Nuove classi di antiretrovirali: quali conseguenze metaboliche?

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Adverse Effects of ARVs and Drug Classes

EACS Guidelines 2021

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTIs										
ABC	Rash	Nausea* Diarrhoea*		IHD						*Systemic hypersensitivity syndrome (HLA B*57:01 dependent)
3TC /FTC										
TDF(iii)			Hepatitis		↓ BMD, Osteoma-lacia	↓ **eGFR**, Fanconi syndrome				
TAF(iii)									**Weight gain**	
NNRTIs										
EFV	Rash		Hepatitis				**Neuropsychi- atric events including: depression, sleep disturbance, headache**		**Dyslipi-daemia,** Gynaeco-mastia	↓ **plasma 25(OH) vitamin D**
RPV	Rash		Hepatitis			↓ eGFR(iv)	Depression, Sleep disturbance, Headache			
DOR							Sleep disturbance, Headache			

PIs										
DRV(v)	Rash	**Nausea and** (vii) **Diarrhoea**		IHD		Nephrolithiasis			Dyslipi-daemia	
Boosting										
RTV		**Nausea and diarrhoea**				↓ **eGFR**(iv)			**Dyslipidae-mia**	
COBI		Nausea and diarrhoea				↓ **eGFR**(iv)			Dyslipidae-mia	

INSTI										
RAL		Nausea			Myopathy, Rhabdomy - olysis		Sleep disturbance, Headache		**Weight gain**	Systemic hypersensitivity syndrome(viii)
DTG	Rash	Nausea				↓ eGFR(iv)	**Sleep disturbance, Headache**		**Weight gain**	Systemic hypersensitivity syndrome (< 1%) ↑ Risk of neural tube defects (pre-concep- tion)(ix)
EVG/c		**Nausea,** Diarrhoea				↓ **eGFR**(iv)	Sleep disturbance, Headache		**Weight gain**	
BIC						↓ eGFR(iv)	Sleep disturbance, Headache		**Weight gain**	
CAB	Injection site reac-tions(x)						Sleep disturbance, Headache			Pyrexia(xi)

- Weight gain & INSTI
- Weight gain & TAF
- Diabete & INSTI/TAF
- Rischio cardiovascolare & INSTI
- Popolazioni speciali ed aumento di peso (anziani, giovani, donne in gravidanza)

