Weight Gain

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LT attended advisory boards or served as consultant or received grants for conferences participations from Gilead Sciences, ViiV Healthcare and Janssen and research grants for her institution from Gilead Sciences

Aggiornamento 2022-2023

- Weight gain: aggiornamento su nuovi e vecchi farmaci
- Reversibilità del fenomeno di weight gain dopo lo switch
- Weight gain ed outcomes clinici

Aggiornamento 2022-2023

- **Weight gain: aggiornamento su nuovi e vecchi farmaci**
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	Skin	Digestive	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTIs							
TAF(iii)						**Weight gain**	
NNRTIs							
DOR				Sleep disturbance, Headache			
INSTI							
DTG	Rash	Nausea	↓ eGFR(iv)	**Sleep disturbance, Headache**		**Weight gain**	Systemic hypersensitivity syndrome (< 1%) Minimal non-significant increase in neural tube defects(ix)
BIC			↓ eGFR(iv)	Sleep disturbance, Headache		**Weight gain**	
CAB	Injection site reac- tions(x)			Sleep disturbance, Headache			Pyrexia(xi)

EACS guidelines 2022

CABOTEGRAVIR

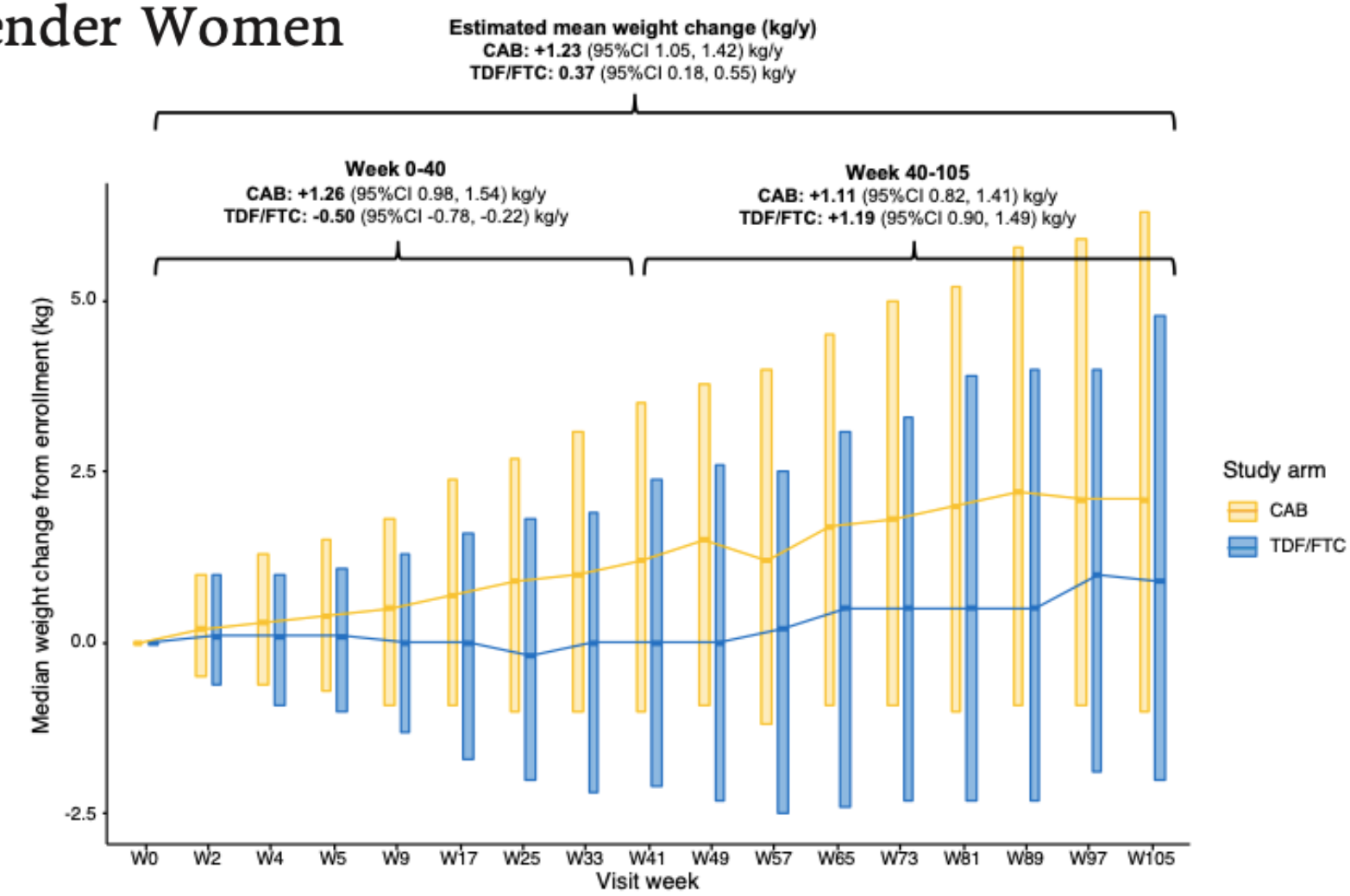
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Landovitz et al., N Engl J Med. 2021 Aug 12;385(7):595-608

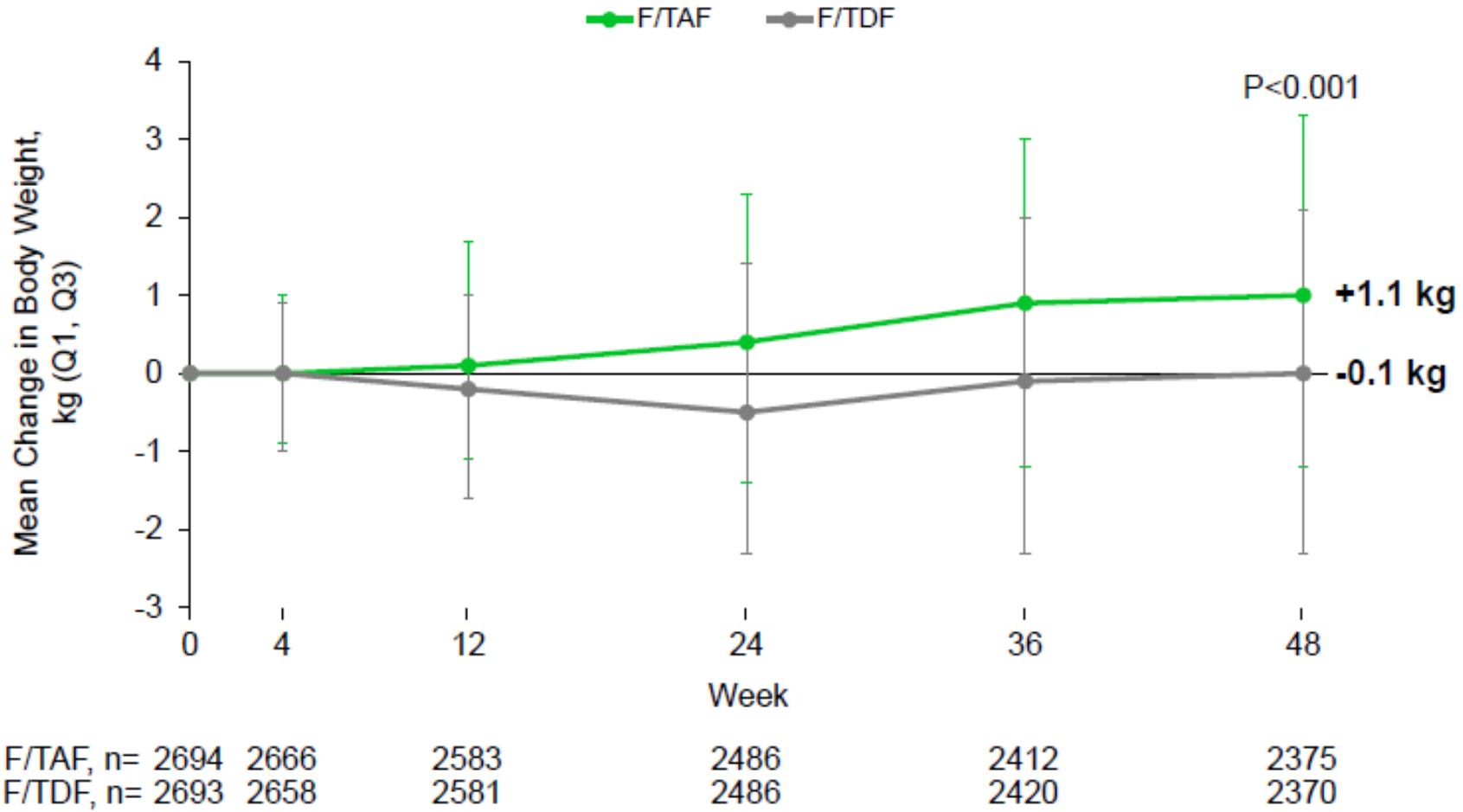
Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

In a post hoc analysis, a mean annualized in- crease in body weight of 1.23 kg per year (95% CI, 1.05 to 1.42) was noted in the cabotegravir group, as compared with an increase of 0.37 kg (95% CI, 0.18 to 0.55) in the TDF–FTC group.



