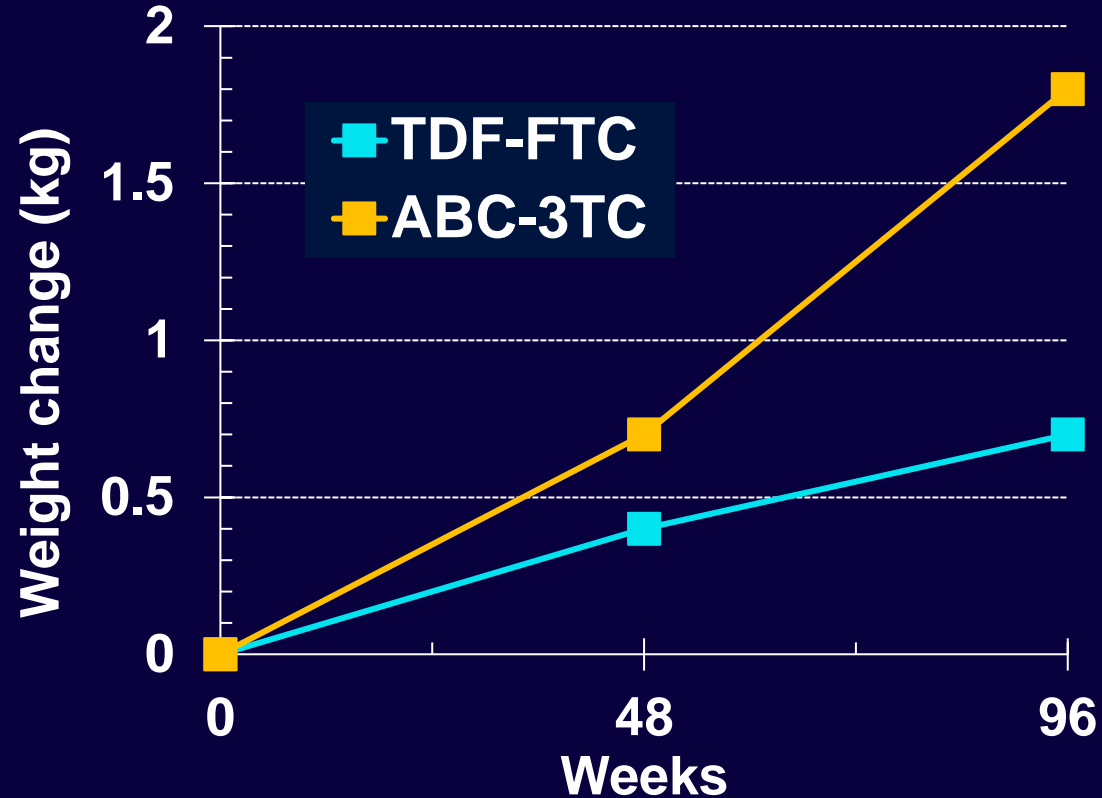
Time to switch (months)	INSTI (n=3281)	NNRTI (n=1452)	Plx (n=746)
-60 to 0	0.42	0.66	0.31
0 to 9	2.64	2.25	1.98
9+	0.29	0.20	-0.11

- Similar findings in Asian cohort from TDF-ART to EVGc/F-TAF (+0.5 kg in 48 weeks pre-switch vs. +1.8 kg in 48 weeks after switch)

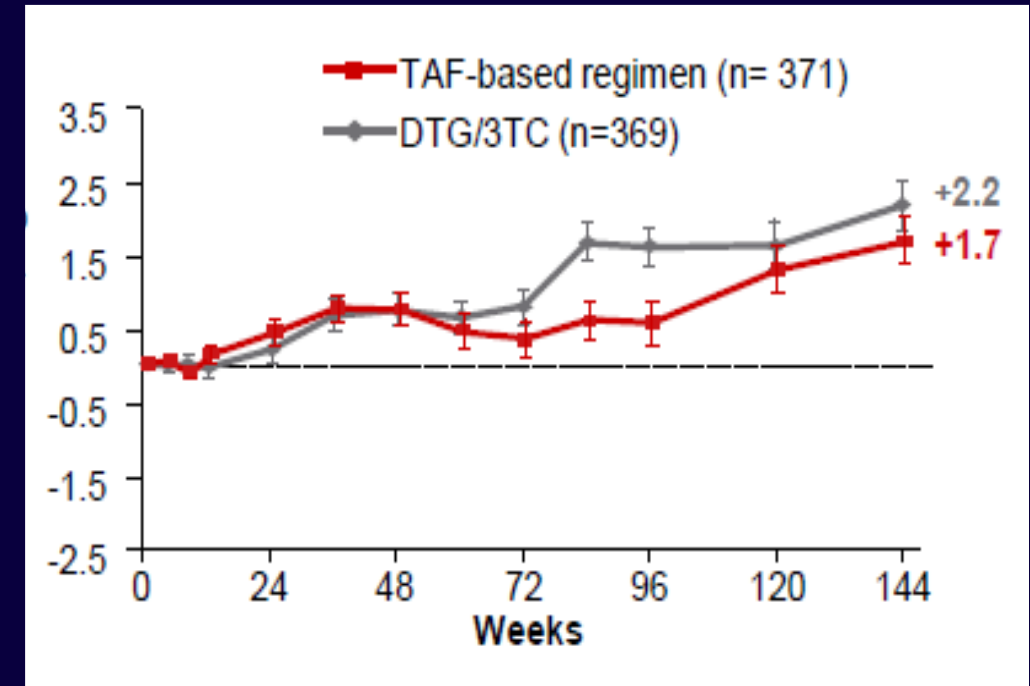
INSTIs, weight gain and CVD

Switch RCTs: TDF / TAF

NRTI switch to TDF-FTC or ABC-3TC (STEAL)

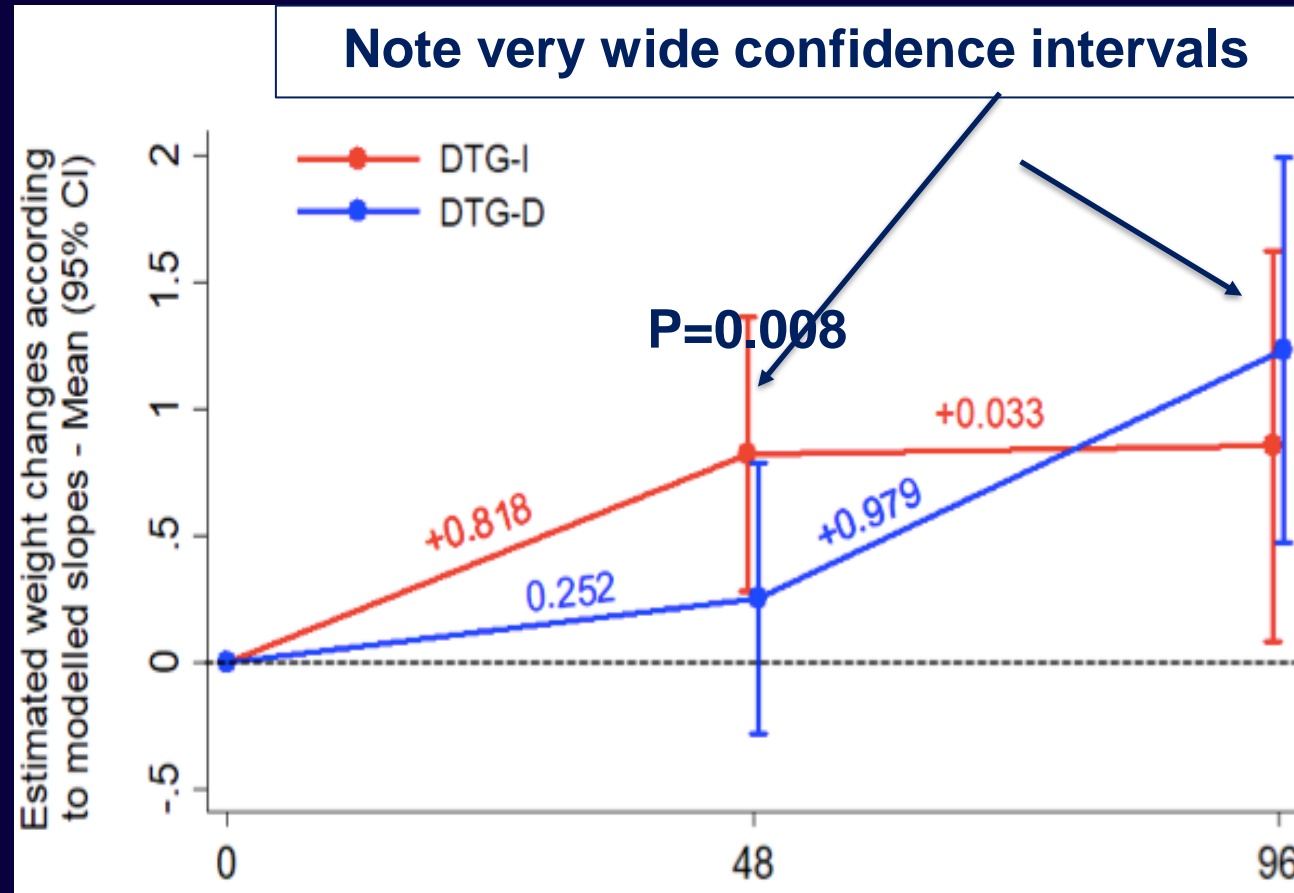


TAF-based ART to DTG-3TC (TANGO)



