

# Session 5: Distance Learning and Dolutegravir Controversy

Dolutegravir and Weight Gain – Where are We?

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# Weight gain and dolutegravir: an update

Nov 2020

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Ezintsha, University of the Witwatersrand, Johannesburg



**Thanks to Andrew Hill,  
ADVANCE study team**

# Disclosures: Francois Venter

**Research Support:** USAID; Unitaid; South African Medical Research Council; Bill and Melinda Gates Foundation; study drug donations from ViiV Healthcare and Gilead Sciences; study support Merck and ViiV

**Speaker's Bureau:** Merck, Gilead Sciences, AbbVie, Cipla, Johnson and Johnson, ViiV Healthcare, Mylan and Southern African HIV Clinicians Society

**Board Member/Advisory Panel:** Gilead Sciences, ViiV Healthcare, Merck, Mylan

**BMI:** 24.8



# How on earth did we get here?



# HIV-positive people are leading normal lives – which means they will gain weight if prone



- Uganda/ US/ UK – ‘higher life expectancy that matched populations
- HIV positive people are going to get old

Annals of Internal Medicine | ORIGINAL RESEARCH

**Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries: A Cohort Analysis From Uganda**

Edward J. Mills, PhD, MSc, LL.M.; Celestin Bakanda, MSc; Josephine Birungi, MBChB; Keith Chan, MSc; Nathan Ford, PhD, MPH; Curtis L. Cooper, MD, MSc; Jean B. Nachega, MD, PhD; Mark Dybul, MD; and Robert S. Hogg, PhD, MA

1. Expect a normal life expectancy:  
May et al. AIDS 2014

- UK CHIC: 21 388 people started ART 2000-2010

	life expectancy		
CD4	Baseline	1 year ART	5 years ART
<200	71		& VL>50 54
200-349	78	78	
>350	77	81	& VL<50 80
General population	78		

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal  
Great information to give to people newly diagnosed and encourage good adherence

Annals of Internal Medicine | EDITORIAL

**Life Expectancy in Africa: Back to the Future?**

From 1950 to 1990, life expectancy in sub-Saharan Africa... challenges global trade rules and regulations, etc.

10 | 16 August 2011 | Annals of Internal Medicine | Volume 155 • Number 4

Thanks: Julie Fox, Guys

# First reports of weight gain with new regimens...

- Mid-2017
- Case report of someone switching INSTI due to weight gain

# Weight gain reported with....

- Most modern drugs but worse with
  - Newer integrase inhibitors (not cabotegravir)
  - Tenofovir alafenamide (TAF)
  - Also rilpivirine
- Weight not reported in dolutegravir or bictegravir registration studies
- In context where >30 million people moving to dolutegravir across the world; and where TAF and bictegravir are extensively used in richer countries



# Are new antiretroviral treatments increasing the risks of clinical obesity?

Andrew Hill<sup>1\*</sup>, Laura Waters<sup>2</sup> and Anton Pozniak<sup>3</sup>

<sup>1</sup>Department of Translational Medicine, University of Liverpool, UK

<sup>2</sup>Central and North West London NHS Trust, Mortimer Market Centre, London, UK

<sup>3</sup>Chelsea and Westminster Hospital, London, UK; London School of Hygiene and Tropical Medicine, UK

**Table 1.** Effects of raltegravir, dolutegravir and bicitegravir on body weight in randomised trials

Study [ref]	Design	Results
<b>Raltegravir</b>		
NEAT 001 [12] (naïve, n=126)	DRV/r+RAL DRV/r + TDF/FTC	DEXA sub-study: trunk fat 7.3% higher DRV/r/RAL vs TDF/FTC/RAL at week 96 (P=0.021)
ACTG 5260s [10,11] (naïve, n=126)	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	Higher risk of severe weight gain for RAL vs ATV/r
<b>Dolutegravir</b>		
NEAT 022 [13] (switch, n=415)	NRTIs + DTG NRTIs + PI/r	+1 kg increase in body weight to week 48 (P=0.002)
SPRING-1 [13] (naïve, n=204)	TDF/FTC/EFV TDF/FTC/DTG	Increases in body weight higher in DTG arms
Gilead 1490 [15] (naïve, n=645)	TAF/FTC/DTG TAF/FTC/BIC	+3.9 kg increase in body weight to week 96 +3.5 kg increase in body weight to week 96
MONODO [9] (naïve, n=8)	DTG monotherapy	+4.1 kg increase in body weight to week 24

ATV/r; atazanavir/ritonavir; BIC: bicitegravir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitors; PI/r: ritonavir-boosted protease inhibitor; RAL: raltegravir; TAF: tenofovir AF; TDF: tenofovir DF.

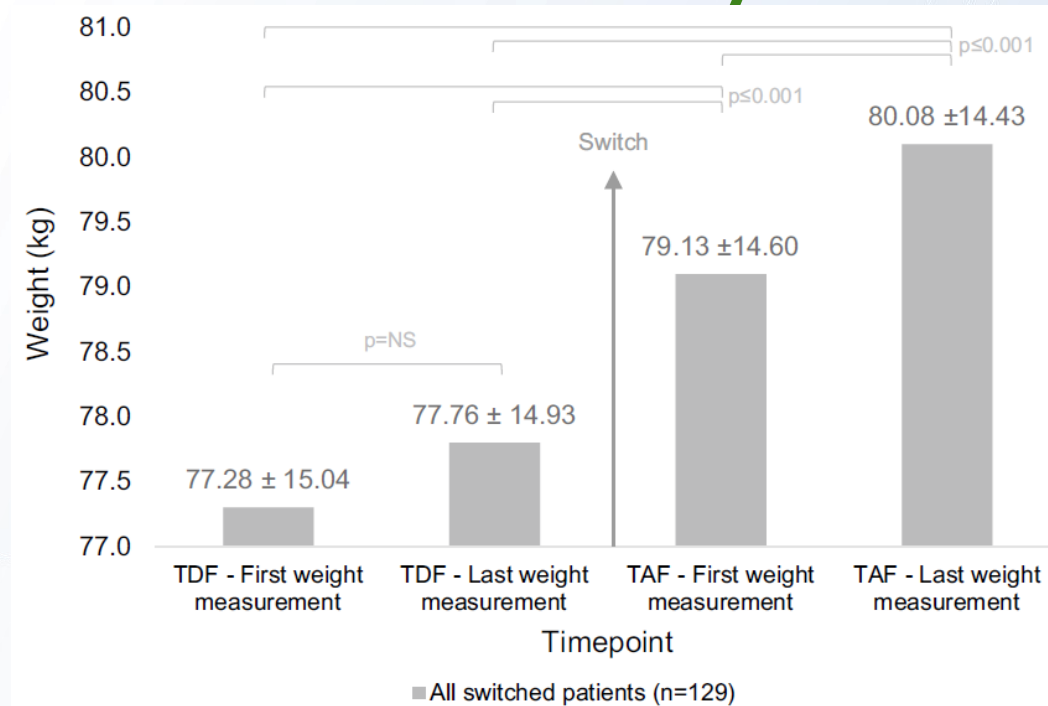
# Use of TDF versus TAF or ABC – effects on body weight

DISCOVER trial (PrEP): +1kg on TAF/FTC, versus +0kg on TDF/FTC

STEAL trial (treatment): +1kg on ABC/3TC versus +0kg on TDF/FTC

AMBER trial (treatment): +1.8kg on TAF/FTC/DRV/c vs +0.8kg on TDF/FTC/DRV/c

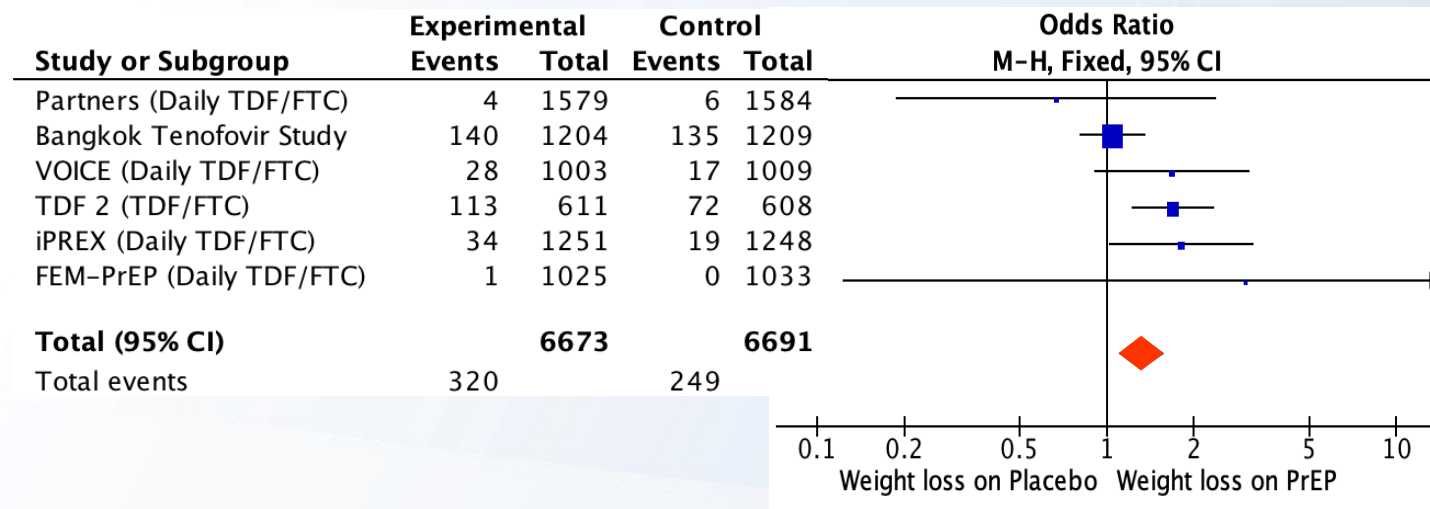
## Change in body weight after switch from TDF to TAF – German cohort study



Only switch patients are shown, “TDF (TAF)—first/last weight measurement” denotes the first/last weight measured on TDF (TAF) treatment; results shown for weight in kg; NS not statistically significant