…ripensando al TAF in PREP…

Over half of participants (2876 [54%] of 5387) were overweight (defined by a body-mass index of >25 kg/m2) at baseline (table 1). Participants in the emtricitabine and tenofovir disoproxil fumarate group lost weight in the first 24 weeks and returned to baseline weight at week 48 (mean change in bodyweight between baseline and 48 weeks was –0·1 kg), whereas those in the emtricitabine and tenofovir alafenamide group had a mean increase in bodyweight of 1·1 kg at week 48.



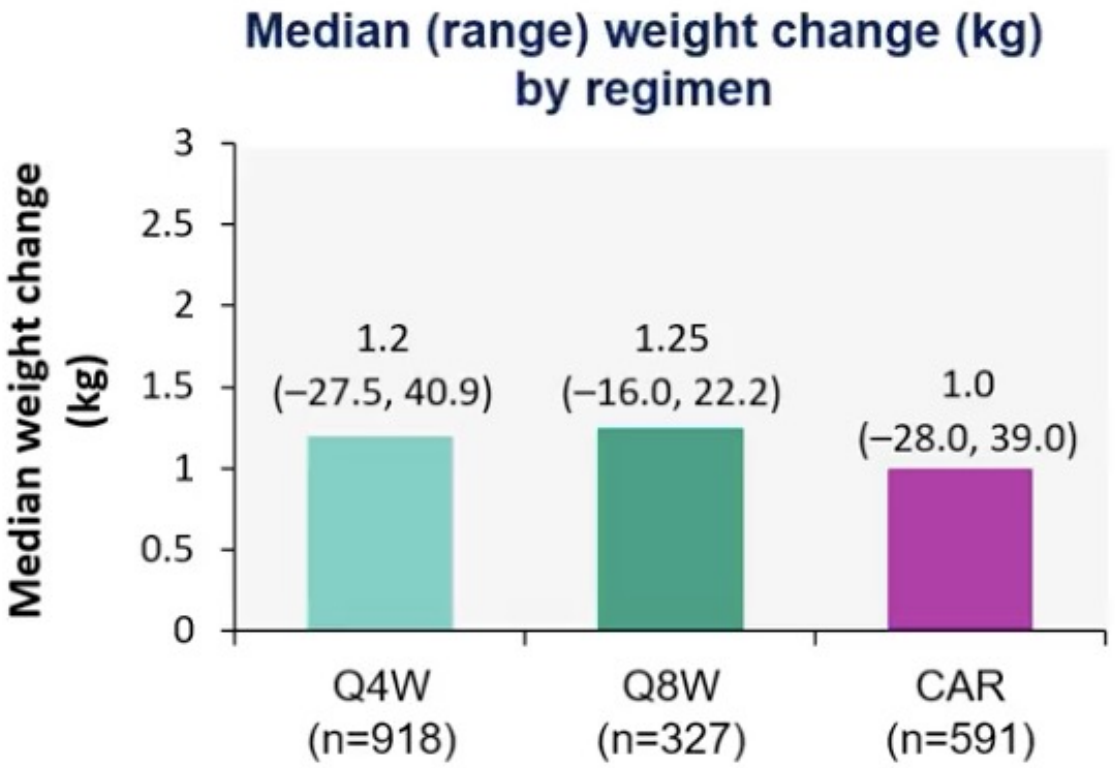
Kenneth H Mayer et al., Lancet 2020; 396: 239–54

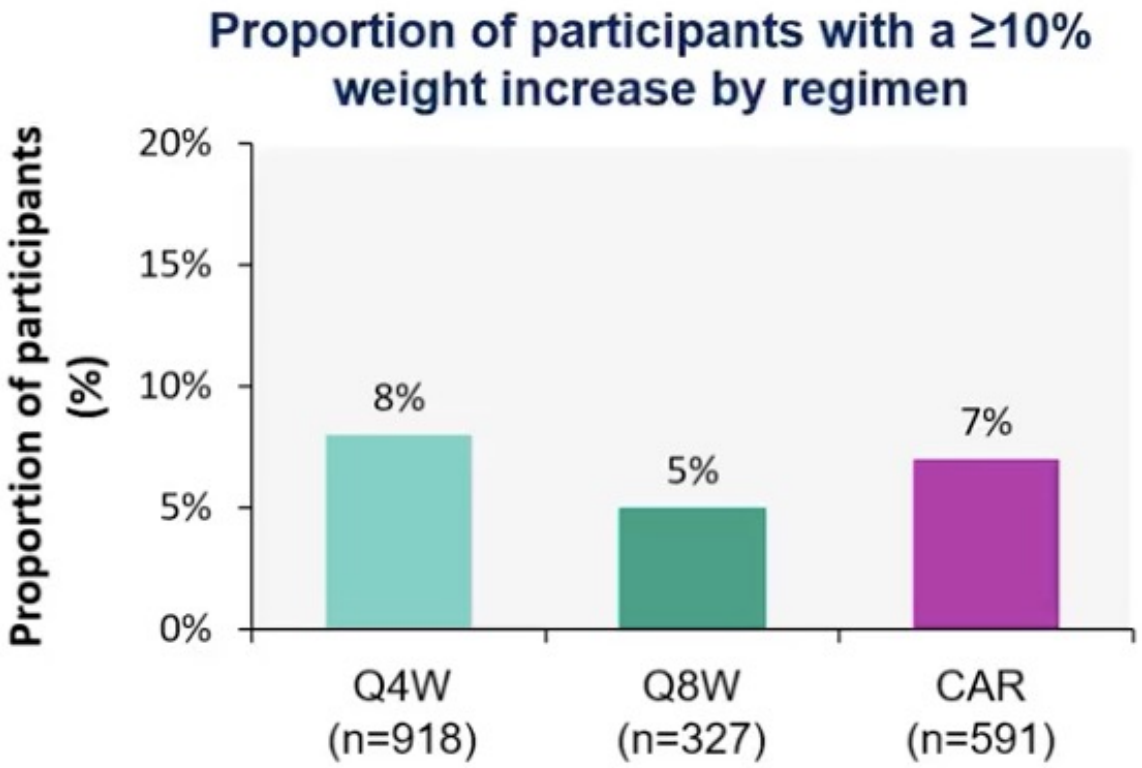
WEIGHT AND LIPID CHANGES IN PHASE 3 CABOTEGRAVIR AND RILPIVIRINE LONG-ACTING TRIALS

Baseline demographics/characteristics (ITT-E population)	Pooled Q4W arm ATLAS, FLAIR,* and ATLAS-2M (n=918)†	Q8W arm ATLAS-2M (n=327)‡	Pooled CAR arm ATLAS and FLAIR* (n=591)
Median age (range), years	39 (19–74)	41 (20–83)	38 (18–82)
Female (sex at birth), n (%)	237 (26)	73 (22)	168 (28)
Black or African American race, n (%)	154 (17)	57 (17)	133 (23)
Median CD4 count at baseline (cells/mm³)	661	643	641
BMI category, n (%)			
Underweight (<18.5 kg/m²)	20 (2)	4 (1)	12 (2)
Normal (18.5–25 kg/m²)	440 (48)	151 (46)	298 (50)
Overweight (25–30 kg/m²)	306 (33)	113 (35)	178 (30)
Obese (≥30 kg/m²)	152 (17)	59 (18)	103 (17)
Weight (kg), median (IQR)	76.0 (67.0, 85.9)	77.0 (68.0, 77.0)	75.2 (65.4, 85.7)
Baseline lipids, mean (SD)			
TG (mmol/L)	1.43 (1.014)	1.46 (0.954)	1.43 (1.051)
TC (mmol/L)	4.73 (1.014)	4.82 (1.052)	4.72 (1.055)
LDL (mmol/L)	2.74 (0.855)	2.78 (0.899)	2.71 (0.835)
HDL (mmol/L)	1.34 (0.420)	1.39 (0.421)	1.36 (0.428)
TC/HDL ratio	3.82 (1.538)	3.73 (1.276)	3.72 (1.197)
Medical history, n (%)			
Hypertension	92 (10)	51 (16)	76 (13)
Diabetes	22 (2)	11 (3)	22 (4)
Select co-medications, n (%)			
Anti-hypertensives	11 (1.2)	6 (1.8)	3 (0.5)
Anti-diabetes	16 (1.7)	10 (3.1)	17 (2.9)
Anti-lipids	90 (9.8)	39 (11.9)	30 (5.1)
SSRIs	54 (5.9)	14 (4.3)	28 (4.7)
Antipsychotics	13 (1.4)	9 (2.8)	7 (1.2)
Pre-switch ART regimen, n (%)§			
IN-based	526 (57)	136 (42)	382 (65)
PI-based	81 (9)	40 (12)	54 (9)
NNRTI-based	311 (34)	151 (46)	155 (26)