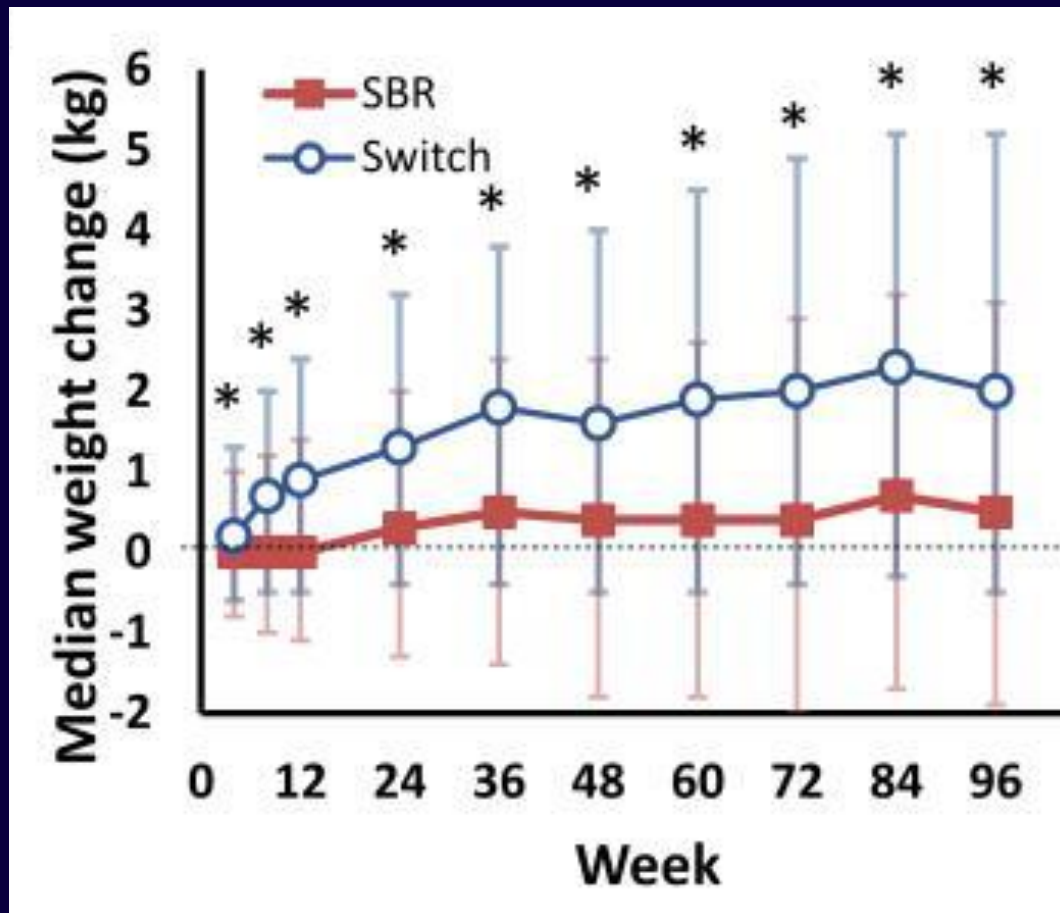
INSTIs, weight gain and CVD

Switch RCTs: Plr to Dolutegravir (NEAT022)

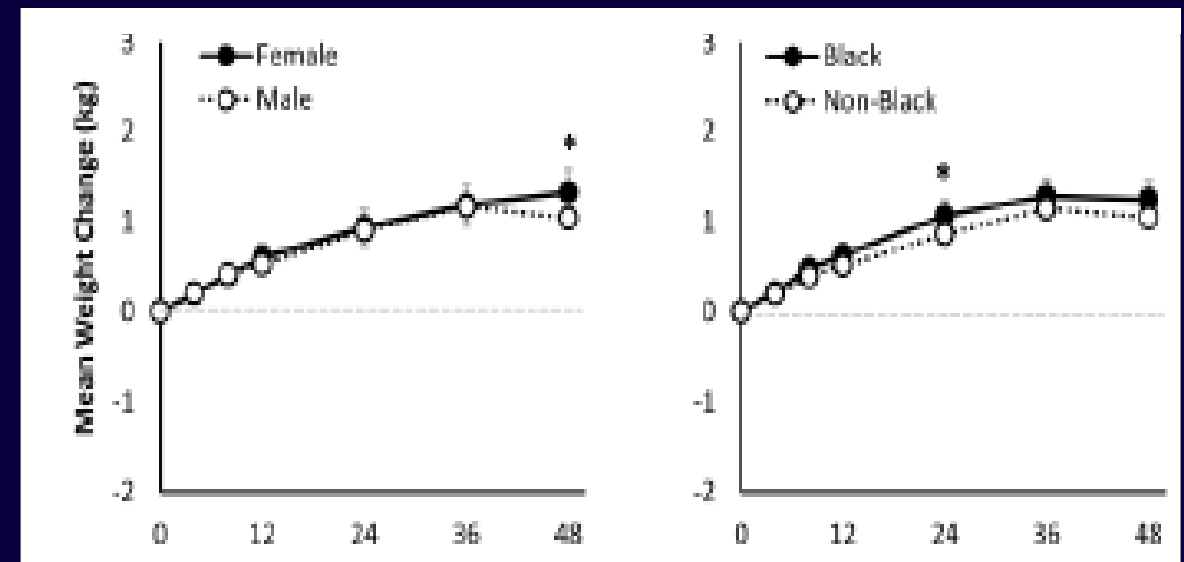


INSTIs, weight gain and CVD

Switch RCTs: Gilead

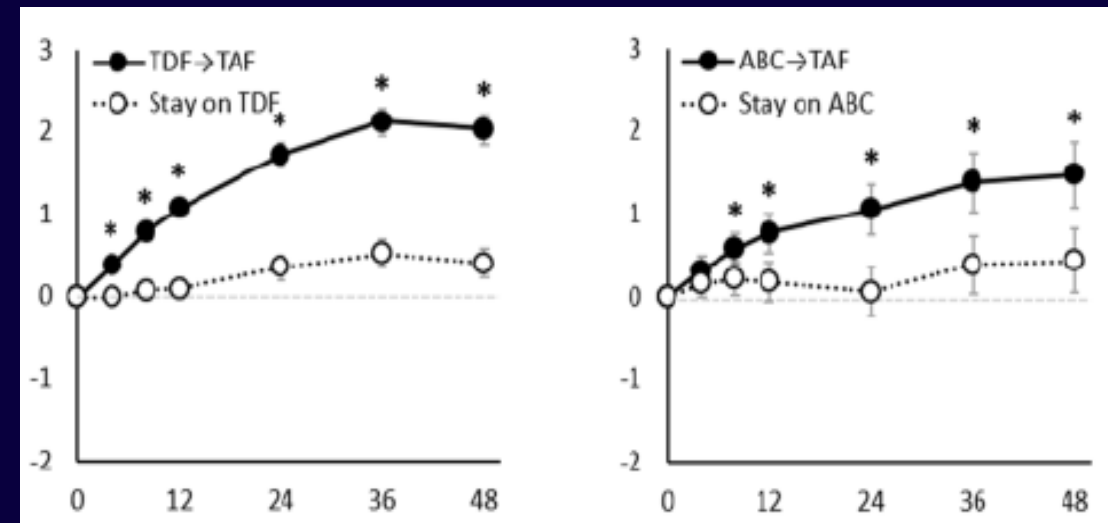
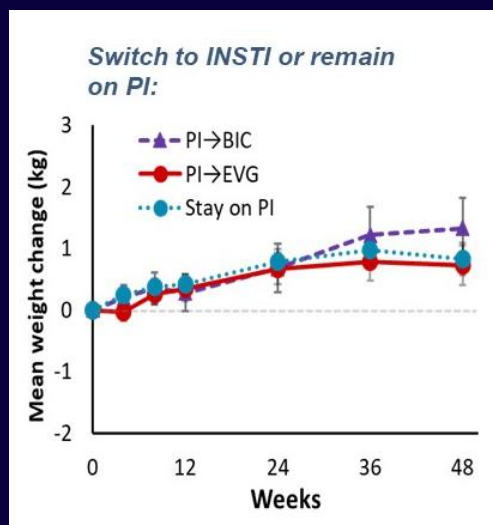
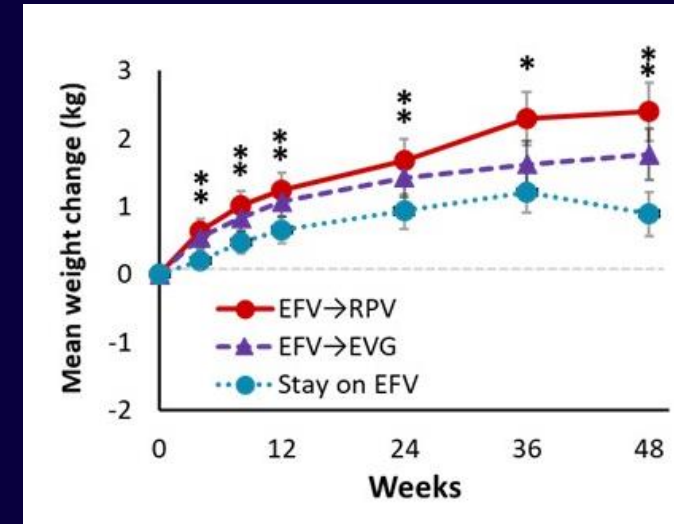
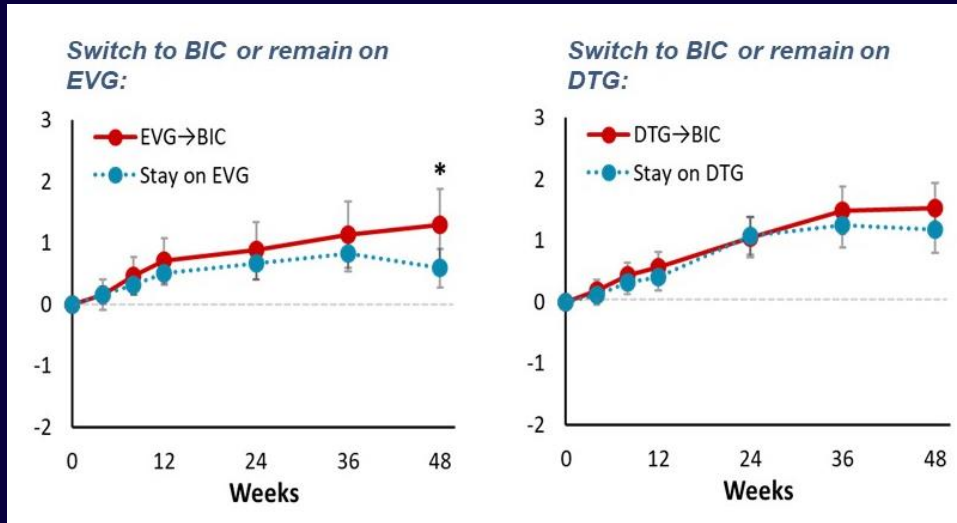