Gomez et al. Weight Gain switching TDF to TAF. Infection 2018

## TDF as PrEP: weight loss >5%



**Odds Ratio = 1.32 (1.11 to 1.58)**

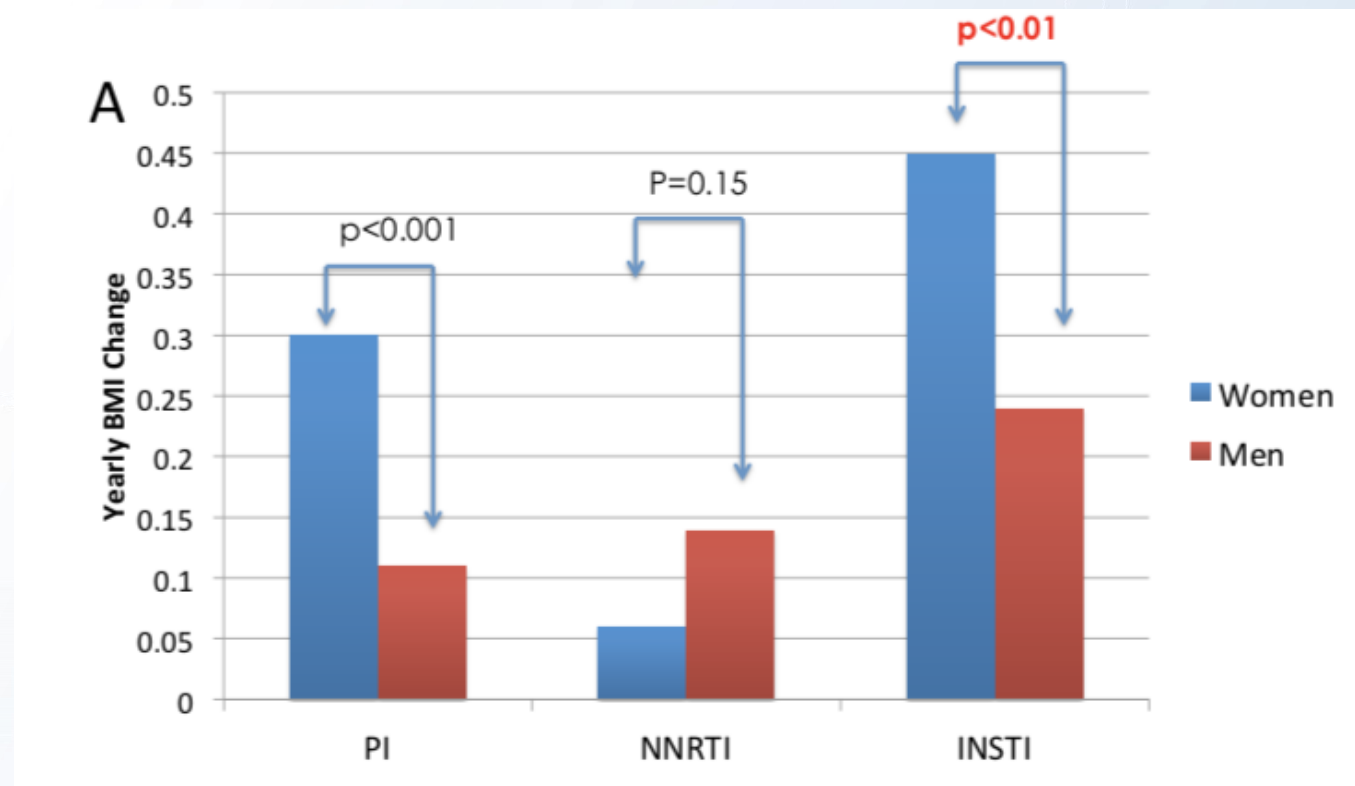
**P = 0.002**

# Then came the INSTI's....

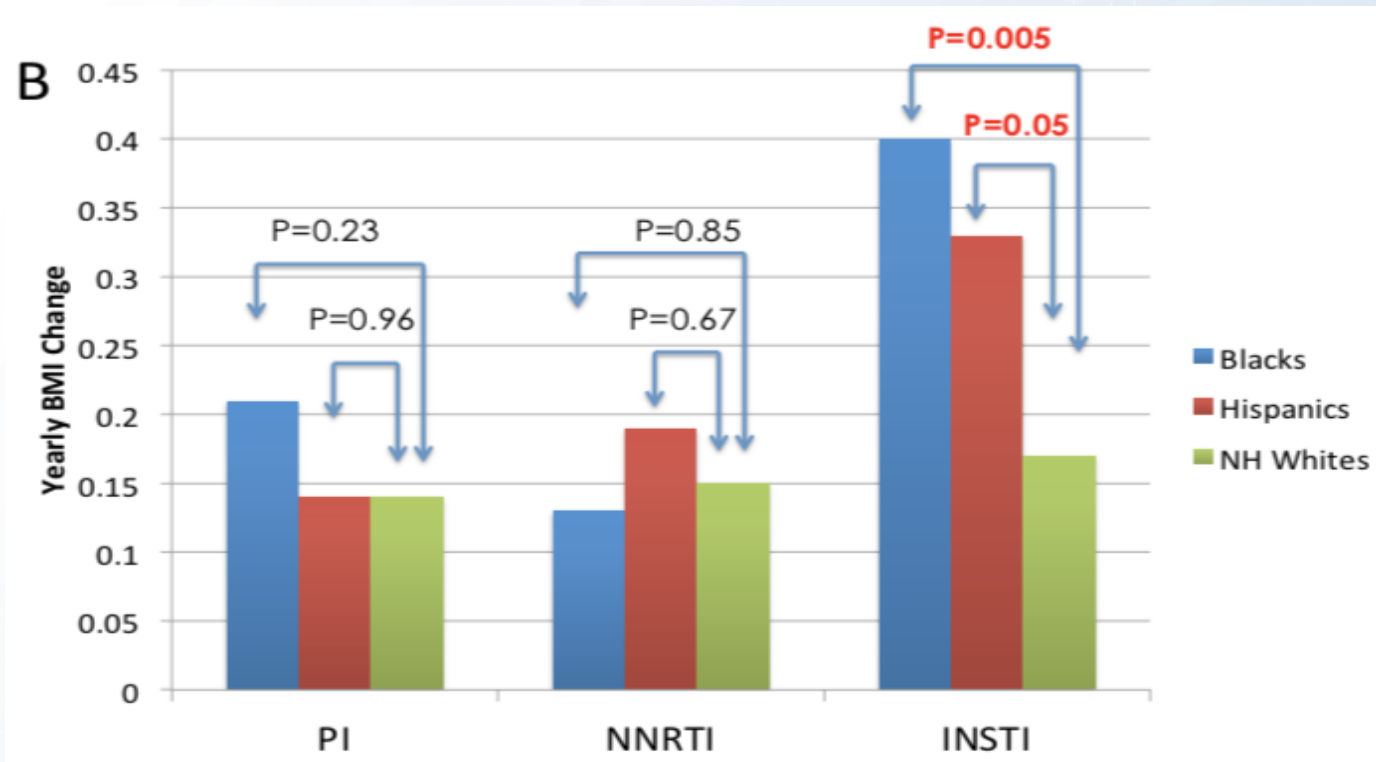
- Rapidly became standard of care
- 2 years later, at CROI – issue raised in themed discussion

**Weight gain themed discussion : CROI 2019 <http://www.croiwebcasts.org/s/2019croi/TD-08>**

# Weight gain on INSTI – women gain 2x more than men (US cohort study)



# Weight gain on INSTI – black people gain 2x more than whites (US cohort study)



## Randomised trials – similar effects of DTG and BIC

Trial	Design	Outcomes
NEAT 022 (N=415, switch)	NRTIs + DTG NRTIs + PI/r	+1kg rise in body weight to Week 48 (p=0.002)
SPRING-1 N=204, naïve	TDF/FTC/EFV TDF/FTC/DTG	rises in body weight higher in DTG arms
Gilead 1490 96 N=645, naïve 96	TAF/FTC/DTG TAF/FTC/BIC	+3.9kg rise in body weight to Week +3.5kg rise in body weight to Week
Gilead 1489 96 N=645, naïve 96	ABC/3TC/BIC TAF/FTC/BIC	+2.4kg rise in body weight to Week +3.6kg rise in body weight to Week
MONODO N=8, naïve	DTG mono	+4.1kg rise in body weight to Week 24





## Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

Paul E. Sax,<sup>1</sup> Kristine M. Erlandson,<sup>2</sup> Jordan E. Lake,<sup>3</sup> Grace A. McComsey,<sup>4</sup> Chloe Orkin,<sup>5</sup> Stefan Esser,<sup>6</sup> Todd T. Brown,<sup>7</sup> Jürgen K. Rockstroh,<sup>8</sup> Xuelian Wei,<sup>9</sup> Christoph C. Carter,<sup>8,9</sup> Lijie Zhong,<sup>9</sup> Diana M. Brainard,<sup>9</sup> Kathleen Melbourne,<sup>9</sup> Moupali Das,<sup>9</sup> Hans-Jürgen Stellbrink,<sup>10</sup> Frank A. Post,<sup>11,12</sup>

**Table 5. Risk factors for significant ( $\geq 10\%$ ) weight gain in individuals initiating ART.**

Variable	OR	95% CI	p value
CD4 (<200 vs. $\geq 200/\mu\text{L}$ )	4.36	3.6, 5.27	<0.001
HIV RNA (>100k vs. $\leq 100\text{k c/mL}$ )	1.98	1.65, 2.37	<0.001
BMI (normal vs. overweight)	1.54	1.27, 1.87	<0.001
BMI (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	1.1, 1.59	0.003
Third agent (BIC/DTG vs. EFV)	1.82	1.24, 2.66	0.002
Third agent (EVG/c vs. EFV)	1.36	1.04, 1.78	0.026
Third agent (RPV vs. EFV)	1.51	1.03, 2.2	0.035
Third agent (ATV/r vs. EFV)	0.92	0.59, 1.45	0.73
NRTI (TAF vs. AZT)	1.75	1.04, 2.95	0.034
NRTI (TDF vs. AZT)	1.19	0.76, 1.87	0.44
NRTI (ABC vs. AZT)	0.93	0.47, 1.8	0.82
NRTI (TAF vs. ABC)	1.9	1.25, 2.88	0.003
NRTI (TDF vs. ABC)	1.29	0.79, 2.11	0.31
NRTI (TAF vs. TDF)	1.47	1.14, 1.9	0.003

Sax, CID, 2019

## Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

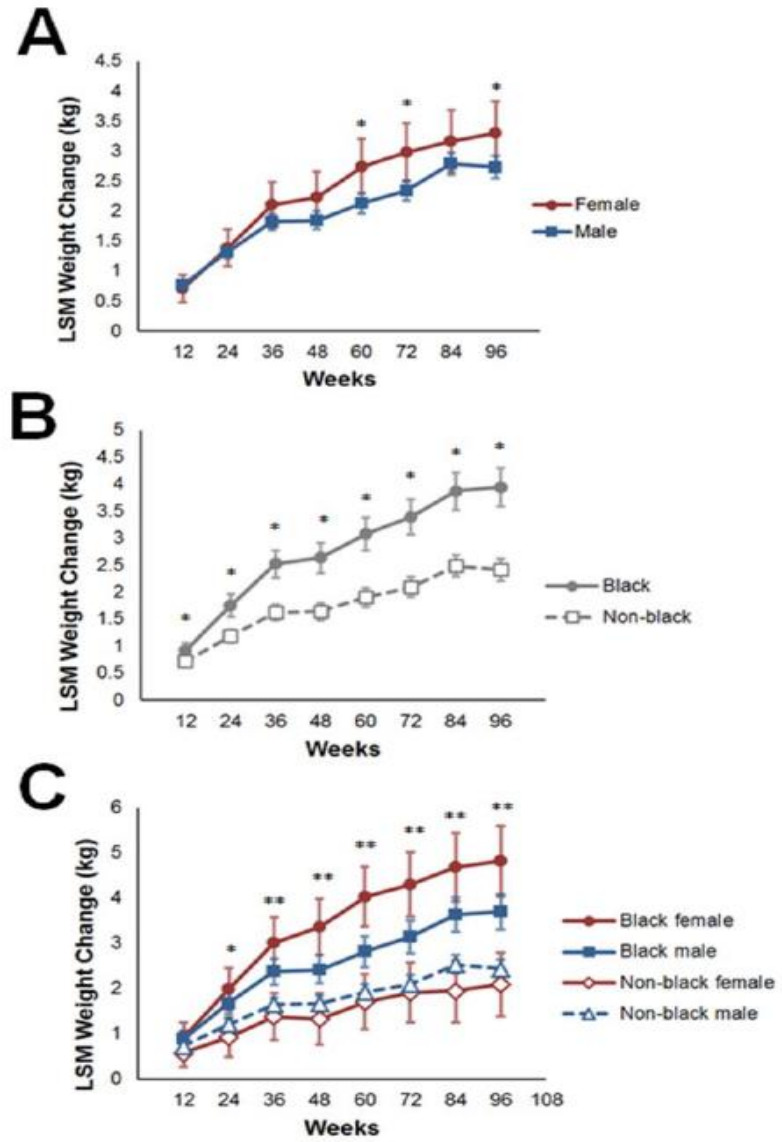
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Sax, CID, 2019