Patel et al., CROI 2021, Abstract 505

WEIGHT AND LIPID CHANGES IN PHASE 3 CABOTEGRAVIR AND RILPIVIRINE LONG-ACTING TRIALS





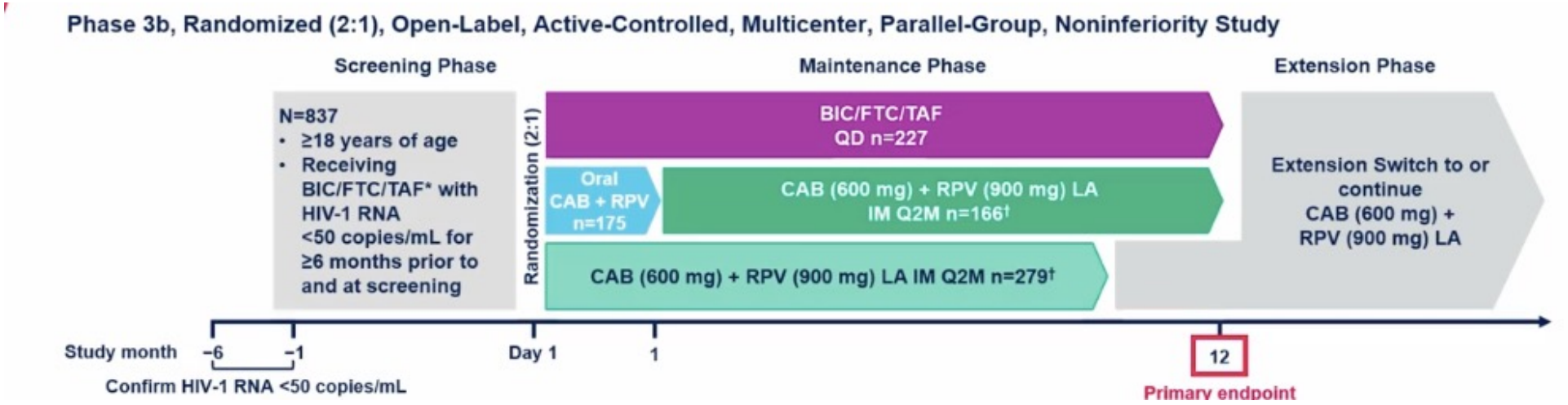
- Median weight increased from baseline* across all regimens, with slightly higher increases observed in participants receiving CAB + RPV LA vs. those receiving CAR

Patel et al., CROI 2021, Abstract 505

WEIGHT AND METABOLIC CHANGES WITH CABOTEGRAVIR+RILPIVIRINE LONG-ACTING OR BICTEGRAVIR

687 participants randomized (2:1; n=6 not dosed)

- 454 switched to CAB+RPV LA Q2M
- 227 continued on B/FTC/TAF

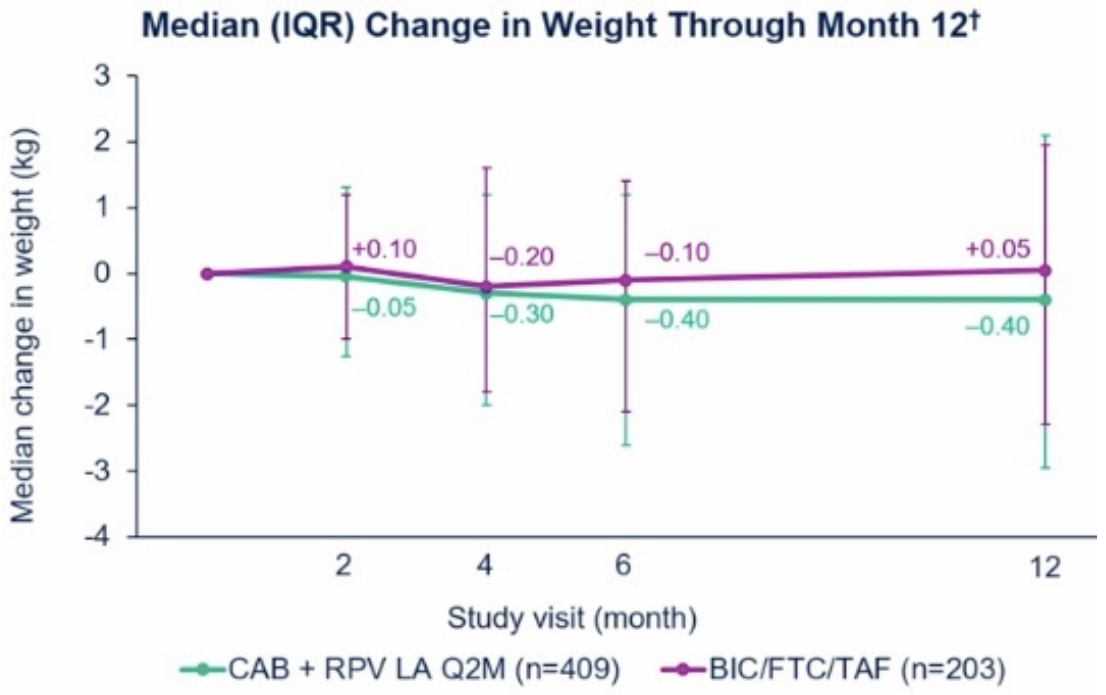


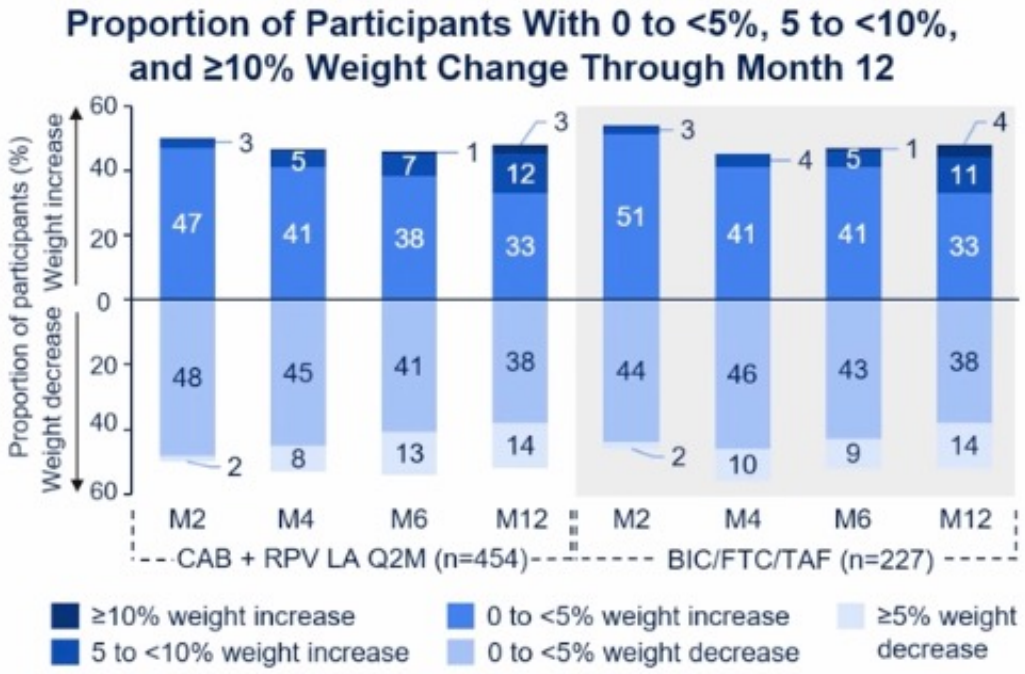
Changes from BL in body weight, body mass index (BMI) category, waist and hip circumferences (WC, HC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), muscle mass, total body fat, and proportion of participants with insulin resistance or metabolic syndrome were analyzed at M11 (LA without OLI)/M12 (LA with OLI and B/FTC/TAF).