- **>10% weight gain associated with**
 - younger age
 - lower baseline weight



INSTIs, weight gain and CVD

Switch RCTs: Gilead

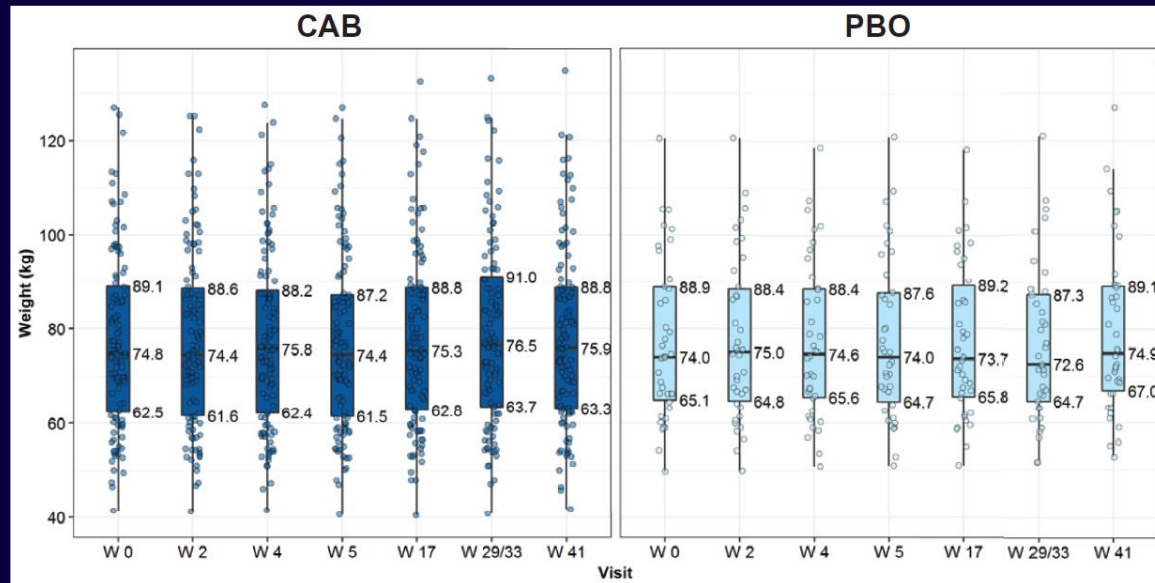


INSTIs, weight gain and CVD

PrEP: Cabotegravir vs. placebo or TDF

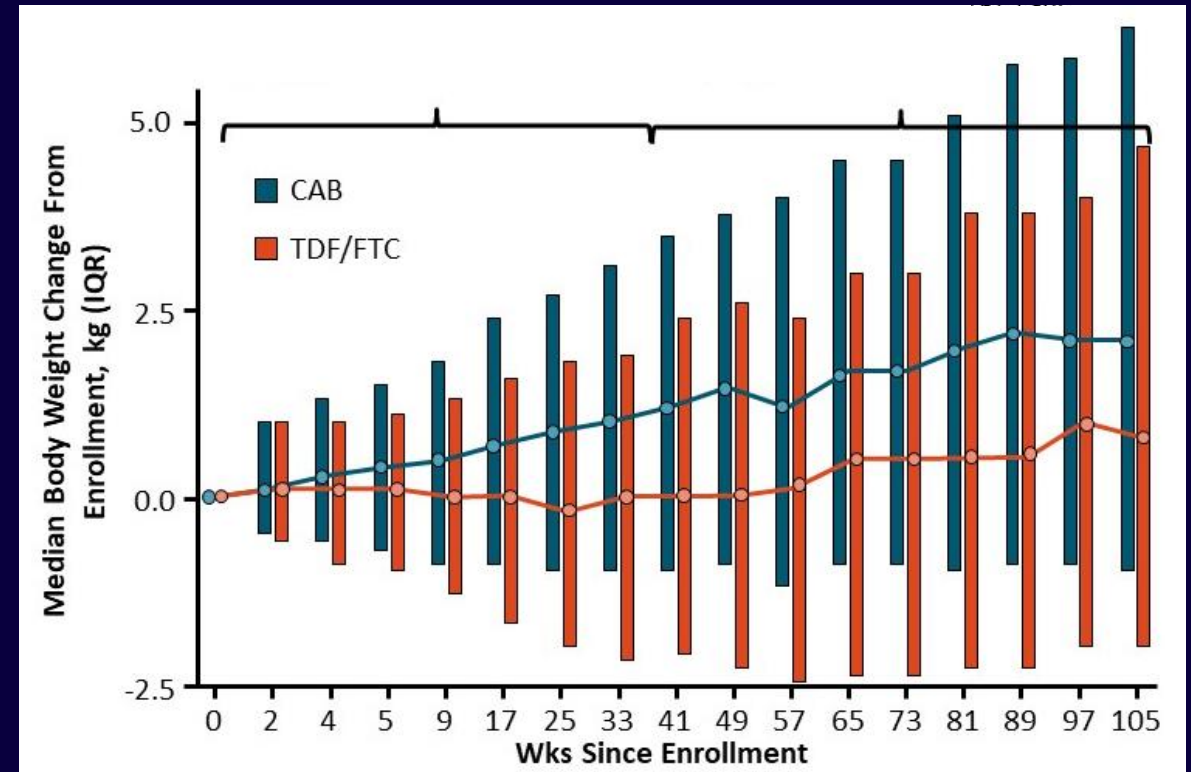
Cabotegravir vs. Placebo (HPTN077)

CAB: +1.1kg, Pbo: +1.0, P=0.66



Cabotegravir vs. TDF-FTC (HPTN083)

CAB: +1.3kg, TDF-FTC: +0.3, P<0.001

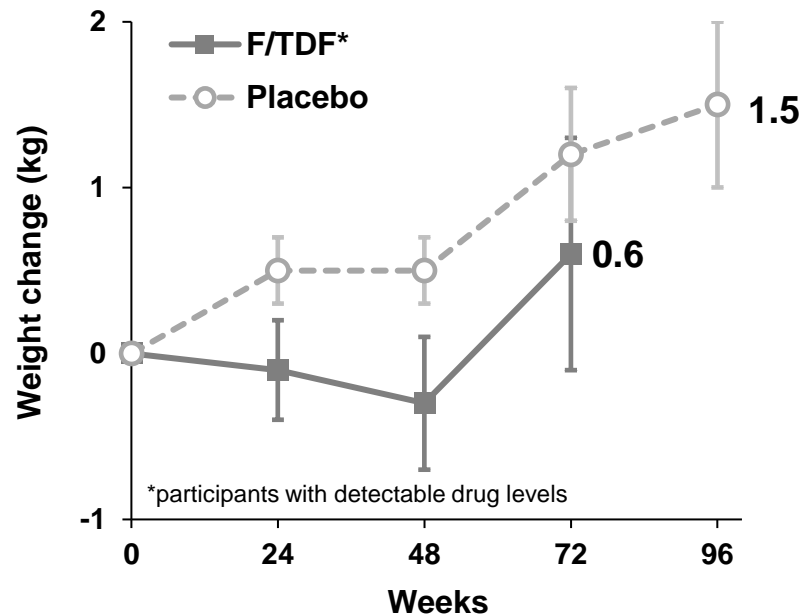


INSTIs, weight gain and CVD

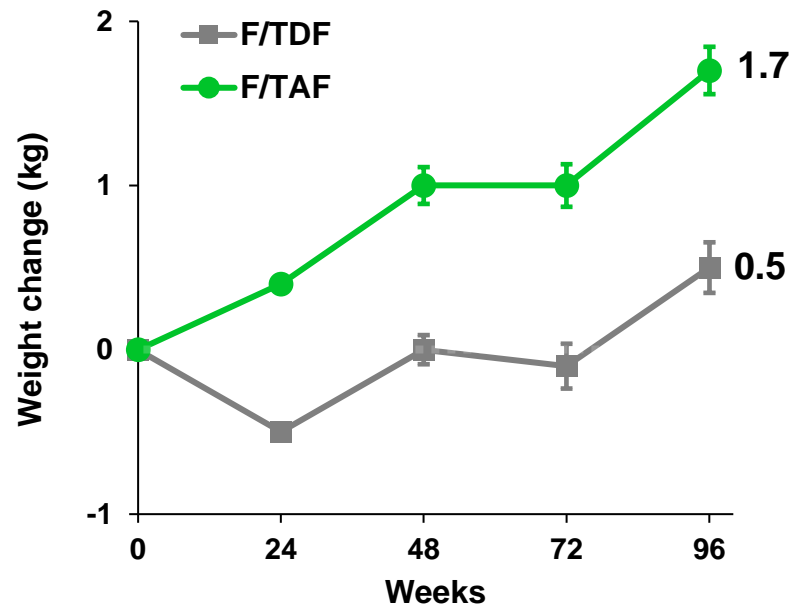
PrEP / HBV: TDF vs. placebo or TAF

TDF-FTC vs. Placebo (iPrEx)

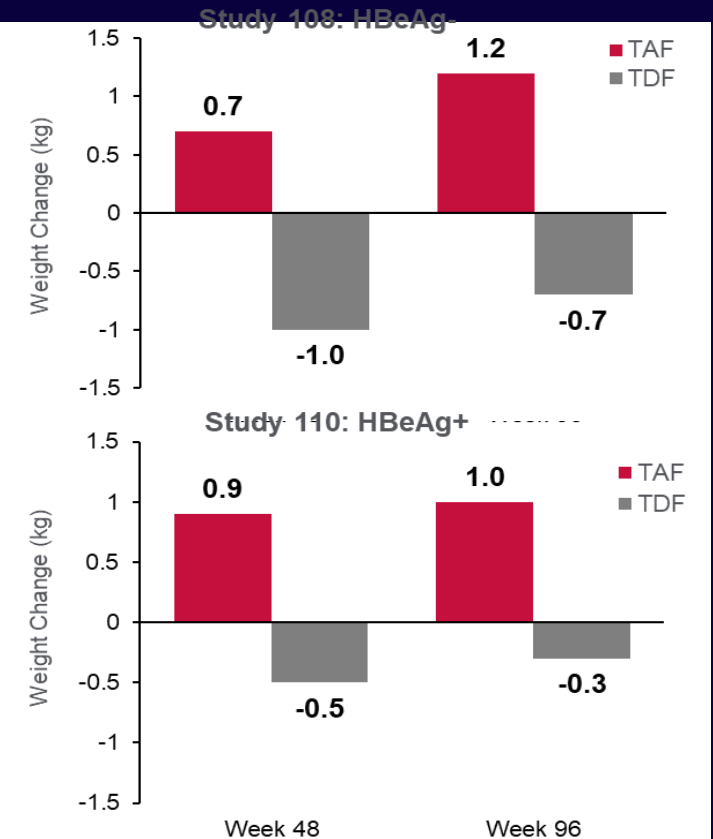
Difference Wk 24 = -0.8%, P=0.02



TAF-FTC vs. TDF-FTC (DISCOVER)



TAF vs. TDF (HBV monoinfection)