Figure 2



Sax, CID, 2019

# OPERA: Longitudinal Prospective Cohort Analysis

- Routine EHR data collected from ~ 8% of US PWH receiving care (> 115,000 individuals across 65 cities in 19 states and Puerto Rico)
- Current analysis restricted to adults receiving TDF-containing 3-drug ART at BL with  $\geq 2$  consecutive HIV-1 RNA < 200 copies/mL who switched TDF to TAF

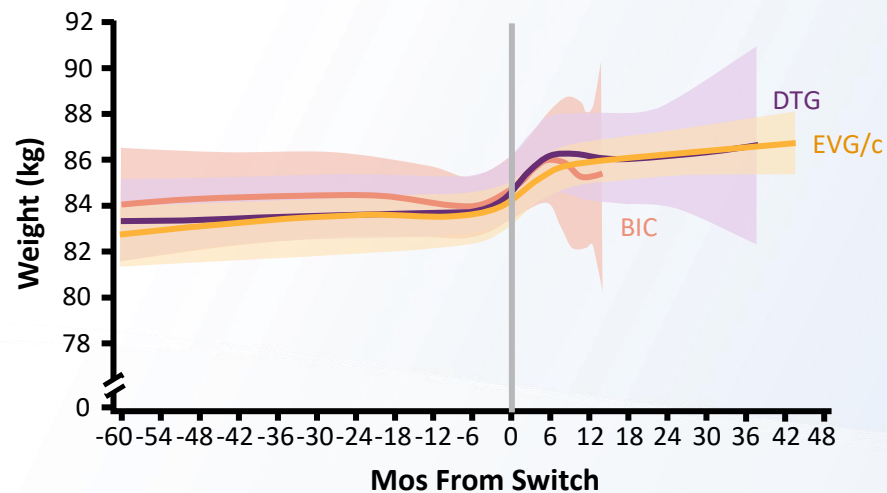
Anchor Agent by Class, % (n)		Maintained Other ARVs (n = 5479)
INSTIs (n = 3281)	▪ Elvitegravir/cobicistat	73 (2389)
	▪ Dolutegravir	20 (643)
	▪ Raltegravir	8 (249)
NNRTIs (n = 1452)	▪ Rilpivirine	85 (1238)
	▪ Nevirapine	12 (176)
	▪ Efavirenz	2 (26)
	▪ Etravirine	1 (12)
Boosted PIs (n = 746)	▪ Darunavir	68 (504)
	▪ Atazanavir	28 (211)
	▪ Lopinavir	3 (22)
	▪ Fosamprenavir	1 (9)

Mallon. AIDS 2020. Abstr OAB0604.

Slide credit: [clinicaloptions.com](https://clinicaloptions.com)



# OPERA: Weight Change With Switch From TDF to TAF While Also Switching to an INSTI

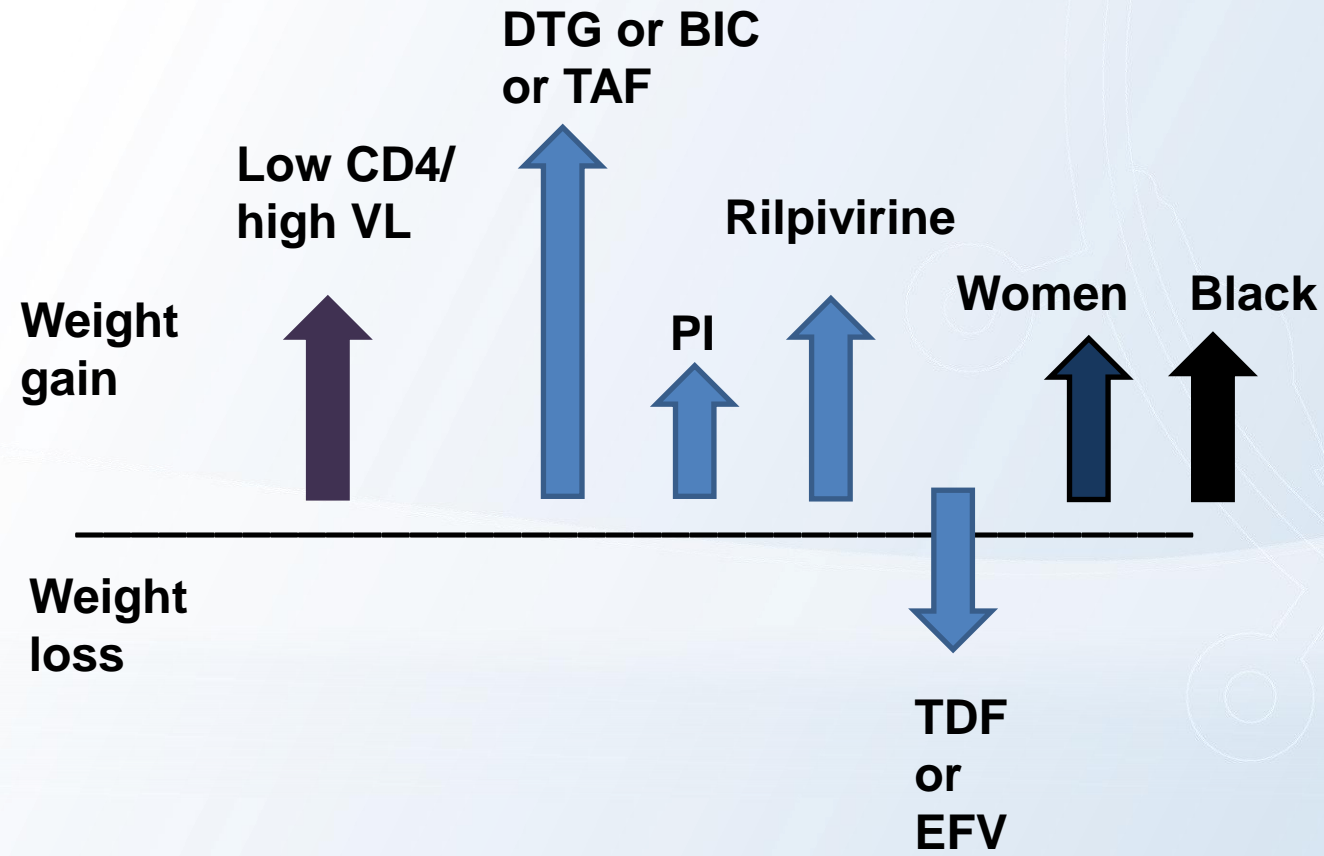


Estimated Weight $\Delta$ by Time From TDF to TAF Switch, kg/yr (95% CI)	EVG/c (n = 1120)	DTG (n = 174)	BIC (n = 129)
-60 to 0 mos	0.24 (0.04 to 0.43)	0.22 (-0.08 to 0.52)	0.01 (-0.38 to 0.39)
0 to 9 mos	2.55 (1.86 to 3.24)	3.09 (1.26 to 4.93)	4.47 (0.81 to 8.13)
9+ mos	0.26 (-0.10 to 0.61)	-0.23 (-1.62 to 1.16)	-9.97 (-23.79 to 3.85)

Mallon. AIDS 2020. Abstr OAB0604. Reproduced with permission.

Slide credit: [clinicaloptions.com](https://clinicaloptions.com)

# Drivers of weight gain / loss



## Phase 3 trials of new antiretrovirals are not representative of the global HIV epidemic

Toby Pepperrell<sup>1</sup>, Andrew Hill<sup>2\*</sup>, Michelle Moorhouse<sup>3</sup>, Polly Clayden<sup>4</sup>, Kaitlyn McCann<sup>5</sup>, Simiso Sokhela<sup>3</sup>,  
Cecilia Serenata<sup>6</sup>, Willem Daniel Francois Venter<sup>3</sup>

<sup>1</sup>Faculty of Medicine, Imperial College London, UK

<sup>2</sup>Department of Translational Medicine, Liverpool University, Pharmacology, Liverpool, UK

- Most registration studies done in white males for almost all newer antiretrovirals