Darrell H. S Tan et al., CROI 2023

- Median change in body weight was
  - –0.40 kg (–2.95, 2.10) LA
  - +0.05 kg (–2.30, 1.95) B/FTC/TAF

- Mean (standard deviation) change in WC and HC was
  - +0.19 cm (8.01) and +0.26 cm (7.81) LA
  - +1.64 cm (9.19) and +0.51 cm (11.44) B/FTC/TAF





There were no clinically relevant changes from BL to M11/12 in participants' WHtR, WHR, or the proportion of participants with metabolic syndrome, abdominal obesity, or insulin resistance in either arm.

Inconsistent with TAF *causing* weight gain

DORAVIRINA

Effect of doravirine on body weight and body mass index in treatment naïve adults with HIV-1

C Orkin[1], R Elion[2], M Thompson[3], J Rockstroh[4], ZJ Xu[5], EA Martin[5], C Hwang[5], P Sklar[5] and F Alvarez Bognar[5]

Changes in weight and BMI in ART naive adults at **1** and **2 years** after starting TDF/XTC +

- Doravirine **1.7 (1.0) kg**; **2.4 (1.5) kg**
- ritonavir-boosted darunavir **1.4 (0.6)kg** ; **1.8 (0.7) kg**
- Efavirenz **0.6 (0.0)kg** ; **1.6 (1.0)kg**

Effects on Body Weight and BMI by Treatment Group (DOR, DRV+r, EFV)

	Combined DOR Group		DRV+r Group		DOR vs DRV	Combined EFV Group		DOR vs EFV
Change in Body Weight (kg) from Baseline, Median (IQR)								
Week 48	N=751	1.00 (−1.20,3.90)	N=316	0.59 (−1.90,3.42)	p=0.117	N=402	0.00 (−2.60, 2.80)	p<0.001
Week 96	N=677	1.50 (−1.00,4.94)	N=268	0.70 (−1.85, 5.10)	p=0.147	N=362	1.00 (−2.20,4.60)	p=0.020
Proportion of Participants with≥5% Weight Gain (kg) from Baseline								
Week 48	N=751	26.5%	N=316	23.1%	p=0.245	N=402	20.6%	p=0.028
Week 96	N=677	31.8%	N=268	32.8%	p=0.749	N=362	32.0%	p=0.925
Proportion of Participants with Increased BMI								
Week 48	N=751	11.4%	N=315	11.1%	p=0.828	N=402	7.9%	p=0.062
Week 96	N=677	15.8%	N=267	15.3%	p=0.829	N=362	14.2%	p=0.474

EACS 2019 Abstract Book , HIV Medicine 2019

Changes in weight and BMI with first-line doravirine-based therapy

Chloe Orkin[a], Richard Elion[b], Melanie Thompson[c], Juergen K. Rockstroh[d], Fernando Alvarez Bognar[e], Zhi J. Xu[f], Carey Hwang[g], Peter Sklar[g] and Elizabeth A. Martin[g]

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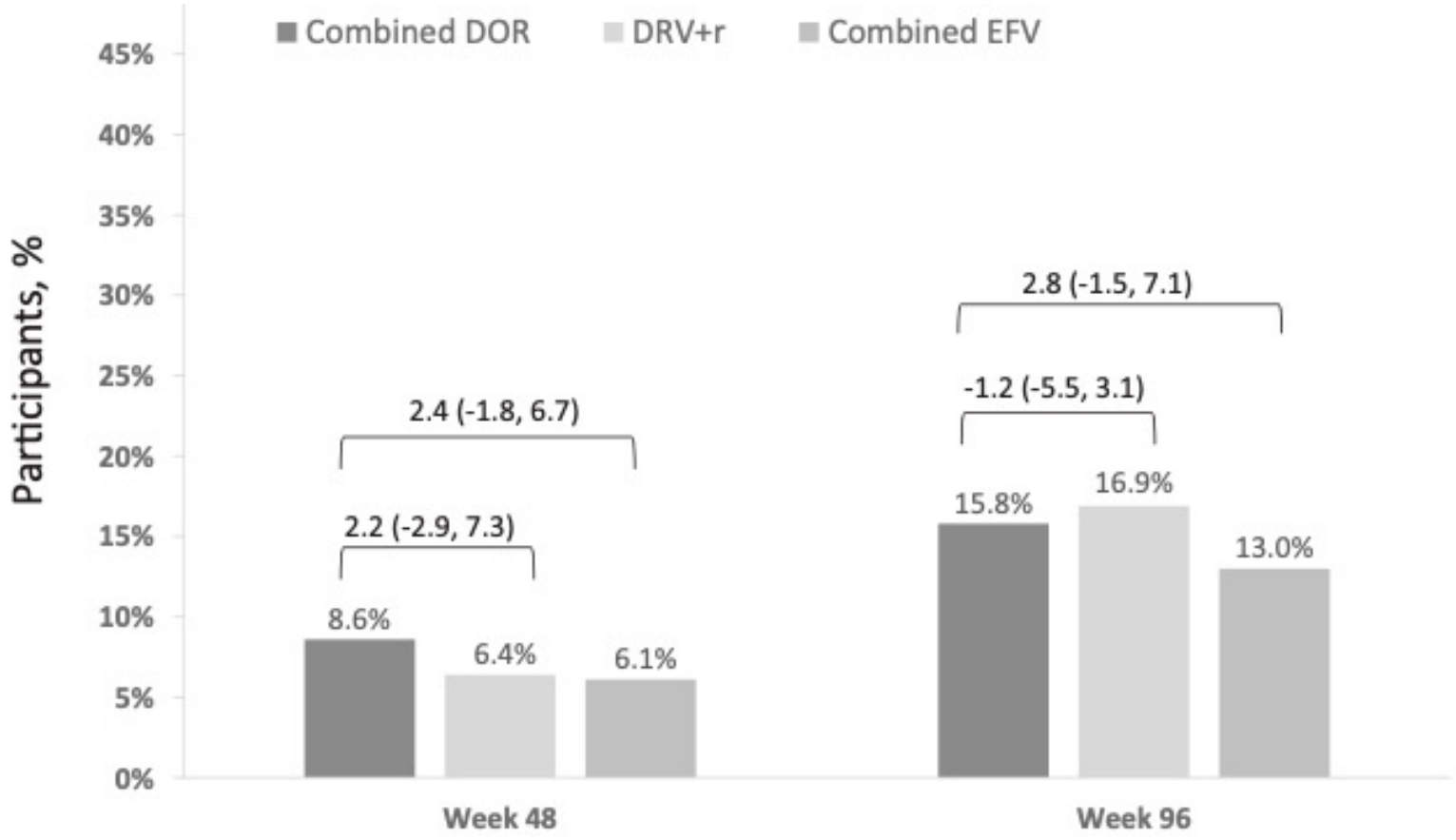
- Efavirenz **0.6 (0.0)kg** ; **1.6 (1.0)kg**

Proportion of participants with at least 10% weight gain.



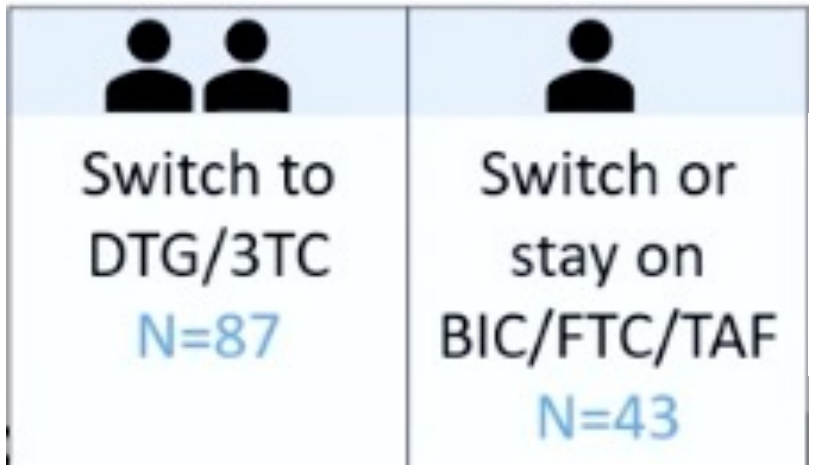
Variable	Week 48 p-value	Week 96 p-value
Treatment	0.347	0.168
Region	<0.001	0.126
Gender	0.134	0.079
Race	0.419	0.443
Age	0.630	0.089
BL Weight	0.682	0.149
BL BMI	0.068	0.138
BL $CD4^+$ cell count	<0.001	<0.001
BL HIV-1 RNA	<0.001	<0.001

AIDS 2021, **35**:91–99

NUOVI STUDI SU «VECCHI» FARMACI

FAVORABLE METABOLIC OUTCOMES 48 WEEKS AFTER SWITCH TO DTG/3TC

- Randomized trial (RUMBA study): switch to 3TC+DTG vs T/F/BIC in people in second generation INSTI