INSTIs, weight gain and CVD

Comorbidities: Delayed recognition

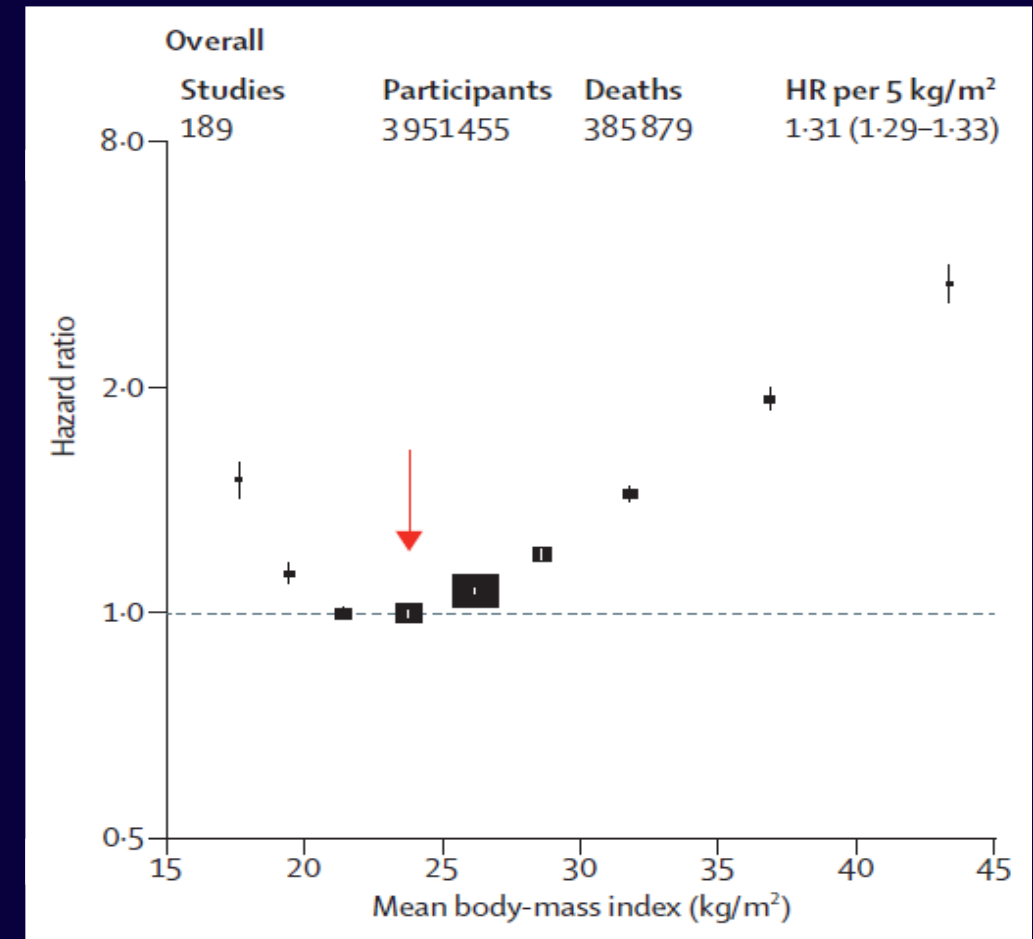
Drug / class	FDA approval	Toxicity	Strong signal	Delay (years)
Zidovudine	1987	lipoatrophy	1999	12
Stavudine	1994	lipoatrophy	1999	5
Nevirapine	1996	hepatitis/rash at high CD4	2005	9
Protease inhibitors	1996	myocardial infarction	2003	7
Efavirenz	1998	suicidality	2013	15
		weight loss		
Abacavir	1998	myocardial infarction	2008	10
Tenofovir	2001	kidney disease	2006	5
		fracture	2012	11
Tenofovir	2001	weight loss	2019	18
Atazanavir	2003	kidney stones	2007	4
Raltegravir	2007	myopathy	2012	5
Dolutegravir	2013	weight gain	2019	6
Bictegravir	2018	weight gain	2020	2

Saint-Marc et al, AIDS 1999; Lundgren et al, NEJM 2003; Pacanowski et al, AIDS 2007; D:A:D Study Group, Lancet 2008
Cooper et al, Clin Infect Dis 2010; Bedimo et al, AIDS 2012; Lee et al, JAIDS 2013; Mollan et al, IDSA 2013

INSTIs, weight gain and CVD

Significance

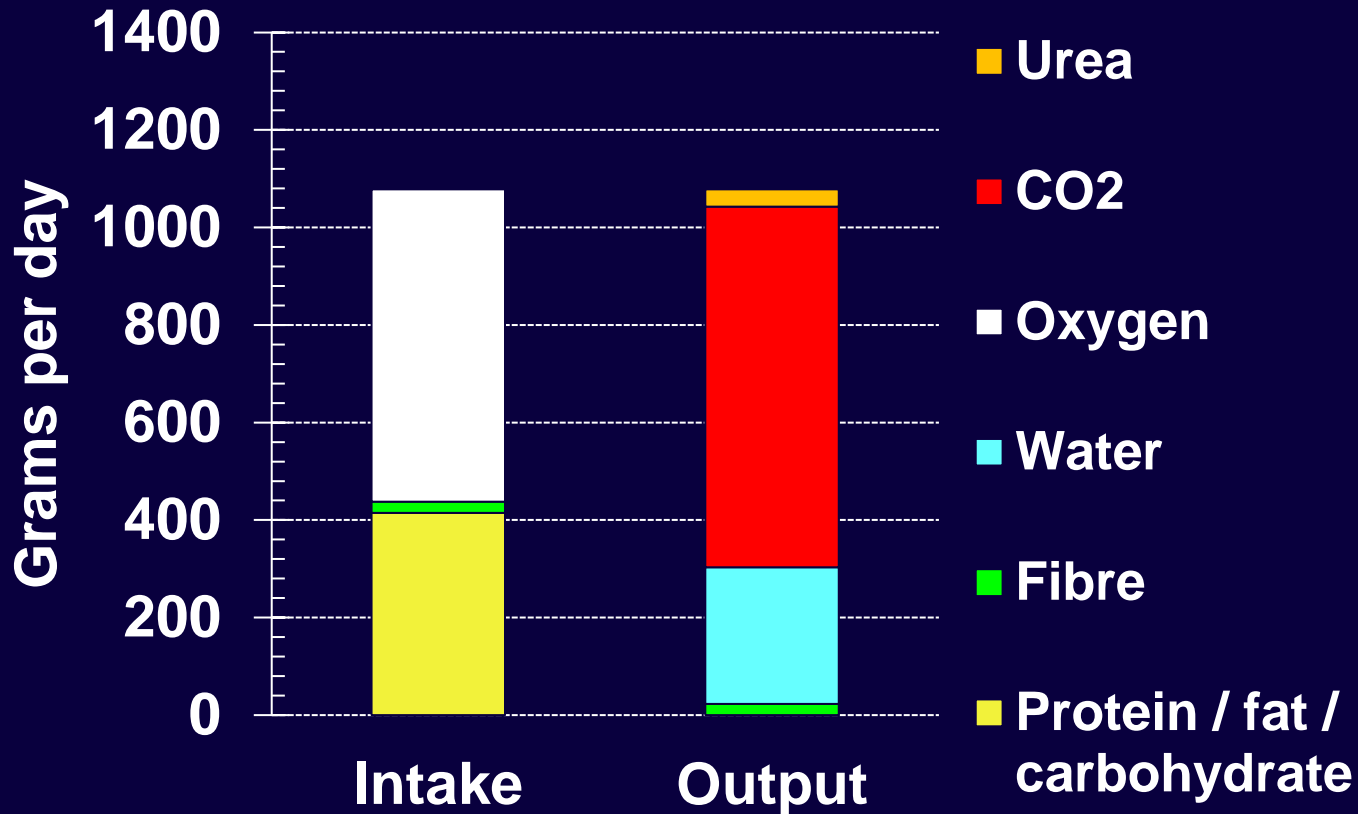
- **Average Australian man:**
86 kg, BMI 27.8 kg/m²
- **Starts TAF / INSTI, weight gain of**
 - 2 kg, so BMI → to 28.5 kg/m²
 - 10 kg, so BMI → to 31.0 kg/m²
- **BMI increase of 5 kg/m² requires a weight increase of 15.6 kg**
- **However, remember that**
 - 40% of weight-related deaths occur in adults who are not obese
 - so more morbidity is possible with smaller BMI increments



INSTIs, weight gain and CVD

Pathogenesis of weight gain

Australians consume $\approx 0.45\text{kg}$ of food a day (+3 litres of water)