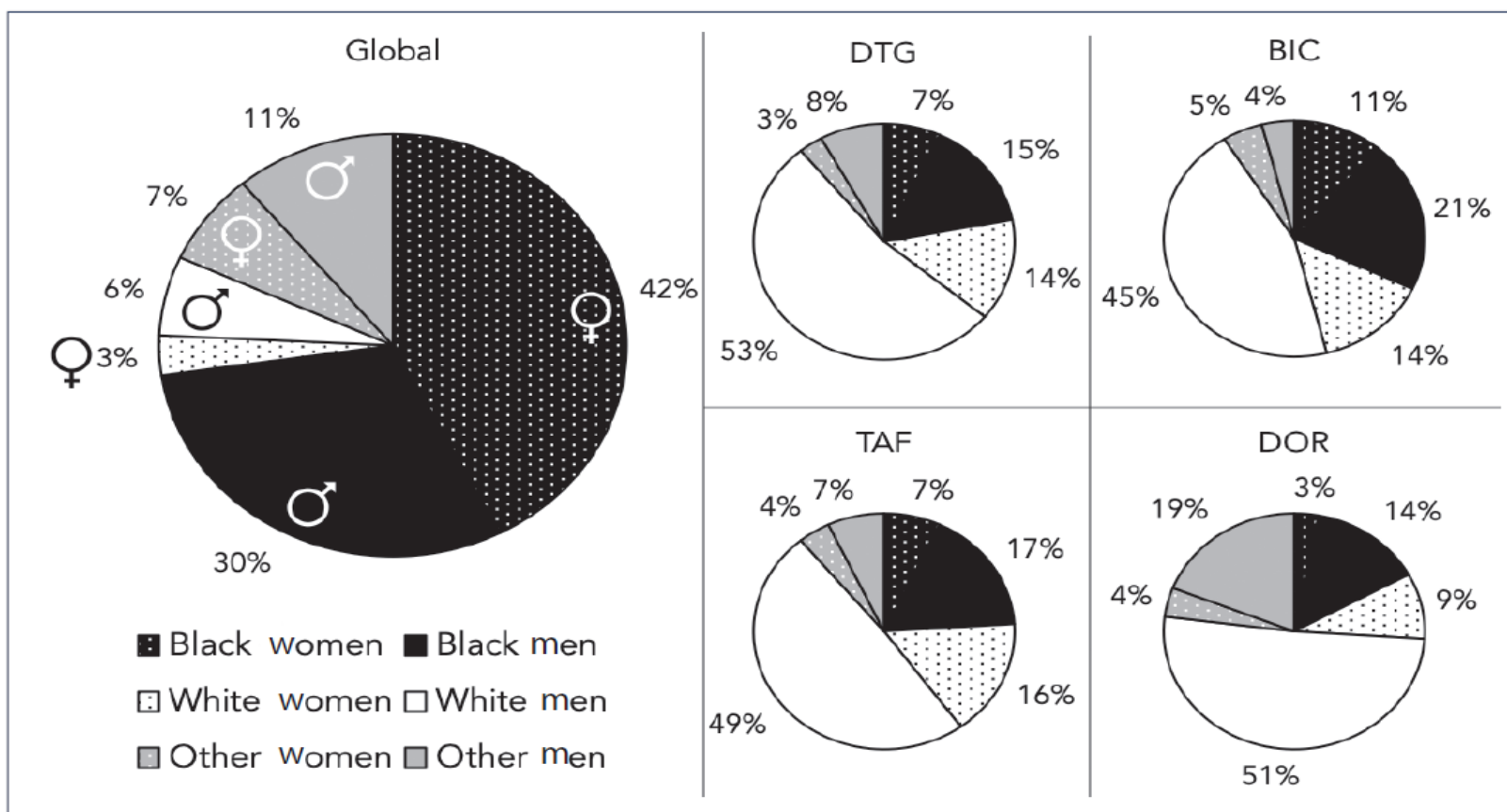
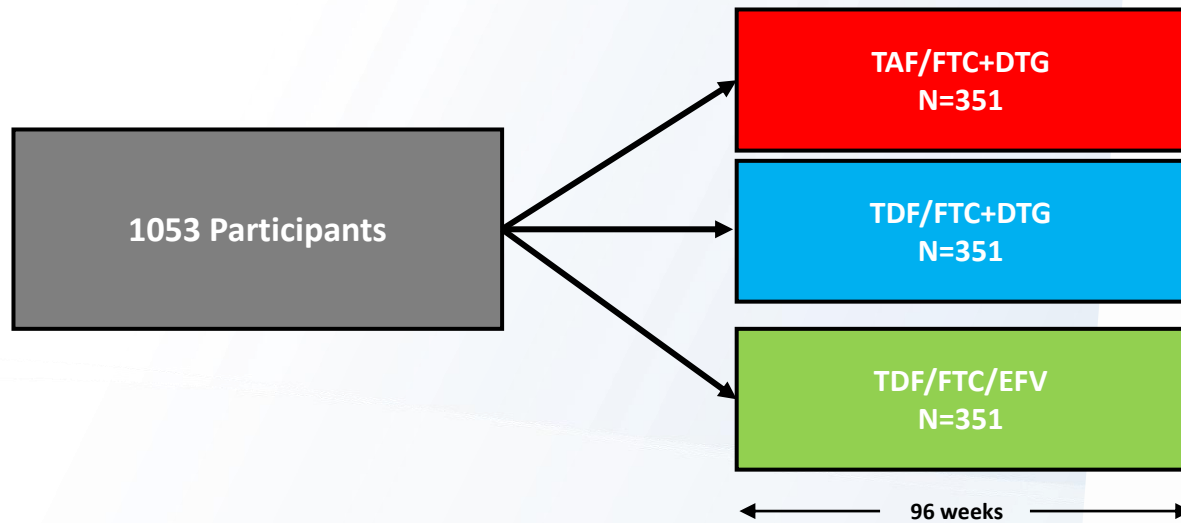


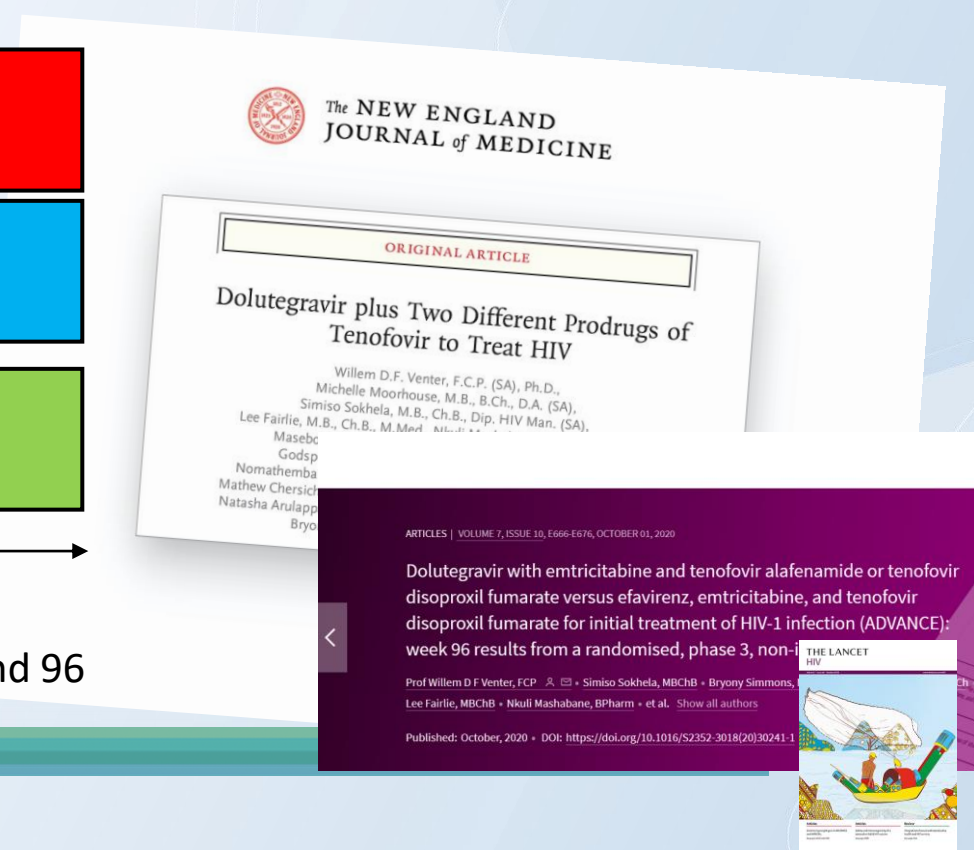
Figure 1. Estimated global demographics of PLWH vs RCT demographics. Percentages may be rounded up to make 100. Data are given as percentage. BIC: bicitegravir; DOR: doravirine; DTG: dolutegravir; PLWH: people living with HIV; RCT: randomised controlled trial; TAF: tenofovir alafenamide.

# ADVANCE: Study design

**Inclusion criteria:** treatment-naïve, HIV-1 RNA level  $\geq 500$  copies/mL, no TB or pregnancy, no baseline genotyping



Open-label, 96-week study in Johannesburg, South Africa  
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84, and 96





And representative by race and gender and geography

## Baseline characteristics (1/2)

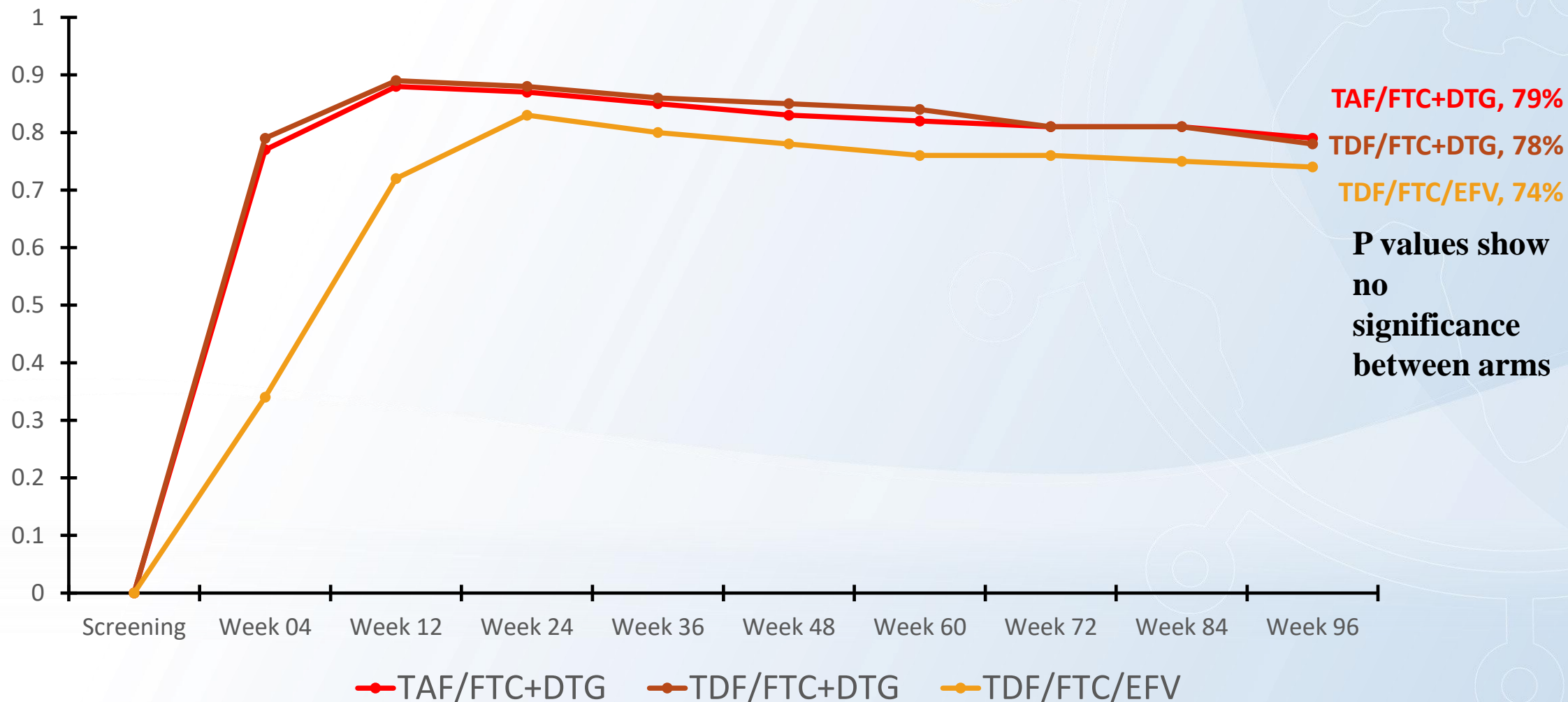
Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Age, mean (SD), years	33 ± 8	32 ± 8	32 ± 7
Female	61%	59%	57%
Black	99%	100%	100%
Baseline HIV-1 RNA			
≤100,000 copies/mL	78%	80%	77%
>100,000 copies/mL	22%	20%	23%
CD4+ cell count, mean (SD), cells/mm <sup>3</sup>	349 ± 225	323 ± 234	337 ± 222

Weight was high even pre-ART!