Baseline characteristics	DTG/3TC (n = 87)	BIC/FTC/TAF (n = 43)	p-value
Weight (kg; mean ± SD)	81 ± 12	75 ± 13	0.013
Waist (cm; mean ± SD)	95 ± 12	89 ± 11	0.006
BMI (kg/m²; median (IQR))	26 (23-28)	25 (22-26)	0.024

Linos Vandekerckhove et al, CROI 2023; ABSTRACT 672

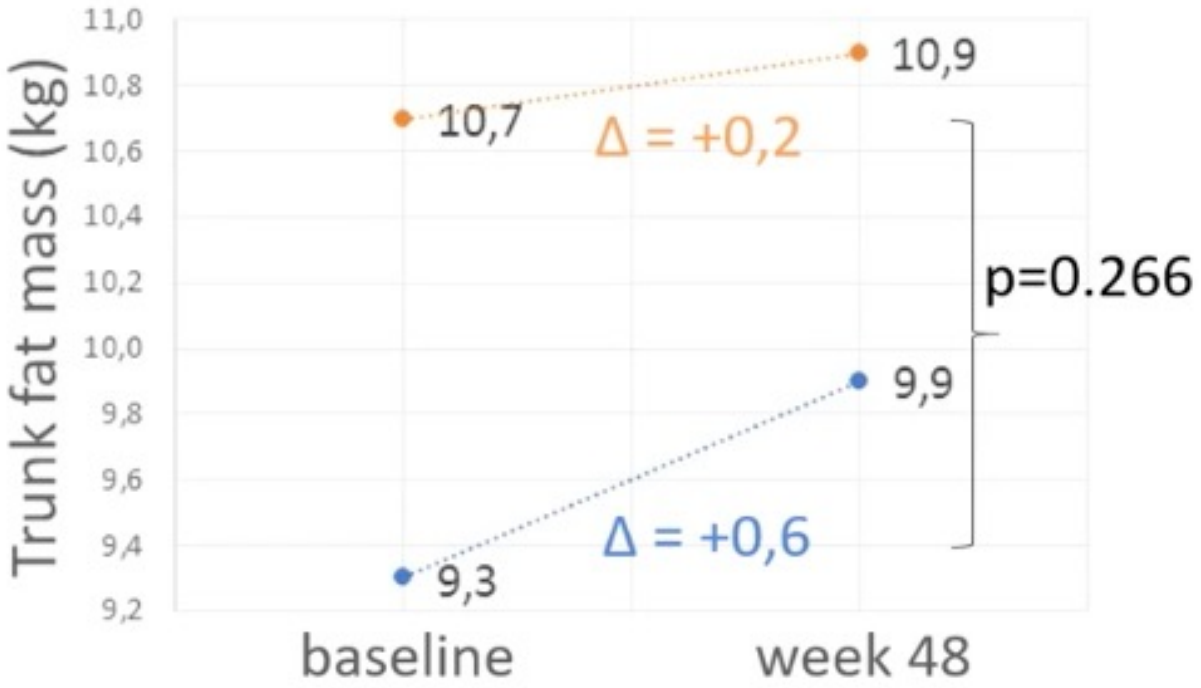
Results at week 48 (linear mixed models, adjusted for basal BMI)

	DTG/3TC	BIC/FTC/TAF	p-value
ALT (U/L)	- 0.73	+ 4.55	0.040
HDL (mg/L)	- 0.043	- 2.84	0.043
Lean trunk mass (gram)	+ 112	- 474	0.032
Trunk fat mass (gram)	+ 41	+ 719	0.043
Fat percentage	- 0.04	+ 1.32	0.003

	DTG/3TC	BIC/FTC/TAF	p-value
Weight (kg)	+0,29	+0,30	0.987
Waist (cm)	-0,07	+ 1,10	0.155
BMI (kg/m²)*	+0,07	+0,04	0.919
Cholesterol (mg/dl)	-2,49	-8,90	0.316
LDL cholesterol (mg/dl)	-1,82	-6,21	0.435
Triglycerides (mg/dl)	-3,82	-20,96	0.206
HOMA-IR	-0,16	-0,43	0.359
FibroCAP (dB/m)	-0,39	-11,61	0.304