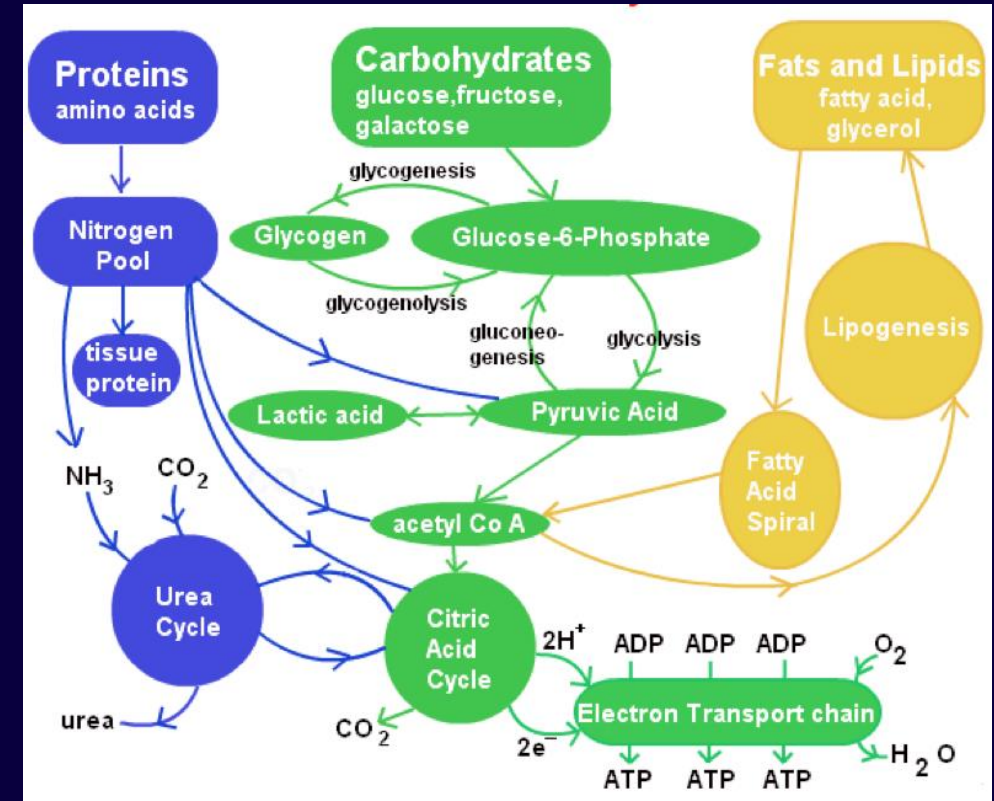
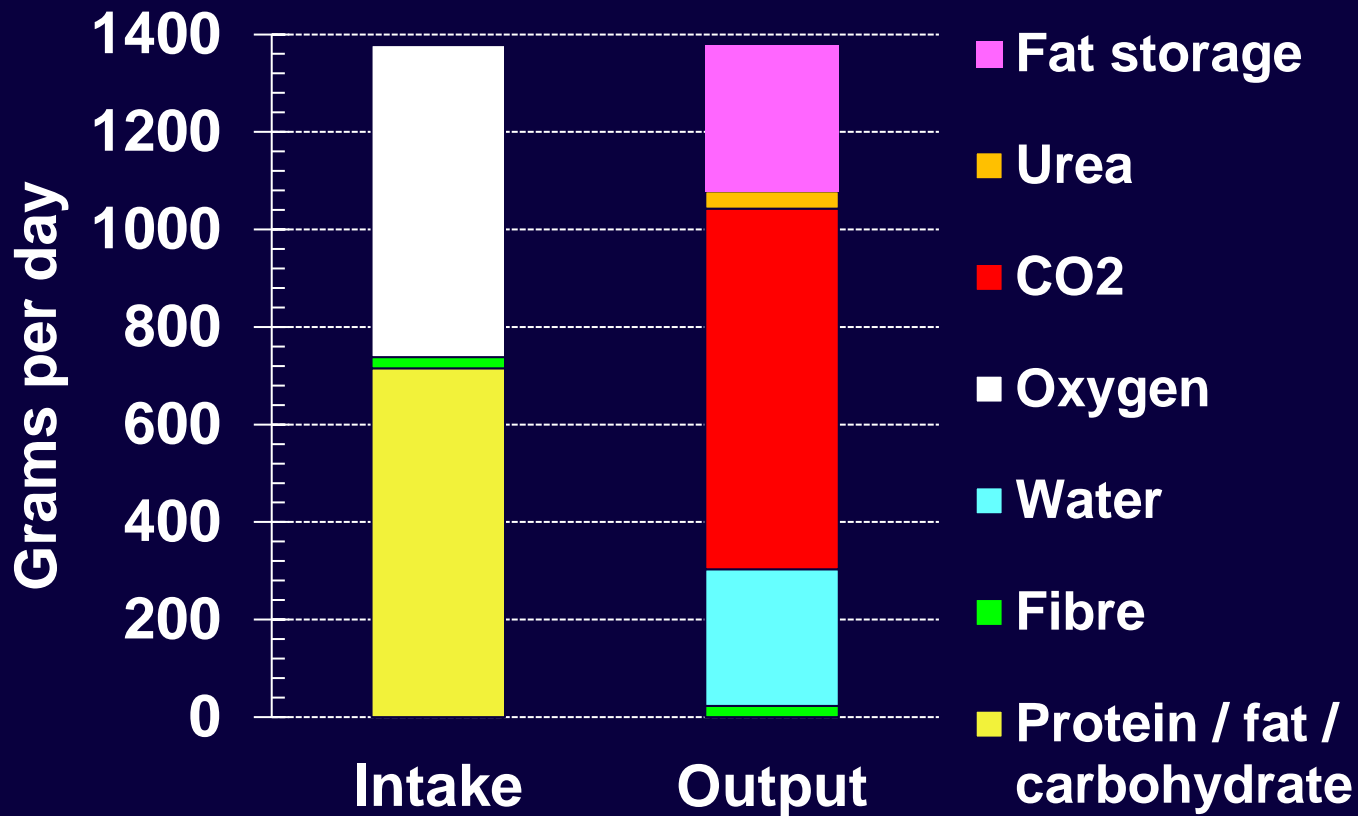
Nutrient intake data: Australian Bureau of Statistics; Australian Health Survey: Nutrition First Results - Foods and Nutrients;

<https://ketoschool.com/the-science-behind-fat-metabolism-60f7a3f678d0>

INSTIs, weight gain and CVD

Pathogenesis of weight gain

Add an extra 0.3kg of food a day with physical activity unchanged



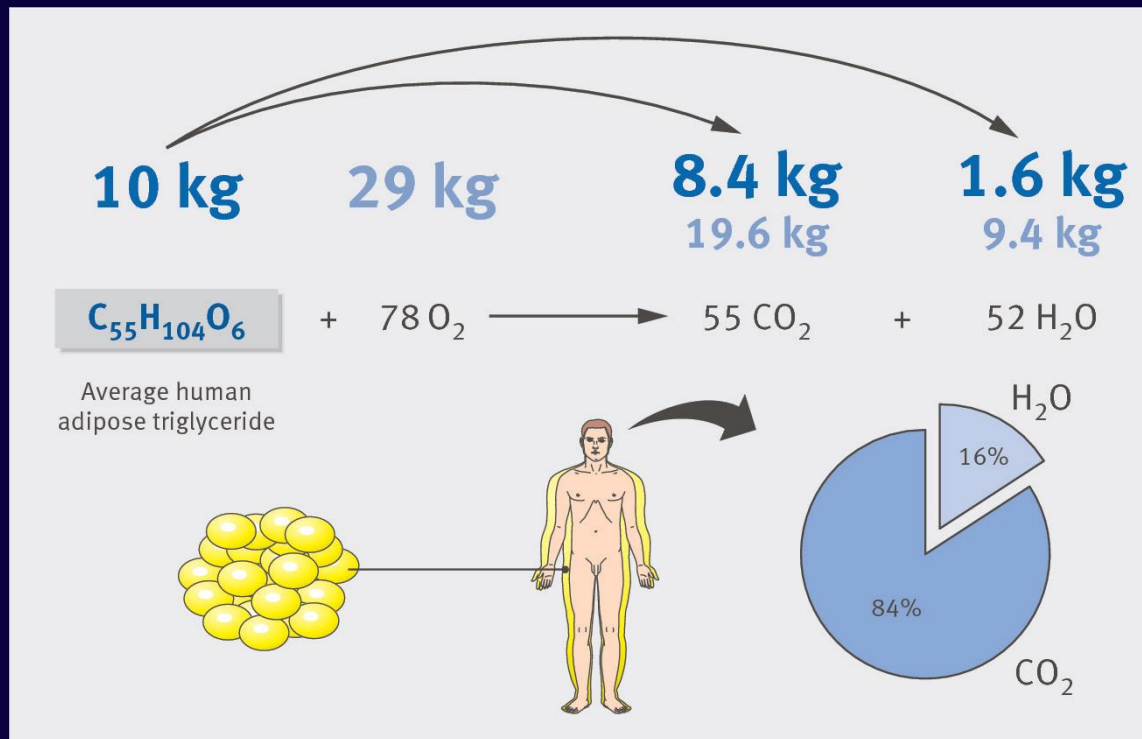
Nutrient intake data: Australian Bureau of Statistics; Australian Health Survey: Nutrition First Results - Foods and Nutrients;

<https://ketoschool.com/the-science-behind-fat-metabolism-60f7a3f678d0>

INSTIs, weight gain and CVD

Interventions for overweight: Calories in, calories out

How do we lose weight?



Definitely

- Calorie restriction (dietician) +
- More physical activity

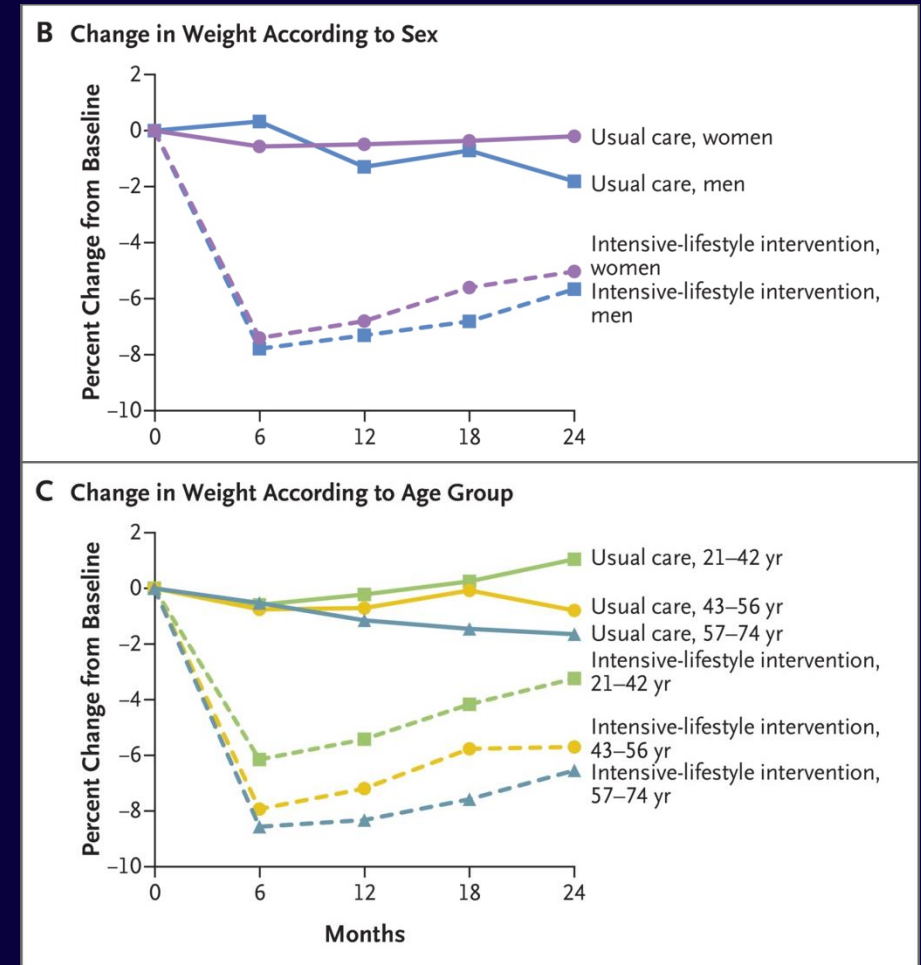
Possibilities

- Switch INSTI / TAF
- (Medication – no data)
- (Bariatric surgery – cases reports only)

INSTIs, weight gain and CVD

Interventions for overweight: Reduced intake and more exercise

- **Reduce energy intake (WHO)**
 - total fat <30% of calories
 - free sugars <10% of calories
 - 0.3 kg weight loss at 6 months
- **Increase physical activity (WHO)**
 - 150 minutes of exercise / week
 - reduce sedentary work
 - change transport
 - more public exercise space
- **Specific diets (121 RCTs, n=21,942)**
 - mean 4-5 kg at 6 mths, 3 kg at 12 mths
 - declines appear greater than with INSTI switching



INSTIs, weight gain and CVD

Interventions for overweight: Consider other medications

Drug family	Medications Associated with weight gain
Antipsychotic	olanzapine, tioridazine, risperidone, clozapine, quetiapine
Steroids	corticosteroids, progestagens, estrogens
Antidepressant	MAOIs, tricyclics, paroxetine, citalopram, escitalopram, imipramine, mirtazapine
Antidiabetic	insulin, sulfonylureas, glitazones, meglitinides
Mood stabilisers	lithium, carbamazepine, gabapentin, valproate
Antihistamine	ciproheptadine
Antihypertensive	terazosin, propranolol

INSTIs, weight gain and CVD

Interventions for overweight: B/F/TAF switch?