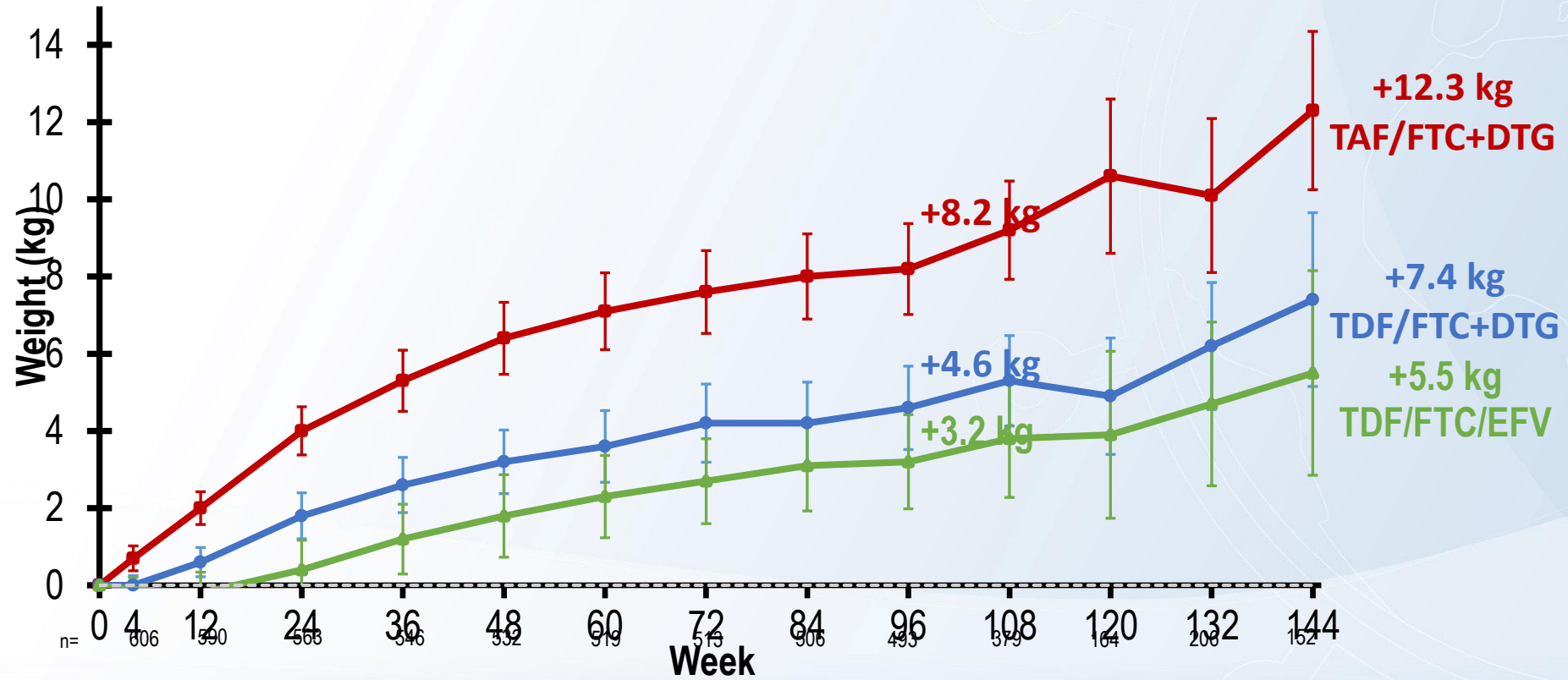
## Baseline characteristics (2/2)

Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
<b>Weight, mean (kg)</b>			
Male	67.9	67.1	67.3
Female	68.8	69.5	70.2
<b>BMI, mean (kg/m<sup>2</sup>)</b>			
Male	21.7	21.6	21.8
Female	25.6	26.1	26.1
<b>Categories of BMI, n (%)</b>			
Underweight (< 18.5)	42 (12%)	35 (10%)	37 (11%)
Normal (18.5-25)	177 (51%)	190 (54%)	193 (55%)
Overweight (25-30)	96 (27%)	78 (22%)	77 (22%)
Obese (> 30)	35 (10%)	48 (14%)	44 (13%)