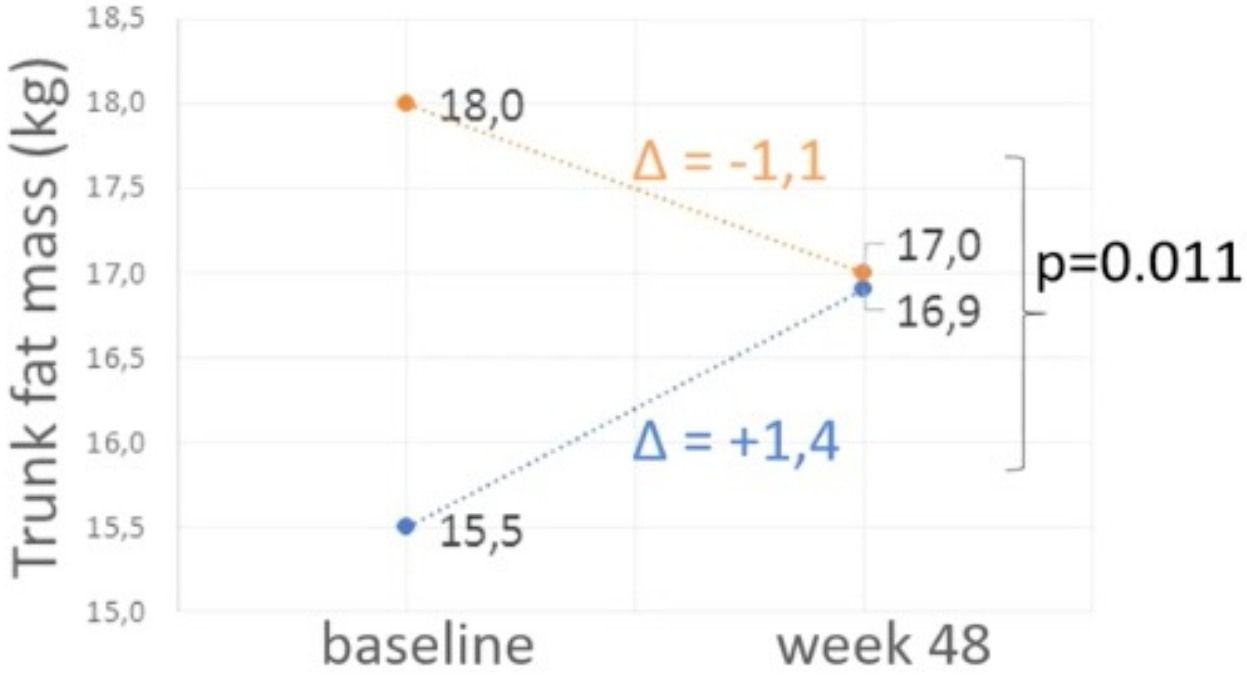
* Unadjusted for BMI baseli

BMI<30



DTG/3TC:	N = 74
BIC/FTC/TAF:	N = 39

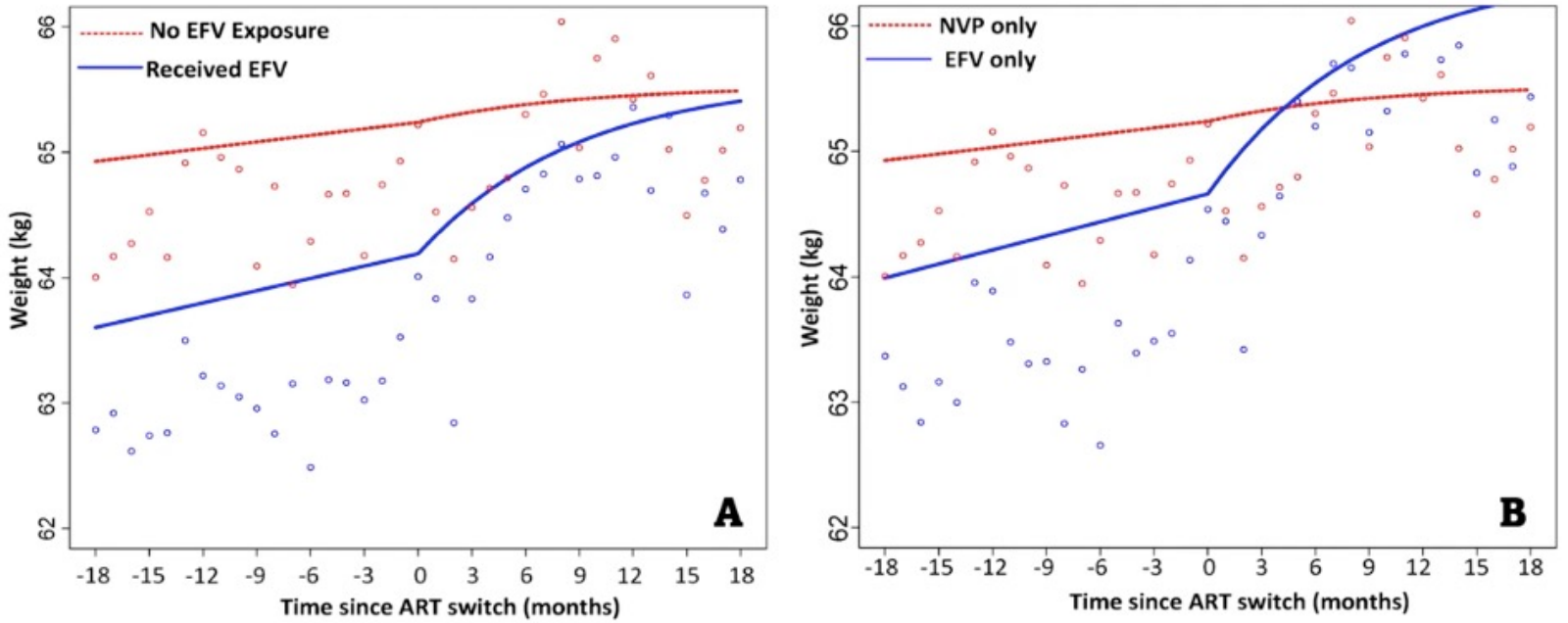
BMI>30



DTG/3TC:	N = 13
BIC/FTC/TAF:	N = 4

WEIGHT GAIN AMONG PARTICIPANTS SWITCHING TO A DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA

Changes in Rate of Weight Gain After Switch by baseline NNRTI drug



(A): EFV group includes participants exposed to both EFV and NVP
(B): EFV group includes participants exposed to EFV only

N

23,131 subjects

Does the INSTI-associated "increased weight gain" phenomenon have more to do the comparator groups than with INSTIs?

Kassem Bourgi CROI 2023, ABSTRACT 674

Aggiornamento 2022-2023

- Weight gain: aggiornamento su nuovi e vecchi farmaci
- **Reversibilità del fenomeno di weight gain dopo lo switch**
- Weight gain ed outcomes clinici

Weight gain stopping/switch rules for antiretroviral clinical trials

W.D. Francois Venter[a], Simiso Sokhela[a], Alexandra Calmy[b], Luckyboy Mkhondwane[c], Bronwyn Bosch[a], Nomathemba Chandiwana[a], Andrew Hill[d], Kenly Sekwese[e], Nkuli Mashabane[a], Anton Pozniak[f], Saye Khoo[d], Mohammed Ali[g], Eric Delaporte[h], Samanta Lalla-Edwards[a], Polly Clayden[i], Vincent C. Marconi[j], Mark J. Siedner[k], Marta Boffito[l], Celicia Serenata[a,*], Mary Carman[m] and Simon Collins[i]

wanting to switch to dolutegravir arms. When investigators discussed switching participants to efavirenz from dolutegravir (initially as it was felt that dolutegravir was the cause of the obesity), many participants expressed dismay; some even said they would go to the state clinics if switched to efavirenz, where dolutegravir is standard of care and where they were very likely to receive that combination. No similar reaction was seen with TAF, probably because of far less community education and media attention on the drug. However, patients,

majority of women are overweight or obese [7]. Many clinicians have expressed concern with the extent of the reported weight gain on ADVANCE, noting that dietary and physical activity modification are usually ineffectual, especially if patients do not view weight gain as unwelcome, and access to many of the foods found in dietary recommendations impractical or expensive. Some

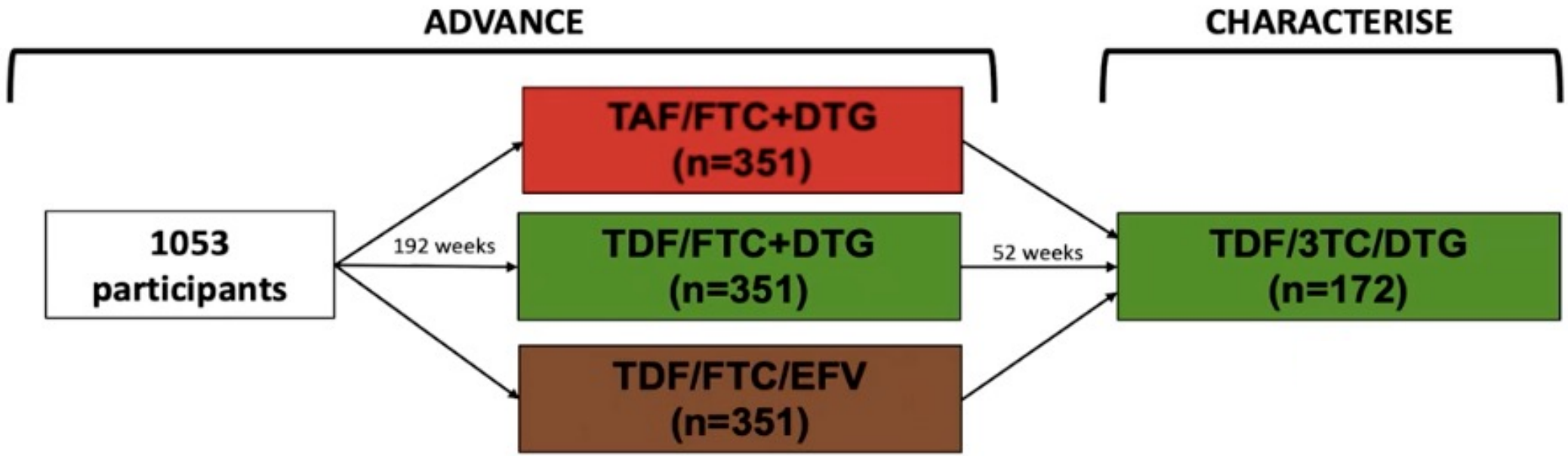
AIDS 2021, **35** (Suppl 2):S183–S188

Weight and metabolic changes after switching from tenofovir alafenamide (TAF)/emtricitabine (FTC)+dolutegravir (DTG), tenofovir disoproxil fumarate (TDF)/FTC+DTG and TDF/FTC/efavirenz (EFV) to TDF/lamivudine (3TC)/DTG

Participants randomised to first-line tenofovir alafenamide (TAF)/emtricitabine (FTC)+dolutegravir (DTG), tenofovir disoproxil fumarate (TDF)/FTC+DTG or TDF/FTC/efavirenz (EFV) for 192 weeks were then switched to TDF/lamivudine (3TC)/DTG for 52 weeks. Participants switching either TAF/FTC+DTG or TDF/FTC/EFV to TDF/3TC/DTG showed statistically significant reductions in weight, low density lipoprotein, triglycerides, glucose and glycated haemoglobin.

Bosch et al., CID 2022

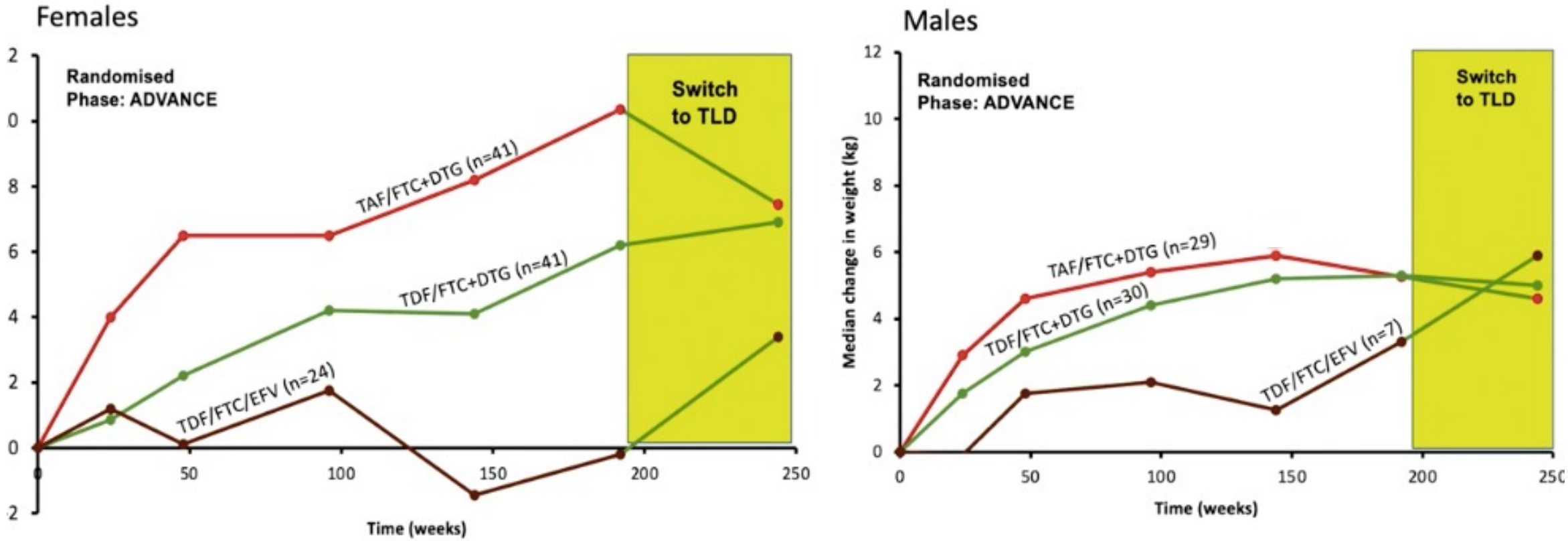
ADVANCE and CHARACTERISE trials



- At follow up, participants were assessed for weight, lipids, fasting glucose, HBA1C and HIV RNA