B/F/TAF to DOR/ISL (MK-8591A-018)

- Placebo-controlled RCT

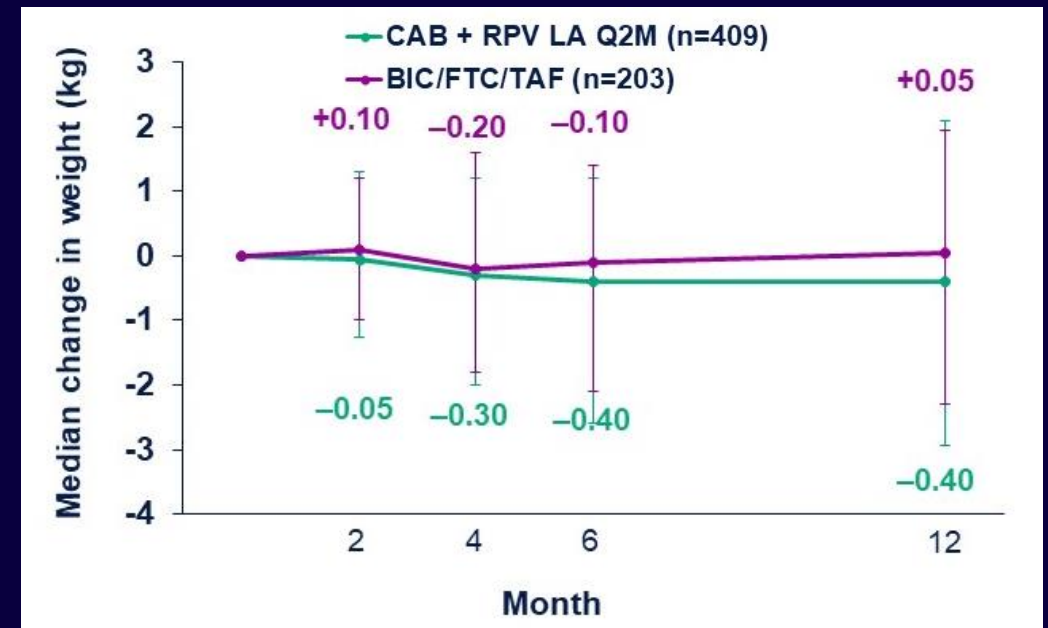
- Changes in weight at Week 48

- B/F/TAF (n=302) 0.55 kg (SD 4.40)
- DOR/ISL (n=306) 0.23 kg (SD 4.19)
- $\Delta = 0.30$ kg (95% CI -0.99, 0.39); p=0.39

- BUT

- most patients were not overweight and had not gained weight on B/F/TAF
- weight loss after pregnancy or after ceasing steroids / antipsychotics is often limited

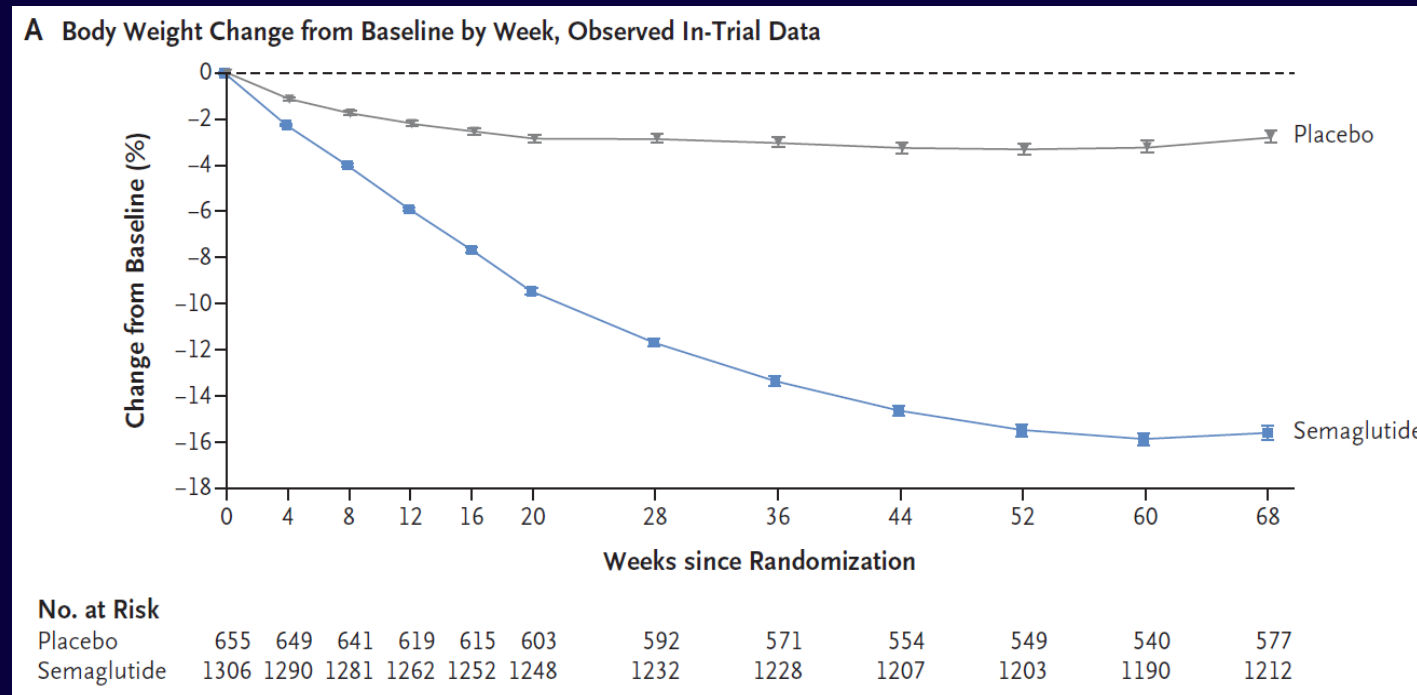
B/F/TAF to CAB+RPV (SOLAR)



INSTIs, weight gain and CVD

Interventions for overweight: Weight loss medication?

Semaglutide (2.4 mg once a week subcut)



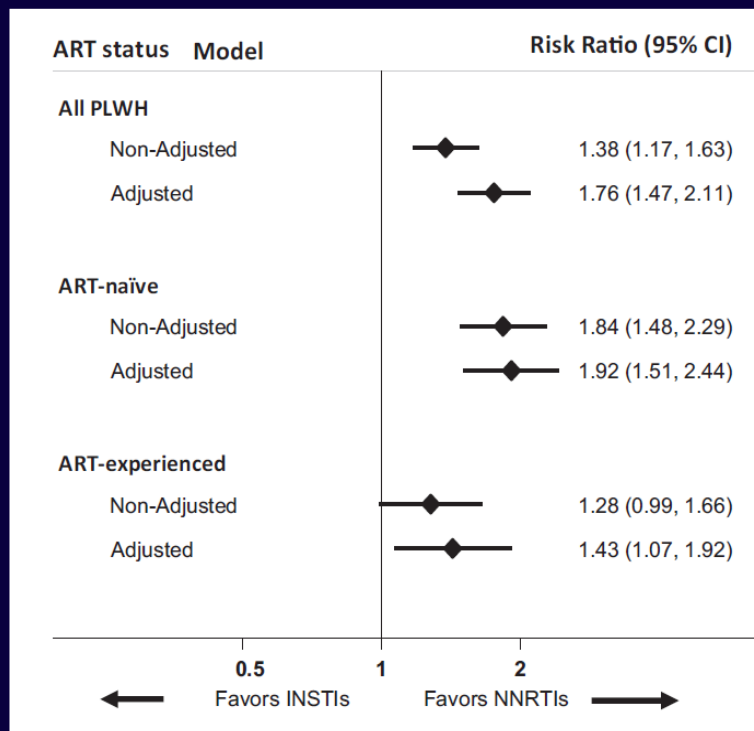
- Ongoing RCT in obese HIV+ adults (although no eligibility requirement for weight gain on ART)

INSTIs, weight gain and CVD

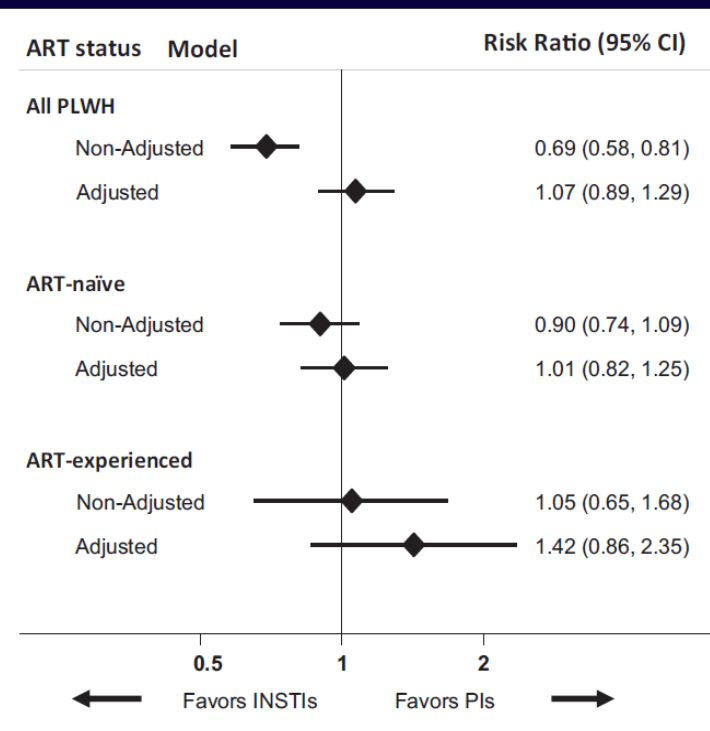
INSTIs and Hypertension (RESPOND)