# Proportion of participants with HIV-1 RNA level <50 copies/mL by time point (ITT)

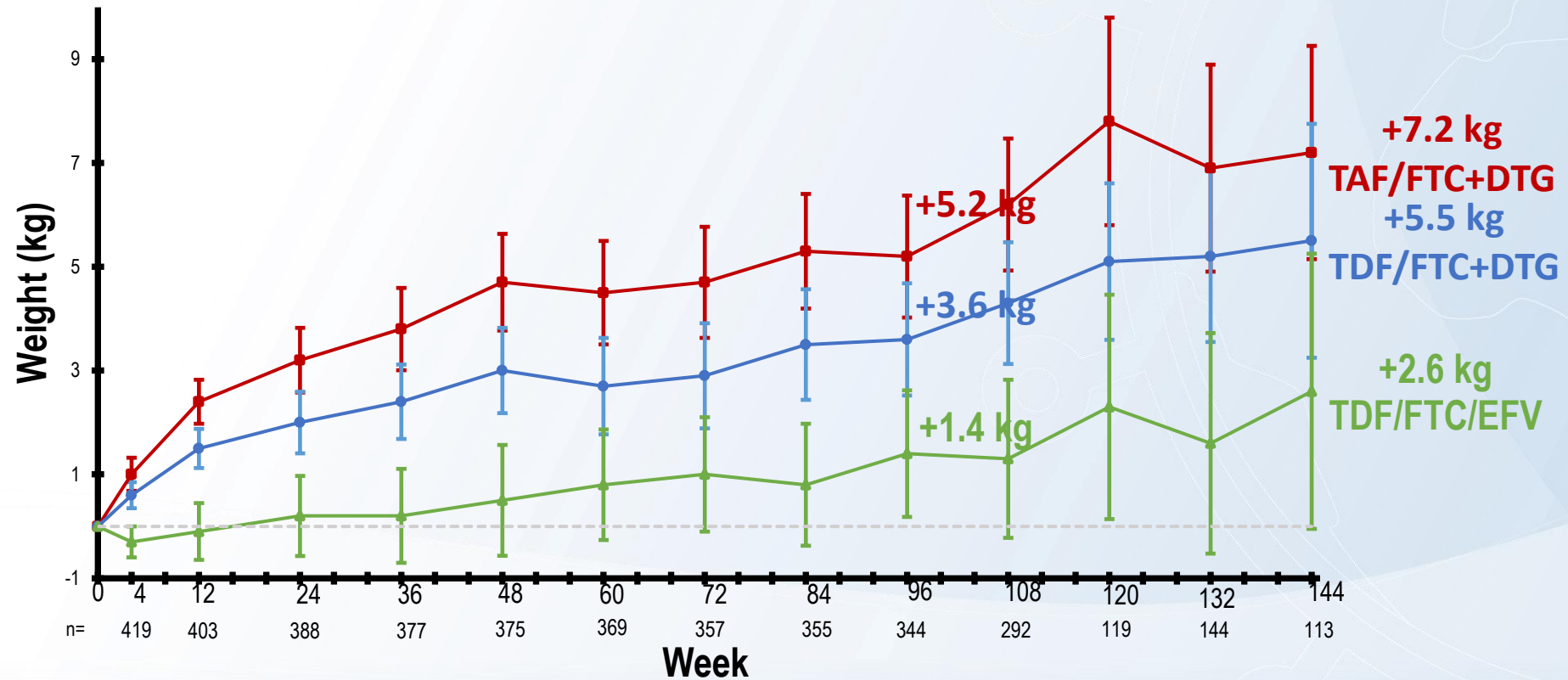


## Mean change in weight (kg): women



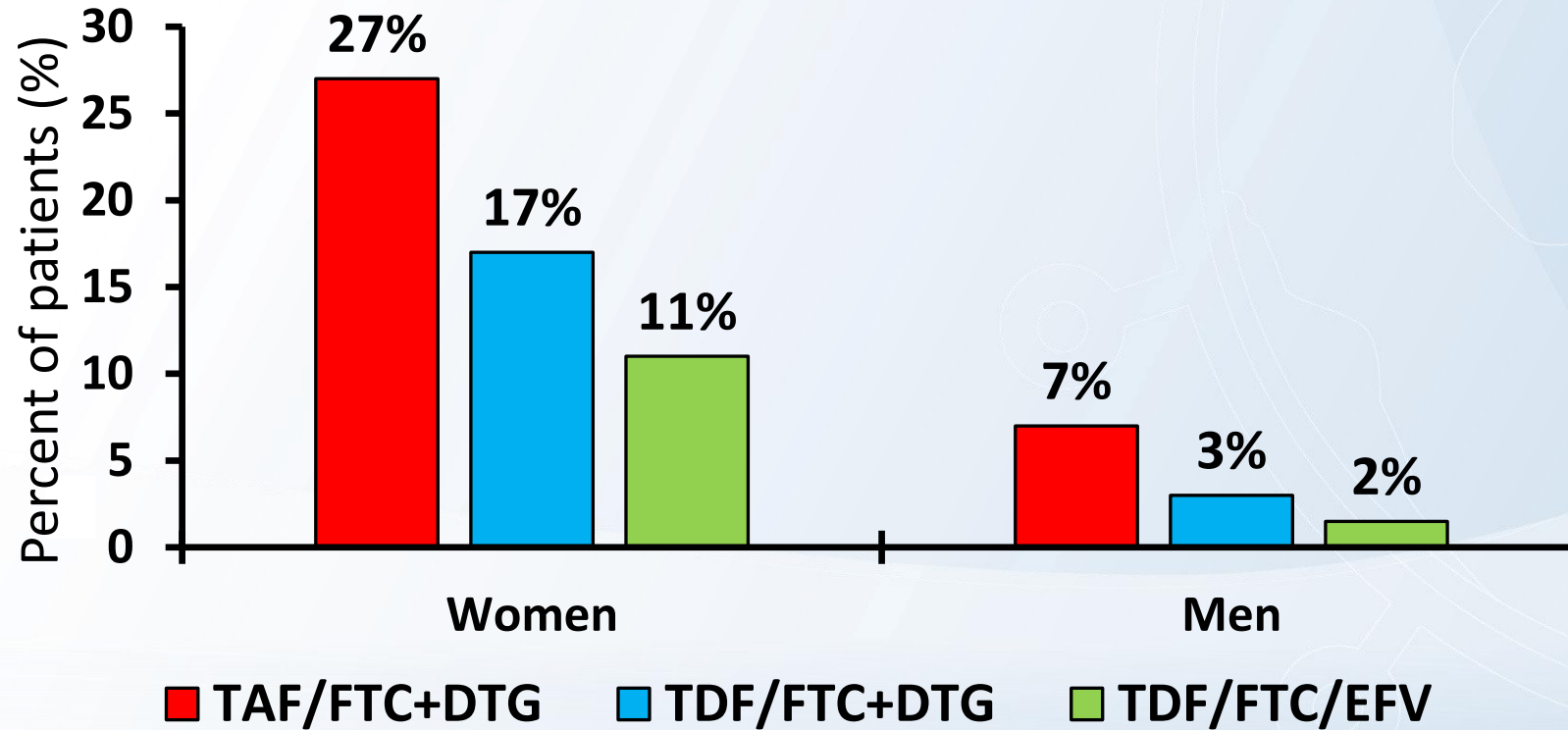
Note: data incomplete to week 144

## Mean change in weight (kg): men

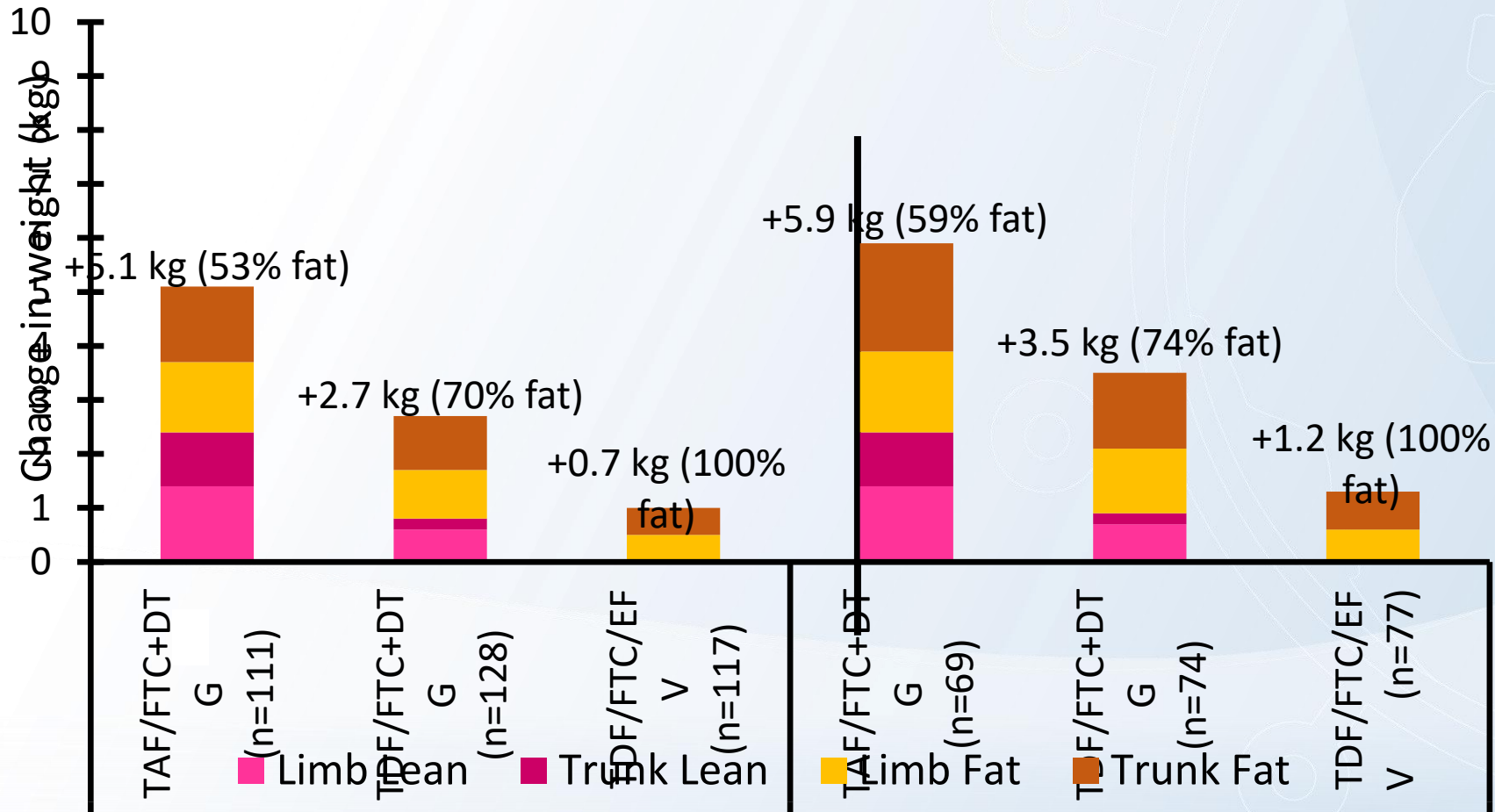


Note: data incomplete to week 144

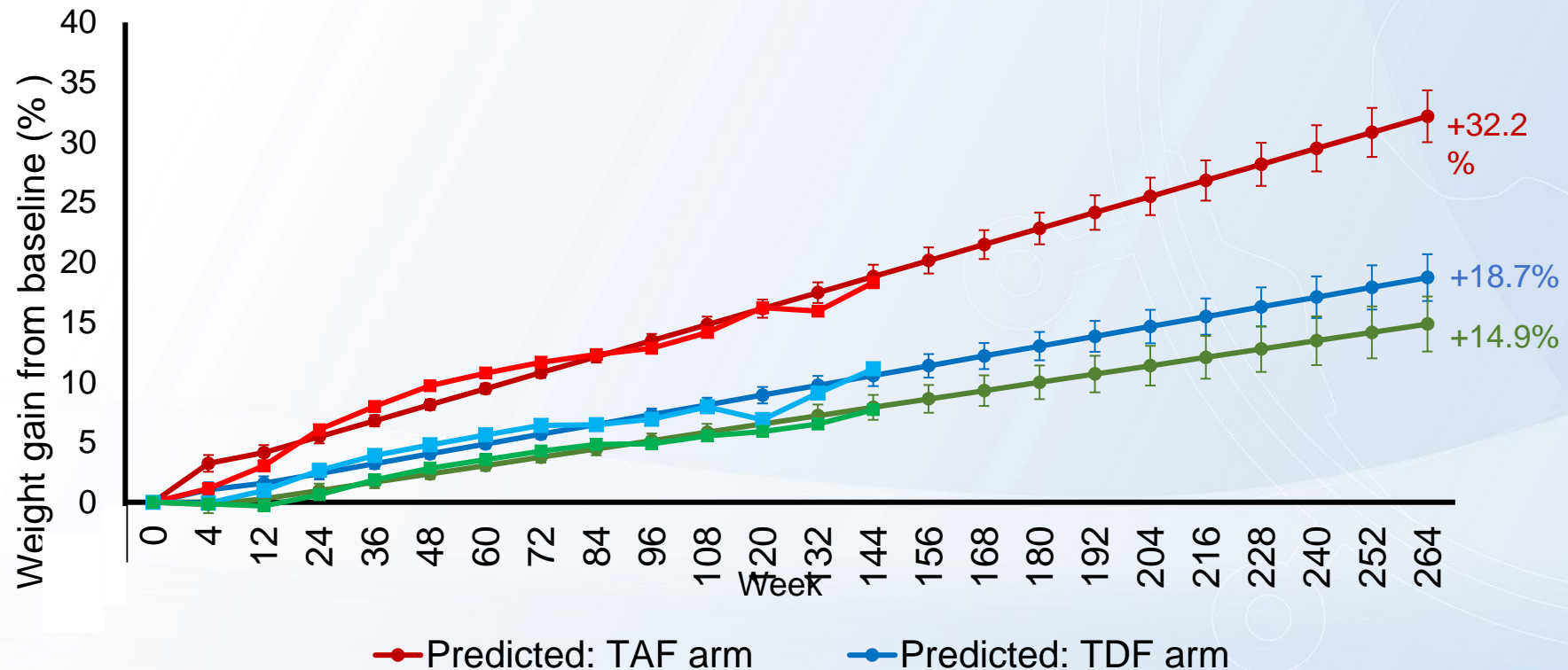
## Treatment-Emergent Obesity at Week 96



# Changes in DXA body composition: Men

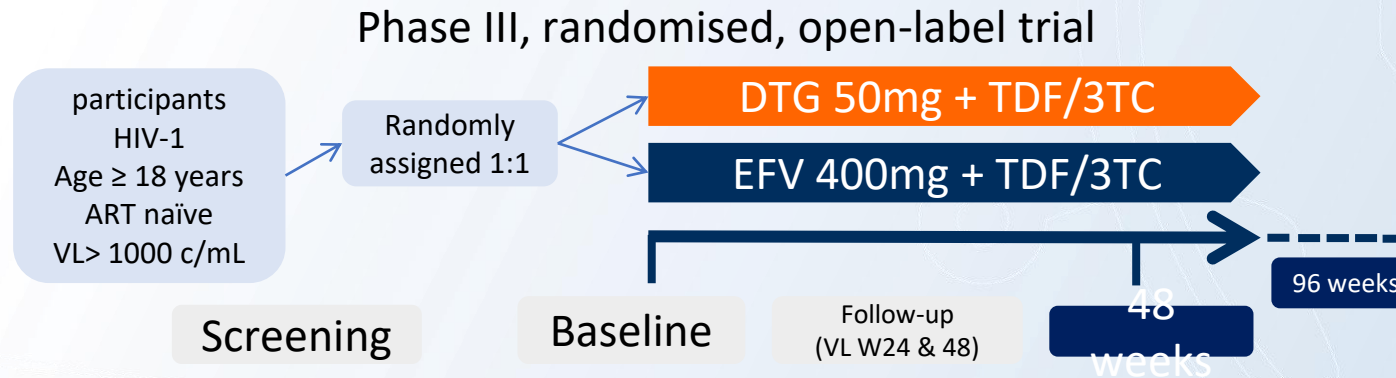


## Linear regression model: predicted mean percentage change in weight from baseline over 5 years in females





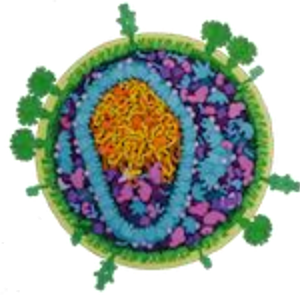
# NAMSAL - Study design



3 study sites in Yaoundé, Cameroon

## Namsal: body weight Week 48 analysis

	TDF/3TC+DTG N=293	TDF/3TC+EFV N=278	p-value
<b>Evolution W48-D0</b>			
<b>Weight gain (kg)</b>	<b>+5.0kg</b>	<b>+3.0kg</b>	<b>&lt;0.001</b>
Weight (% from D0)	+7.3%	+5.3%	0.001
Weight ≥ 10%	38%	29%	0.033
BMI	+1.7	+1.2	<0.001
<b>Obesity incidence (BMI≥30)</b>	<b>36 (12%)</b>	<b>15 (5%)</b>	<b>0.004</b>