- Changes in weight and laboratory parameters during the first 192 weeks of randomized treatment and then after the switch to TDF/3TC/DTG were evaluated in each treatment arm using paired non-parametric tests

Change in weight after switch to TDF/3TC/DTG – Females and Males

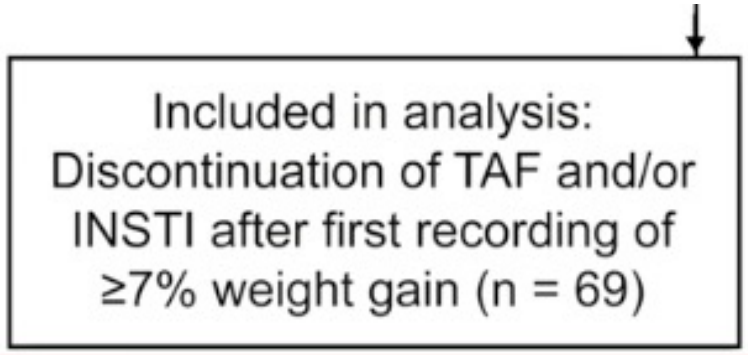


REVERSIBILITY OF TAF- AND/OR INSTI-ASSOCIATED WEIGHT GAIN

- Assess the reversibility of ≥7% TAF- and/or INSTI-associated weight gain (WG) in virally suppressed ART-experienced people with HIV (PWH) from the Dutch ATHENA cohort [1]

- Included: PWH with ≥7% WG within 24 months after a first switch to a regimen containing only TAF, only an INSTI or both TAF+INSTI
- Excluded: hypothyroidism, Cushing's syndrome, congestive heart failure, renal failure, liver cirrhosis, use of corticosteroids, antidepressants or antipsychotics

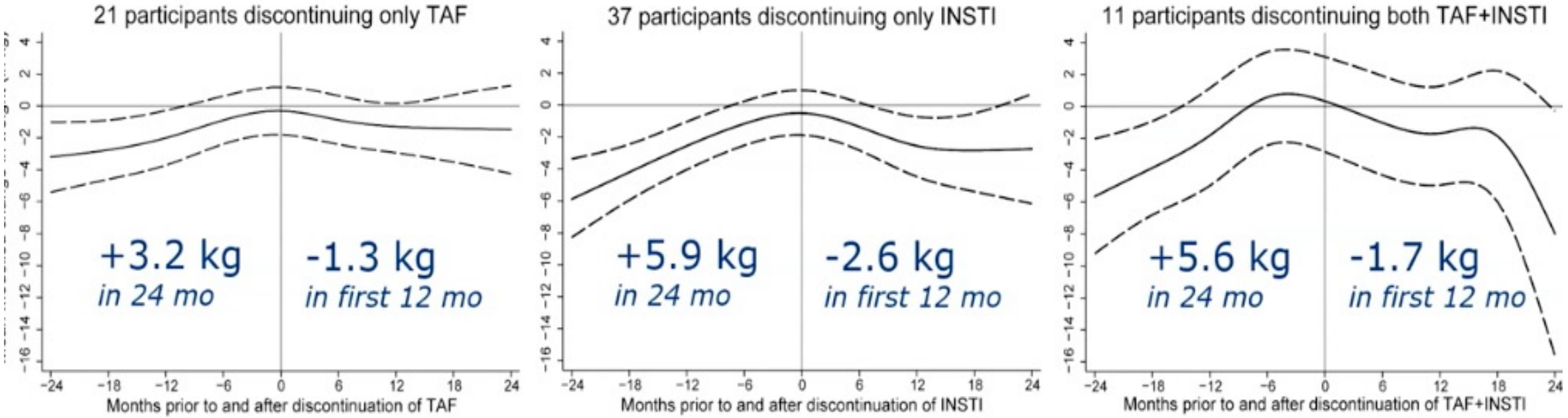
1440 of 6245 eligibe participants gained >=7% weight gain after switch to TAF and/or INSTI



- 21 discontinuing only TAF
- 37 discontinuing only INSTI
- 11 discontinuing both TAF+INSTI

Myrthe L. Verburgh et al., CROI 2023 **ABSTRACT 673**

Adjusted mean modelled weight change prior/after discontinuation



Factors associated with weight change after discontinuation

- BMI ≥30kg/m^2 at discontinuation associated with greater weight loss
  - -5.4 kg/yr more [95%CI, -9.2 to -1.7] vs in individuals with BMI 18.5-24.9kg/m^2
- No independent associations between changes in NRTI backbone or anchor agent at moment of discontinuation and subsequent weight change

Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain

Kai Juhani Kauppinen[a,b], Inka Aho[a,b] and Jussi Sutinen[a,b]

Table 4. Body weight at baseline (BL), follow-up 1 (FU-1), and follow-up 2 (FU-2).

	Weight (kg) at BL	Weight (kg) at FU-1	Weight (kg) at FU-2	*P* value*
Switch group	80.8 (15.5), $n=65$[a]	80.8 (17.7), $n=65$	NA	0.293
Control group	81.9 (17.4), $n=90$[a]	82.8 (17.8), $n=90$	NA	**0.001**
Switch group	83.1 (18.9), $n=95$[b]	NA	83.7 (20.3), $n=95$	0.978
Control group	83.4 (17.6), $n=110$[b]	NA	84.9 (18.6), $n=110$	**0.025**

Switch group switched from TAF to TDF. Control group remained on unchanged TAF-containing regimen. Data are given as mean (standard deviation).

*P-value for the pairwise comparison between BL and FU-1/FU-2 within the study group.

[a]P-value for the comparison between Switch and Control group at Baseline: p=0.686

Aggiornamento 2022-2023

- Weight gain: aggiornamento su nuovi e vecchi farmaci
- Reversibilità del fenomeno di weight gain dopo lo switch
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Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes

- Retrospective data analysis of 217 (TAF/FTC þ DTG), 218 (TDF/FTC þ DTG), and 215 (TDF/FTC/ EFV) ADVANCE participants with 96-week data available

D:A:D, QRISK and Framingham

- Differences were statistically significant between:
  - **TAF/ FTC + DTG and TDF/FTC/EFV for CVD risk using the QRISK** equation, equivalent to one extra case per 1000 people treated over 10 years **NOT with D:A:D and Framingham**
  - between all treatment groups for T2DM risk. **Six extra T2DM** cases were predicted on **TAF/FTC+DTG vs. TDF/ FTC + DTG** using QDiabetes. **Extra three T2DM** cases per 1000 were predicted on **TDF/FTC/ EFV** over TDF/FTC + DTG ($P < 0.01$).