- Hypertension developed in 23% (12.6 per 100 patient years)

INSTIs vs NNRTIs



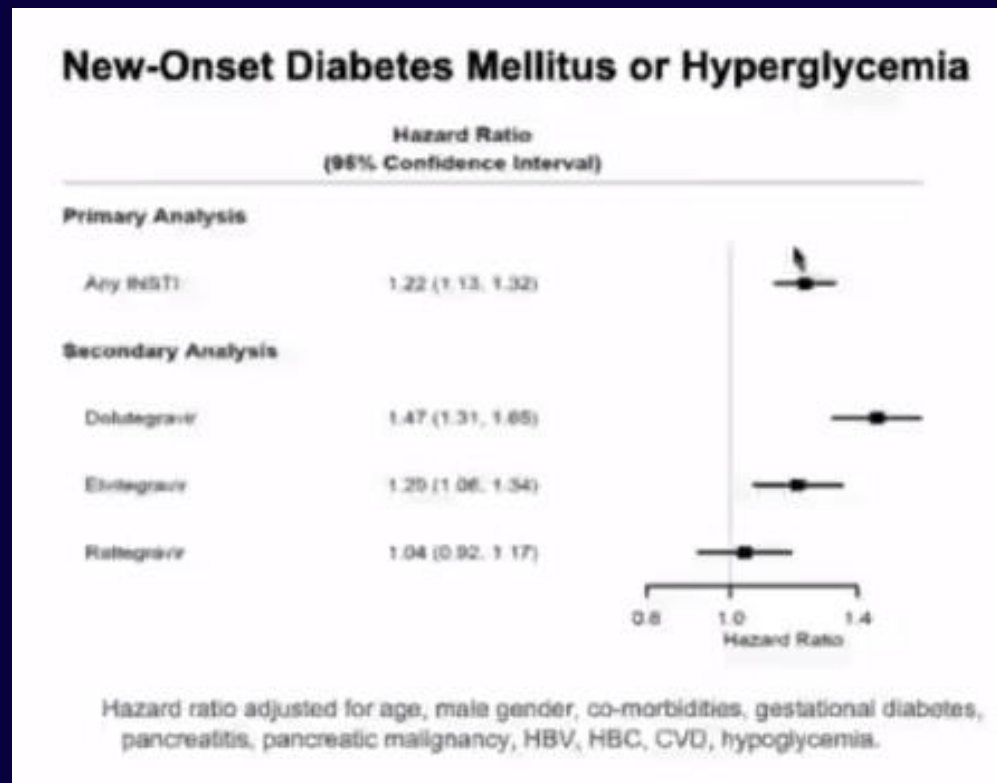
INSTIs vs PIs



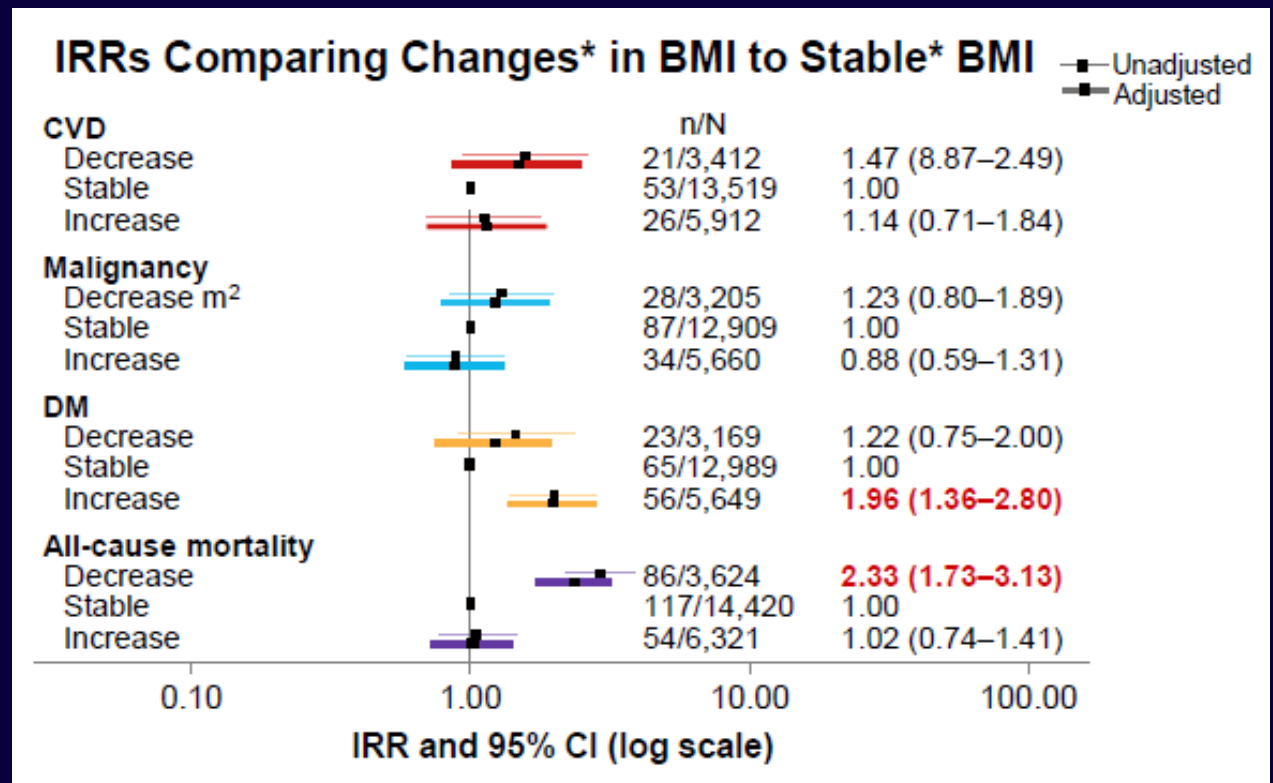
INSTIs, weight gain and CVD

INSTIs and Diabetes

INSTIs and diabetes



Weight gain, diabetes, CVD and death



INSTIs, weight gain and CVD

INSTIs and NAFLD / progression of fibrosis

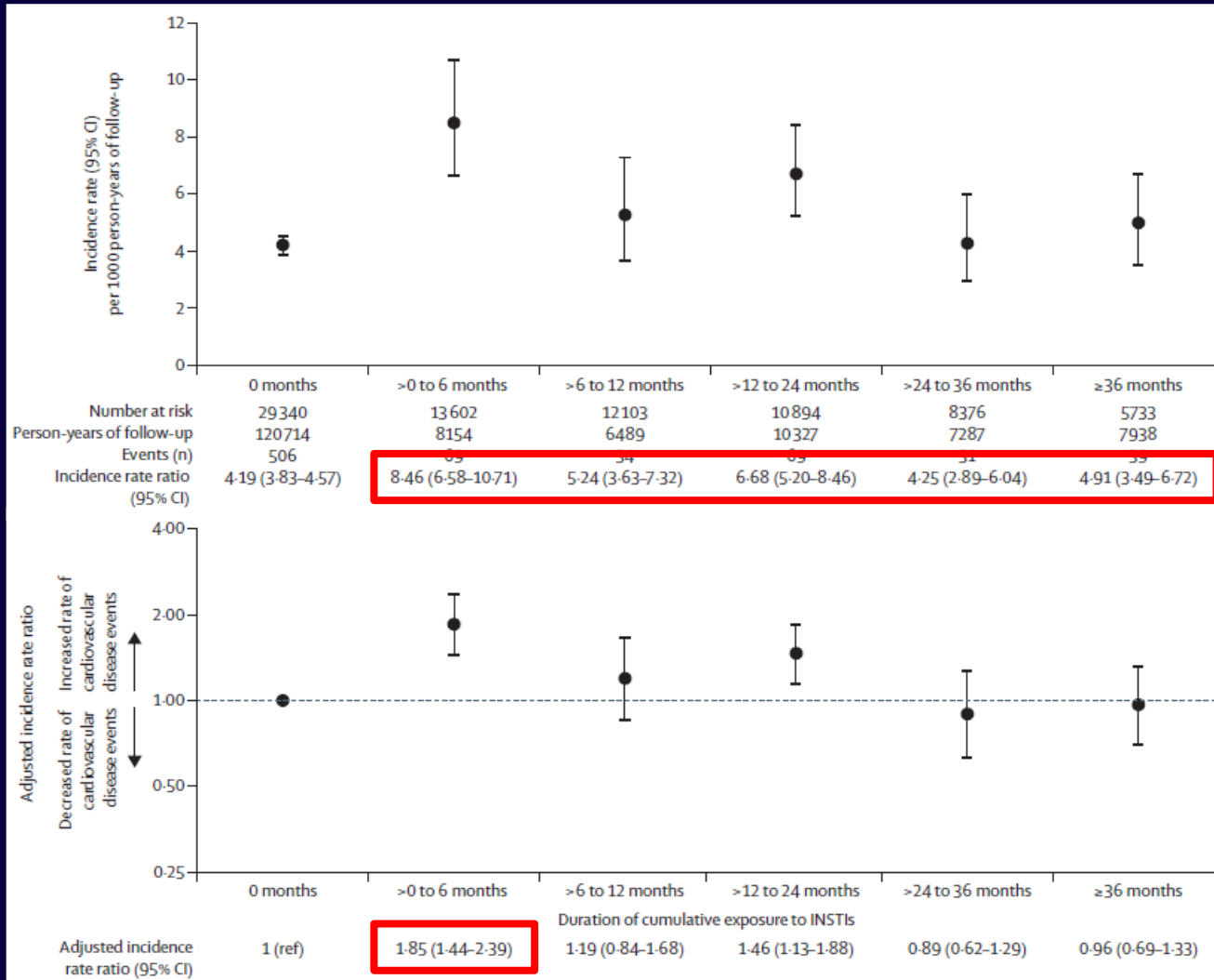
- **Hepatic steatosis / NAFLD**
 - 30.5% of 4798 HIV+ adults
 - higher risk for significant fibrosis (OR 1.91)
 - risk factors
 - diabetes (OR 4.7)
 - BMI (OR 2.1)
 - But not INSTI (OR 0.8)
- **NAFLD associations with hepatic fibrosis**
 - prior tNRTI use (OR 75.4)
 - female (OR 7.3)
 - higher BMI (OR 1.4)
 - older age (OR 1.2)

- **Liver fibrosis (n=1,183)**
 - median 53 yrs, 77% male
 - progression of fibrosis 3.4% / yr