# CROI

Conference on Retroviruses  
and Opportunistic Infections

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## Predicted 10-year risks of diabetes and cardiovascular disease in the ADVANCE trial

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Andrew Hill<sup>1</sup>, Kaitlyn McCann<sup>2</sup>, Ambar Qavi<sup>2</sup>, Bryony Simmons<sup>2</sup>, Victoria Pilkington<sup>2</sup>,  
Michelle Moorhouse<sup>3</sup>, Godspower Akopmiemie<sup>3</sup>, Simiso Sokhela<sup>3</sup>, Celicia Serenata<sup>3</sup>, Alinda Vos<sup>4</sup>,  
Francois Venter<sup>3</sup>

<sup>1</sup> Liverpool University, Pharmacology, Liverpool, United Kingdom, <sup>2</sup> Imperial College London, Faculty of Medicine, London, United Kingdom  
<sup>3</sup> Ezintsha, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa; <sup>4</sup> University Medical Center Utrecht, Epidemiology, Utrecht,  
Netherlands

## QDIABETES Equation Results: Females (Linear Predictions)

Treatment arm / 10 year diabetes risk	Median change from baseline to:				
	Baseline	Week 96 (Observed)	Year 3	Year 4	Year 5
<b>TAF/FTC/DTG</b> n = 120	0.30%	+1.20%	+1.40%	+2.00%	<b>+2.50%</b>
<b>TDF/FTC/DTG</b> n = 111	0.40%	+0.50%	+0.60%	+0.90%	+1.30%
<b>TDF/FTC/EFV</b> n = 116	0.30%	+0.80%	+1.00%	+1.30%	+1.50%

\*TAF/FTC/DTG risk significantly higher than TDF/FTC/DTG at Week 96 (p=0.028); Year 3 (p= 0.025); Year 4 (p= 0.015); Year 5 (p= 0.014)

**12 additional cases of diabetes in TAF vs TDF per 1000 females over 30 treated for 5 years**

Conference on Retroviruses and Opportunistic Infections 2020

# CHANGES IN BODY MASS INDEX AND THE RISK OF CARDIOVASCULAR DISEASE: THE D:A:D STUDY

*Kathy Petoumenos, Locadiah Kuwanda, Lene Ryom, Amanda Mocroft, Peter Reiss,  
Stephane De Wit, Christian Pradier, Andrew Philips, Camilla I Hatleberg, Antonella  
d'Arminio Monforte, Rainer Weber, Caroline Sabin, Jens Lundgren, Matthew G Law*

*On behalf of the D:A:D Study group*



# D:A:D

# Conclusion

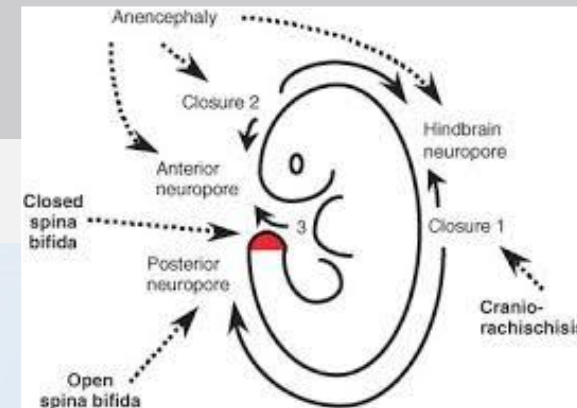
- Increases in BMI across all levels of baseline BMI were consistently associated with increased risk of DM
- Increases in BMI across all levels of baseline BMI were not associated with an increased risk of CVD
  - Some evidence of an increased risk of CVD with a decrease in BMI (especially at low baseline BMI)
- The extent to which these results apply to PLHIV with increased weight while receiving contemporary ART are uncertain ←
- Further analysis of weight change, INSTI/TAF and clinical events is needed

# Tsepamo Update: Prevalence of NTDs by ARV Exposure

Parameter	Conception			Pregnancy	HIV Negative (n = 119,630)
	DTG (n = 3591)	Non-DTG (n = 19,361)	EFV (n = 10,958)	DTG (n = 4581)	
Total NTDs per exposures, n/N	7/3591	21/19,361	8/10,958	2/4581	87/119,630
NTD prevalence, % (95% CI)					
▪ April 2019	0.30 (0.13-0.69)	0.10 (0.06-0.17)	0.04 (0.01-0.11)	0.03 (0.00-0.15)	0.08 (0.06-0.10)
▪ April 2020	0.19 (0.09-0.40)	0.11 (0.07-0.17)	0.07 (0.03-0.17)	0.04 (0.01-0.16)	0.07 (0.06-0.09)
Prevalence diff. with DTG conception, Apr 2020, % (95% CI)	Ref	0.09 (-0.03 to 0.30)			0.12 (-0.03 to 0.30)
NTDs per exposures between April 2019 and April 2020, n/N	2/1908*	6/4569			0,258

Zash. AIDS 2020. Abstr OAXLB01.

\*Includes 1 lumbosacral myelomeningocele (spina bifida) and 1 encephalocele.



[options.com](https://www.options.com)



# Predicting the risk of adverse pregnancy outcomes due to ART-induced weight gain

Sumbul Asif<sup>1</sup>, Evangelina Baxevanidi<sup>1</sup>, Andrew Hill<sup>2</sup>, Celicia Serenata<sup>3</sup>, WD Francois Venter<sup>3</sup>, Lee Fairlie<sup>3</sup>, Masebole Masenya<sup>3</sup>, Nomathemba Chandiwana<sup>3</sup>, Simiso Sokhela<sup>3</sup>

1. Imperial College London, Faculty of Medicine, London, United Kingdom, 2. Liverpool University, Department of Translational Medicine, Liverpool, United Kingdom, 3. Ezintsha, Wits RHI, University of the Witwatersrand, Johannesburg, South Africa



APO	Baseline	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
		96-weeks	96-weeks	96-weeks
Preterm delivery	70	73	71	70
Gestational Hypertension	28	39	34	29
Gestational diabetes mellitus	16	23	19	16
Pre-eclampsia	25	35	30	26
Postpartum haemorrhage	112	115	114	112
Caesarean section	213	232	224	215
Small-for-gestational-age infants	89	87	88	89
Large-for-gestational-age infants	134	154	145	137
Low birthweight infants	64	65	64	64
Macrosomia	31	37	34	31
Stillbirth	4	4	4	4
Neonatal death	2	2	2	2
Neural tube defect	0	0	0	0

## Weight gain likely to have a much greater impact...

- On pregnancy outcomes than DTG teratogenicity!



## ***CYP2B6* Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz**

Rulan Griesel, Gary Maartens, Simiso Sokhela, Godspower Akpomiemie, Francois Venter, Michelle Moorhouse, Phumla Sinxadi



**CID, 2020**

# So many questions...

- Is it new ARVs and multiple off-target toxicities? Or is it simply tolerance and a return to a “normal” weight gain trajectory?
- If former – may see differences in future non-inferiority studies
- If the latter: we should see no change in head-to-head studies with new regimens
- Imperative that done among black women

# Obesity IS an issue... or is it?

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Articles

**Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents**

BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	≥ 25.0
<i>Preobese</i>	25.0 - 29.9
Obese	≥ 30.0
<i>Obese class I</i>	30.0 - 34.9
<i>Obese class II</i>	35.0 - 39.9
<i>Obese class III</i>	≥ 40.0

**“The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents.”**

Review > [J Cachexia Sarcopenia Muscle](#). 2019 Feb;10(1):9-13. doi: 10.1002/jcsm.12378. Epub 2019 Jan 17.

**Flawed methods and inappropriate conclusions for health policy on overweight and obesity: the Global BMI Mortality Collaboration meta-analysis**

Katherine M Flegal<sup>1</sup>, John P A Ioannidis<sup>1 2 3 4</sup>, Wolfram Doehner<sup>5 6 7</sup>

# Weight is culturally sensitive...

- Different communities = different perceptions of what is healthy, desirable, sexy
- Stigma that skinny = HIV, TB, other illness
- Advertising and magazines – steadily skinnier models
- Self-perception is important (and flawed)

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

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

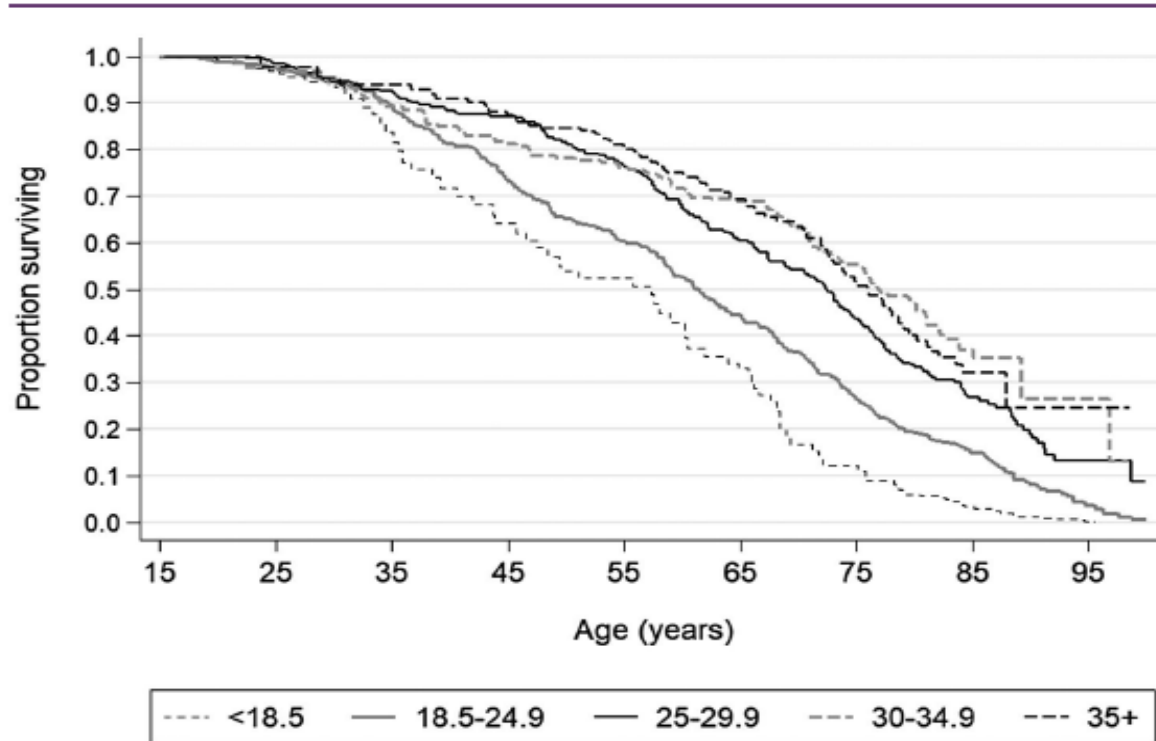


Figure 1 Kaplan-Meier estimates of survival, by BMI group.