McCann et al. AIDS 2021, 35:1657–1665

Changes in body mass index and clinical outcomes after initiation of contemporary antiretroviral regimens

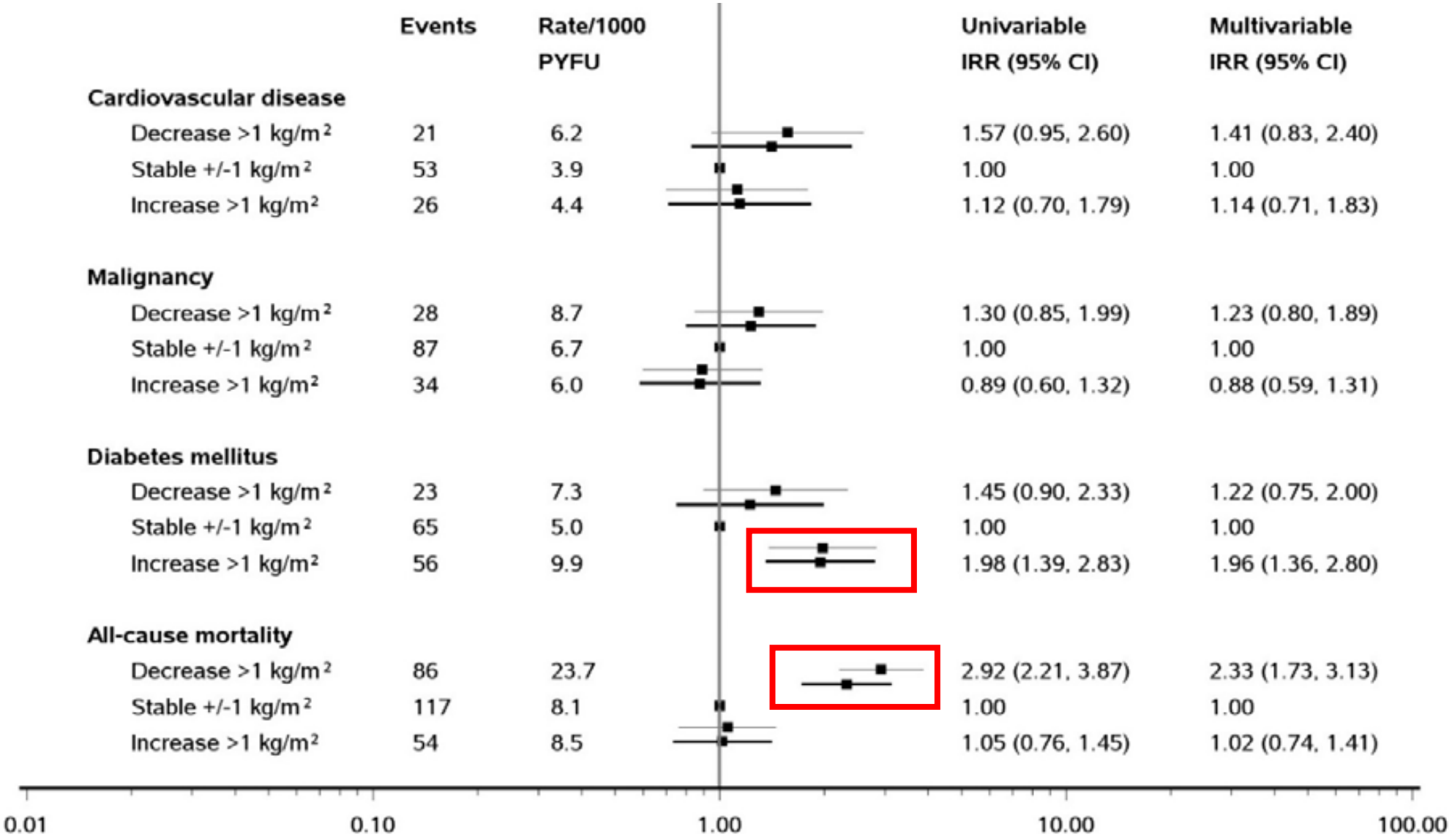
Short title: Changes in BMI and clinical outcomes

Bannister et al., AIDS 2022

Poisson regression was used to assess effect of time-updated BMI changes

6721 PWH were included; 72% male, median age 48 years (IQR 40-55), 8.4% ARV-naïve

5% underweight, 60% healthy weight, 27% overweight, 7.8% obese



Incident diabetes in course of antiretroviral therapy

4,366 PWH included, 73% male, with mean age 46 years

120 incident cases of DM occurred (1.26 cases/100 person year-follow up, 95% CI 1.05-1.50.

- Baseline weight, but not the amount of weight gain, correlated to diabetes incidence (aHR 1.03; 95%CI 1.01-1.04)
- older age (aHR 1.03; 95%CI 1.01-1.06)
- being ART-experienced with detectable HIV RNA (aHR 2.27, 95%CI 1.48-3.49)
- untreated high blood pressure (aHR 2.90; 95%CI 1.30-6.45)
- baseline blood glucose >100 mg/dL (aHR 5.47; 95%CI 3.82-7.85)

Cohort (ref. DTG)	Age- and sex-adjusted hazard ratio*	95% confidence interval	P	Adjusted hazard ratio§	95% confidence interval	P
ATV	1.22	0.63-2.36	0.56	0.97	0.46-2.07	0.94
DRV	1.31	0.77-2.21	0.32	1.02	0.57-1.82	0.95
RPV	0.88	0.34-2.25	0.68	1.10	0.42-2.86	0.84
RAL	2.14	1.33-3.46	0.002	1.71	0.99-2.94	0.052
EVG	1.37	0.68-2.76	0.38	1.54	0.76-3.16	0.23
BIC	1.31	0.64-2.66	0.45	1.10	0.53-2.26	0.80

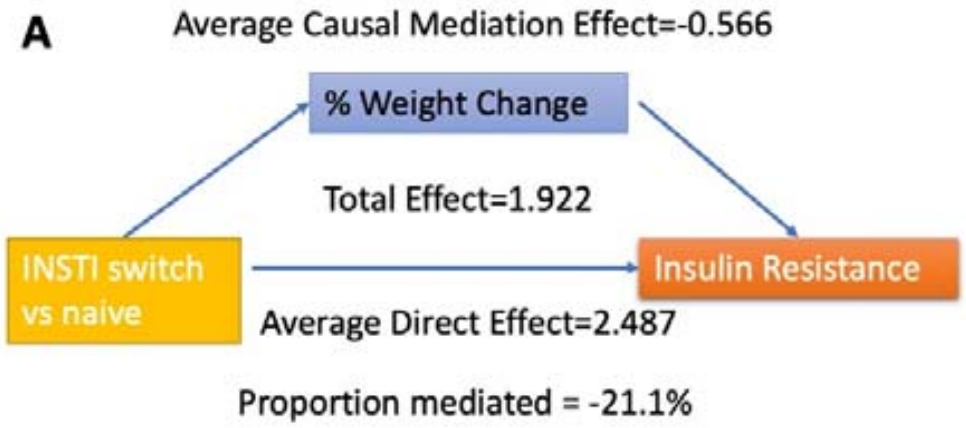
Taramasso L et al., AIDS 2023, Online ahead of print.

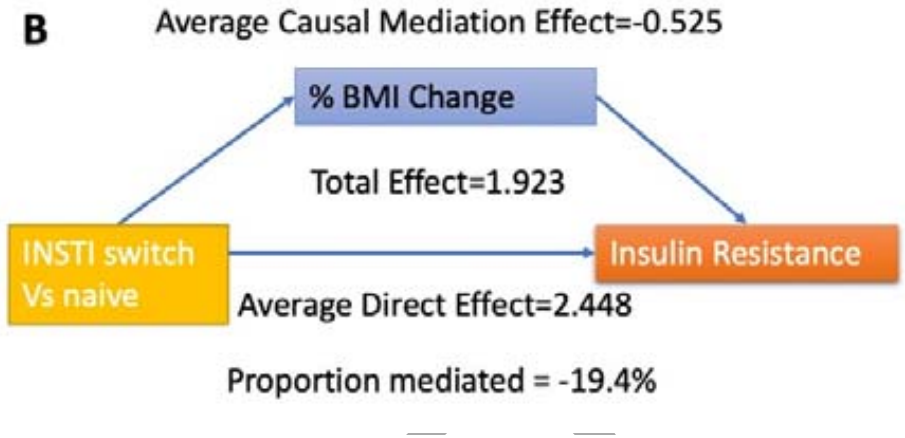
Relationship between weight gain and insulin resistance in people living with HIV switching to INSTI-based regimens

2437 PWH (1025 INSTI-switch, 1412 non-INSTI)

In the subset of 634 PLWH without IR, switching to INSTI associated with a lower risk of IR (HR=0.70, CI95%: 0.51, 0.98).

A weight increase by 1% reduced the total protective effect of INSTI by 21.1% over one year of follow-up, which identifies a 5% weight increase as a clinically meaningful weight gain definition.





Milic J et al., AIDS 2022;36:1643-1653.

Conclusioni: weight gain in corso di ART

- Possibile effetto associato a tutti i moderni farmaci antiretrovirali , ma causalità ancora da dimostrare
- Il fenomeno potrebbe essere almeno in parte reversibile con lo switch terapeutico, ma i dati sono ancora pochi e il rapporto rischio/beneficio dello switch a regimi meno tollerati va messo nel bilancio della scelta
- Fenomeno correlato a maggiore incidenza di diabete ma non vi è una dimostrata associazione con eventi cardiovascolari né con mortalità da tutte le cause, che è anzi maggiore in chi PERDE PESO