Factor	HR	95% CI	P
Current INSTI	1.47	0.61, 3.52	0.39
Current TAF	0.85	0.39, 1.87	0.68
Current NNRTI	0.83	0.32, 2.18	0.70
Current PI	1.53	0.64, 3.63	0.34
Nadir CD4 < 200	0.56	0.27, 1.17	0.12
Chronic HBV	2.08	0.56, 7.69	0.27
Chronic HCV	1.08	0.45, 2.57	0.87
MAFLD	2.50	1.06, 5.89	0.036
BMI gain > 5%	2.64	1.32, 5.26	0.006

INSTIs, weight gain and CVD

INSTIs and CVD (RESPOND)

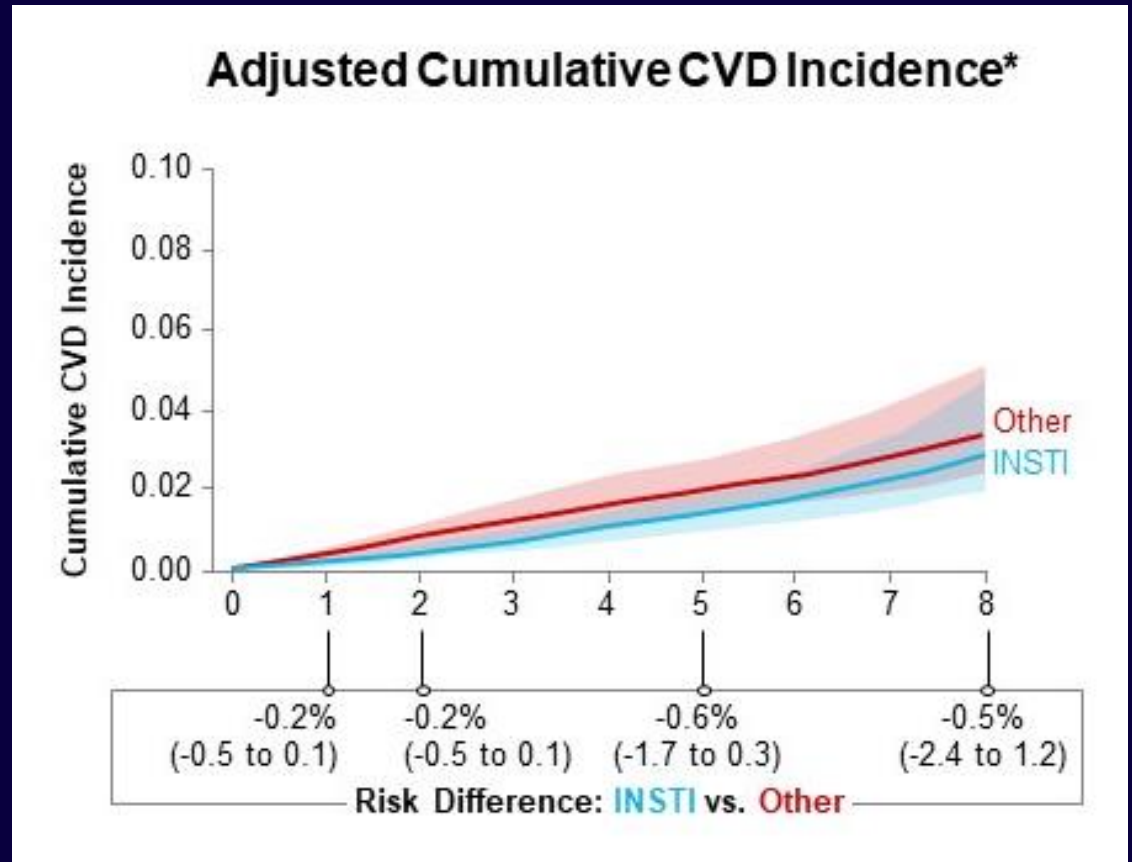


- ART-experienced and ART-naïve adults starting an INSTI
- Unadjusted analysis: incidence rate ratio for CVD increased over 3 years
- Adjusted analysis: risk increased only over first 6 months
- Reduced risk in adjusted analysis suggests those who received INSTIs may have been at greater CVD risk than average

CROI 2023

INSTIs and CVD with initial ART (Swiss HIV Cohort Study)

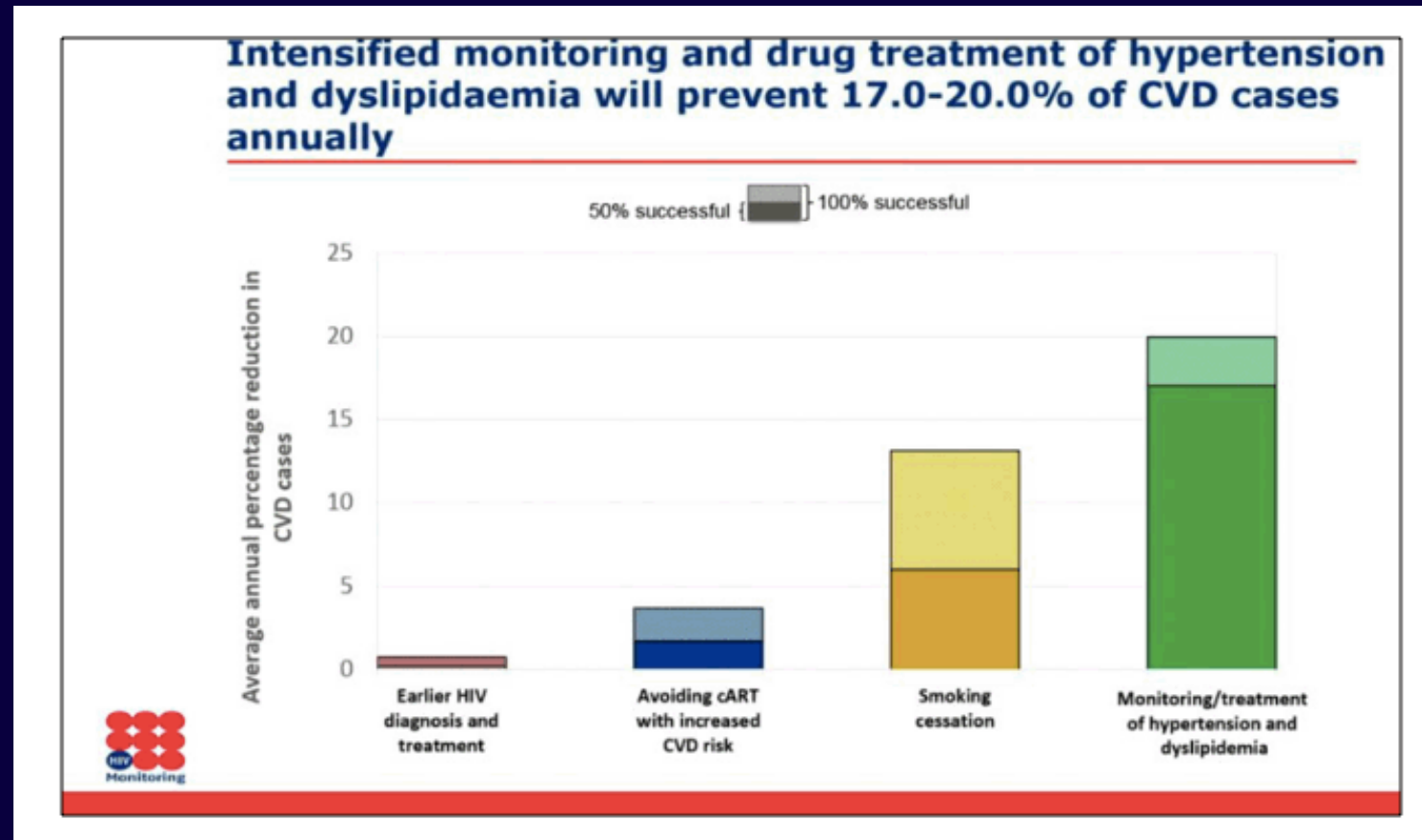
- Risk of AMI or stroke with INSTI (34.3%) or no INSTI (65.7%)
- n = 5,362
 - median age 38 yrs
 - 21% women
 - median follow-up 4.9 yrs
 - big switch to INSTI-ART 2013-16 after change in EACS ART guideline recommendations



INSTIs, weight gain and CVD

CVD risk factors: Conventional vs ART

Traditional risk factors had greater impact than ART in pre-INSTI era



INSTIs, weight gain and CVD

My perspective



INSTIs, weight gain and CVD

My perspective



INSTIs, weight gain and CVD

Conclusions: Weight gain

- Generally not severe after 2 years, but outliers / subgroups exist
- Likely to cause more NCDs and deaths, even without obesity
- Greater after INSTI initiation than with switching or PrEP, partially reflecting “return-to-health” and / or “**return-to-societal norm**”
- **Inhibited by** **TDF** (vs. placebo, ABC and TAF)
 EFV (vs. RPV and DTG)
- **Induced by INSTIs** one DTG switch RCT
 not all INSTIs may cause weight gain
- **Induced by TAF?** can tenofovir cause fat loss at one plasma concentration (TDF) but fat gain at a lower plasma concentration (TAF)?
- Calorie restriction and exercise vs INSTI switching vs both?

INSTIs, weight gain and CVD

Conclusions: Hypertension, diabetes, hepatic steatosis and CVD

- Cohort data only
- Randomised trials of initial ART with INSTI/TAF vs. non-INSTI/non-TAF (e.g. ISL-DOR) will hopefully be reported later this year
- Traditional interventions to prevent and treat established CVD likely to be more beneficial than INSTI/TAF switching (but doing both might be additive)

INSTIs, weight gain and CVD

Acknowledgements

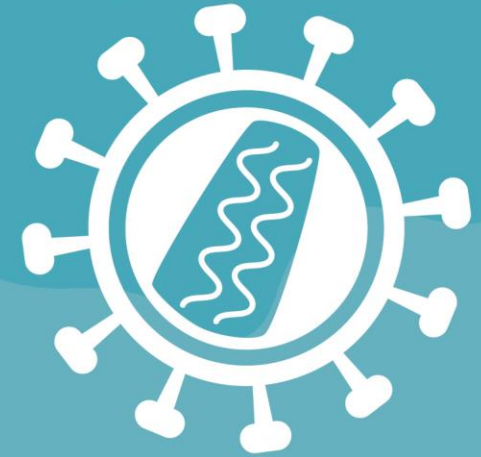
- Anton Pozniak
- Alexandra Calmy

BHIVA



British HIV Association

2023 Spring Conference



Mon 24th - Wed 26th April
Gateshead, UK

www.bhiva.org

#BHIVA23 Follow us on social media