# CDC questioned the impact of weight years ago...

- 2005 – gross overestimation of impact of obesity on disease
- And that BMI is a rubbish marker

BMI classification	
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Obese class III	≥ 40.0

Flegal KM, Graubard BI, Williamson DF, Gail MH.  
Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005 Apr 20;293(15):1861-7

NCHS Data Brief ■ No. 82 ■ January 2012

### Prevalence of Obesity in the United States, 2009–2010

Cynthia L. Ogden, Ph.D.; Margaret D. Carroll, M.S.P.H.; Brian K. Kit, M.D., M.P.H.; and Katherine M. Flegal, Ph.D.

Review > [J Cachexia Sarcopenia Muscle](#). 2019 Feb;10(1):9-13. doi: 10.1002/jcsm.12378.  
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## Flawed methods and inappropriate conclusions for health policy on overweight and obesity: the Global BMI Mortality Collaboration meta-analysis

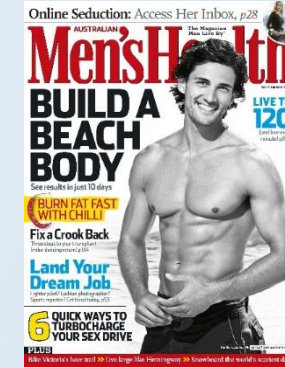
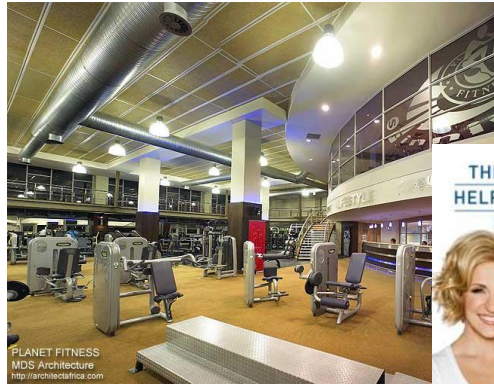
Katherine M Flegal<sup>1</sup>, John P A Ioannidis<sup>1 2 3 4</sup>, Wolfram Doehner<sup>5 6 7</sup>

Flegal KM, Kit BK, Orpana H, Graubard BI, Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013 Jan 2;309(1):71-82



# People make a LOT of money from making you feel horrible about your body – implicated in everything from depression to anorexia

- And we've made many people rich



# And we aren't really sure what is a "healthy diet"

HEALTH

## *A Call for a Low-Carb Diet*

By ANAHAD O'CONNOR SEPT. 1, 2014



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The Lancet, Volume 384, Issue 9953, Pages 1479 - 1480, 25 October 2014  
doi:10.1016/S0140-6736(14)61413-6 [Cite or Link Using DOI](#)

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### Low carbohydrate diets: going against the grain

[Jim Mann](#), [Rachael McLean](#), [Murray Skeaff](#), [Lisa Te Morenga](#)

Low carbohydrate high fat (LCHF) diets continue to attract media attention, despite a subst

PDF

### Long-Term Effects of 4 Popular Diets on Weight Loss and Cardiovascular Risk Factors: A Systematic Review of Randomized Controlled Trials

*Circ Cardiovasc Qual Outcomes.*  
2014;CIRCOUTCOMES.113.000723 published  
online before print November 11 2014,

THE LANCET Diabetes & Endocrinology

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The Lancet Diabetes & Endocrinology, Early Online, 10 October 2014

doi:10.1016/S2213-8581(14)70011-1 [Cite or Link Using DOI](#)

This article can be found in the following collection(s): [Diabetes & Endocrinology](#) | [Health, Nutrition & Metabolism](#) | [Other](#)

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### The effect of rate of weight loss on long-term weight management: a randomised controlled trial

*Lancet Diabetes Endocrinol.* 2014;12(12):953-961 published online before print November 11 2014,

[Kathryn Peacock](#) MSc, [Erling Sandbakk](#) PhD, [Lasse A Thorsen](#) PhD, [Catharina J Svendsen](#) MSc, [Elizabeth Delbridge](#) PhD, [Prof Joseph Proietto](#) PhD

Home » Low-Carb Diet » 23 Studies on Low-Carb and Low-Fat Diets – Time to Retire The Fad

## 23 Studies on Low-Carb and Low-Fat Diets – Time to Retire The Fad

October 15, 2013 | by Kris Gunnars | 104,408 views | [Comments](#)

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

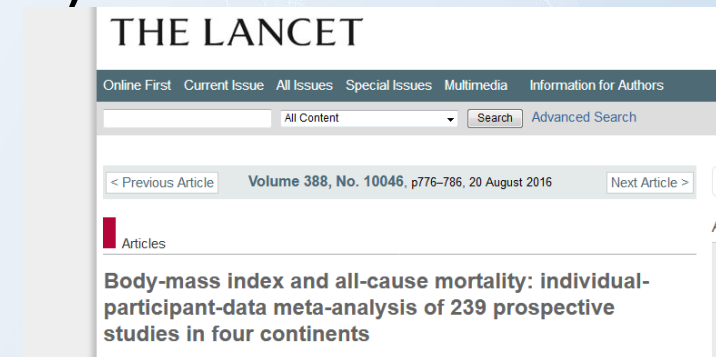
### Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., María Isabel Corella, Ph.D., Dolors Guasch-Riera, Ph.D., Ferran Azúa, M.D., Ph.D.,



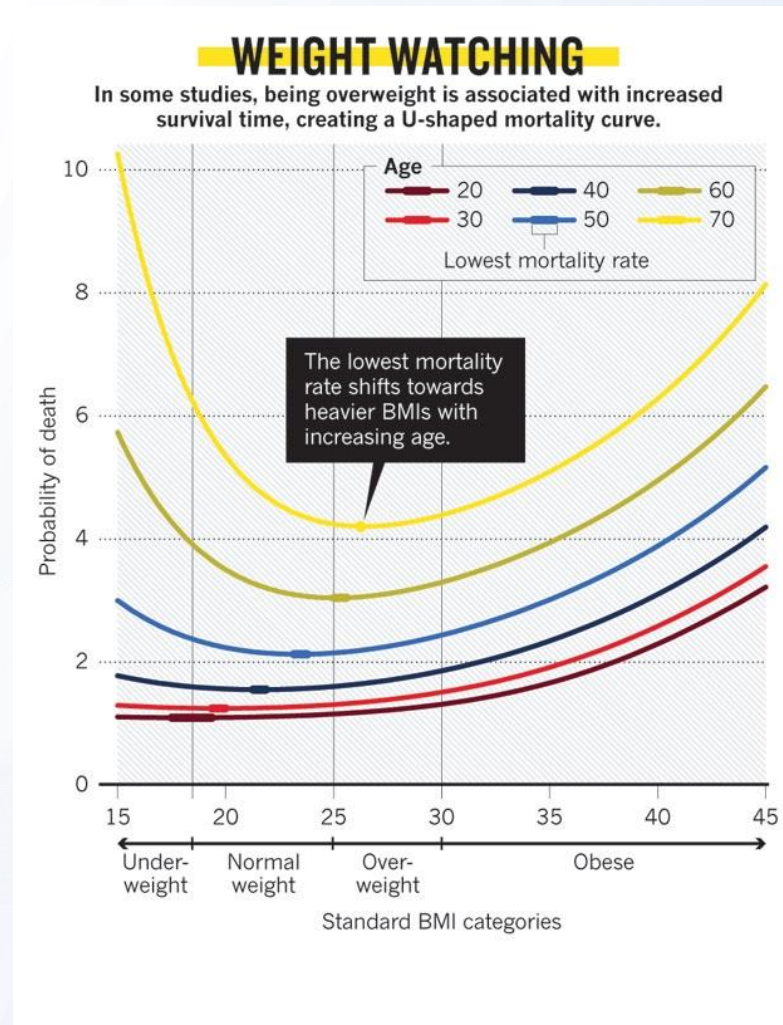
# Being obese is linked to lots of issues

- Diabetes (glucose)
- Hypertension (blood pressure)
- Lipids (cholesterol, LDL ('bad cholesterol'))
- Strokes
- Heart attacks
- Cancer
- Joint pain
- Mental health issues
- Poor COVID outcomes ←



**“The associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents.”**

# But then, so is being skinny.... (like dying!)

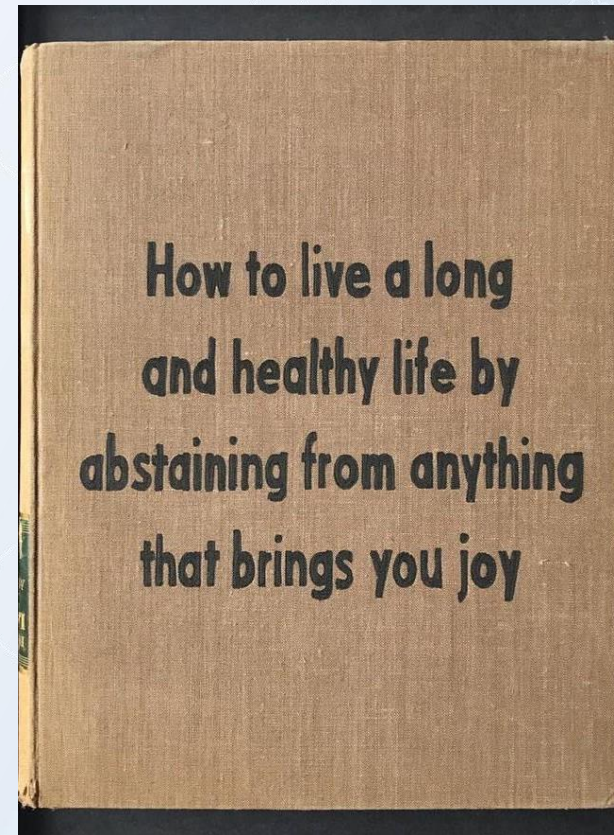


Nature, 2013



**“Seriously, what would you make of all this evidence if nobody ever told you that fat is bad?” -  
Kristin Dunkle, Chief Specialist Scientist, Gender and Health Research Unit, SA  
Medical Research Council**

- “Where health advice is not based on actual evidence, it is likely to give expression to individual and social intuitions, and these frequently seem to express Calvinist moralistic ideas about how we must be improved by self-denial and suffering.” – *Professor Lucy Allais, Centre for Ethics, University of the Witwatersrand*



# Conclusions



## Weighing considerations with newer antiretrovirals

See [Articles page e389](#)

The combination of tenofovir alafenamide, emtricitabine, and bictegravir was approved by the US Food and Drug

sex-aggregated rise of 5 kg. Although this study did not compare tenofovir disoproxil fumarate with tenofovir

- Weight gain is real – definitely associated with DTG/BIC, and with TAF (and rilpivirine)
- DTG may not be as perfect as we hoped – but for most of the world – only efavirenz!
- No data on what to do if someone is gaining weight on either DTG or EFV (or anything else) – Orkin data on doravirine promising
- TAF unlikely to be recommended in Africa (?elsewhere)
- Major public health headache – swapping one epidemic for another – need new options

# Thank you!