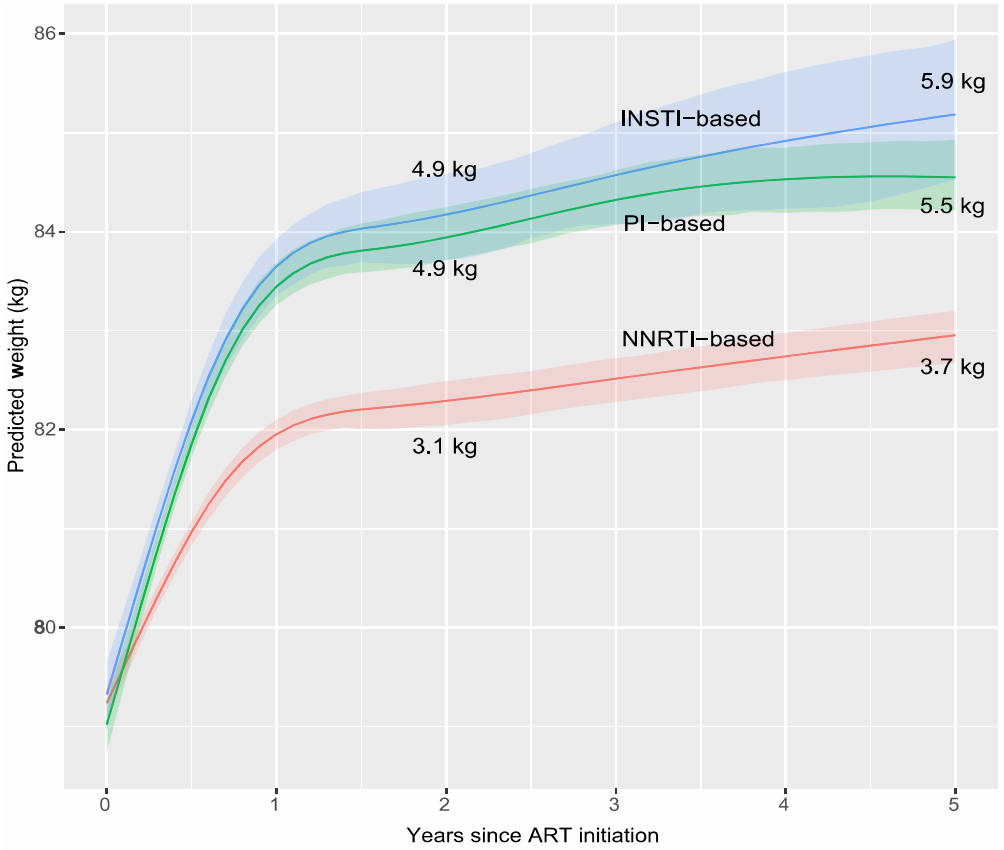
Weight gain

- Obesity is a multifactorial disease that affects individuals the world over, regardless of sex, race, age, racial condition or geography
- In white subjects aged 35–50 years, the average weight gain in 1 year is about 0.5– 1 kg.

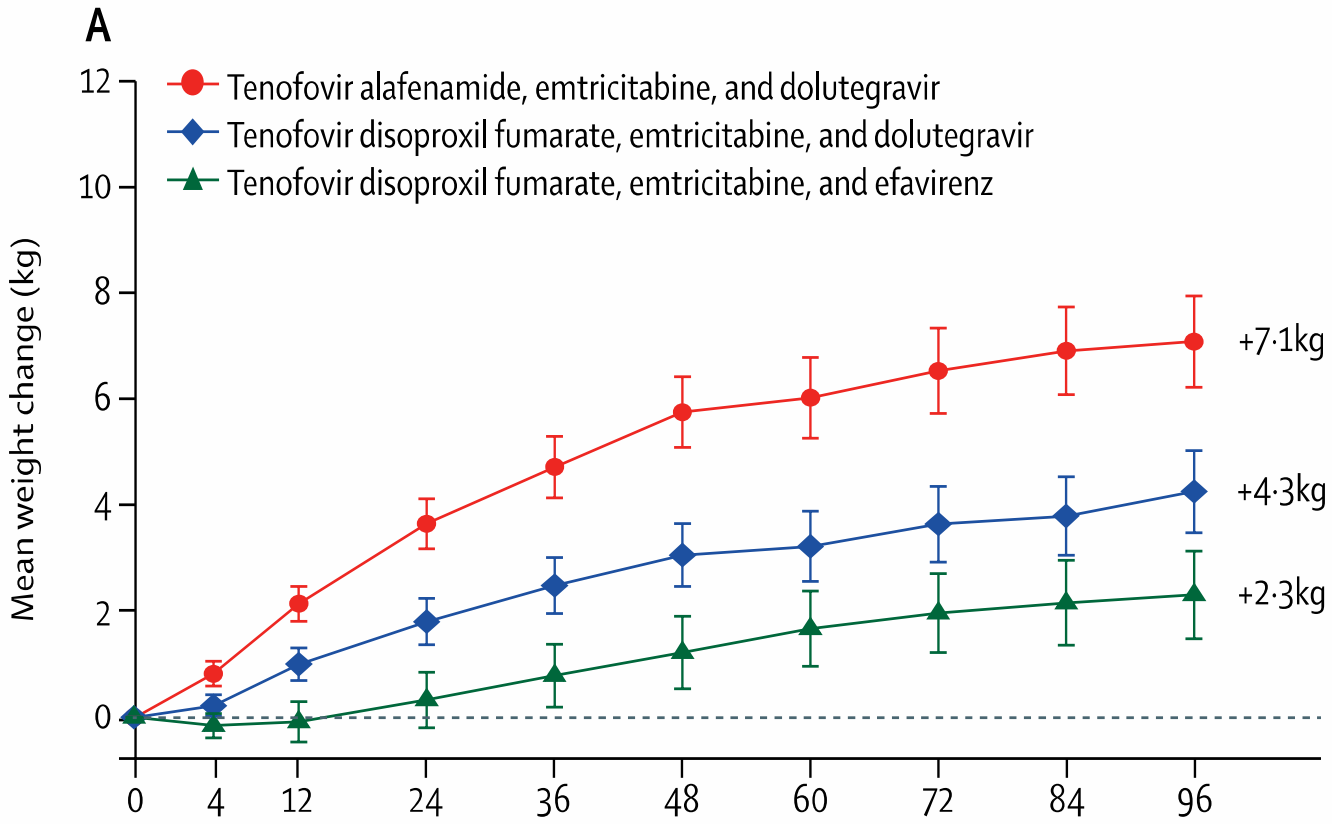
Hill A, J Virus Erad 2019; 5: 41–3. Sax PE, Clin Infect Dis 2019; 71: 1379–89.

Weight gain in naive PLWH

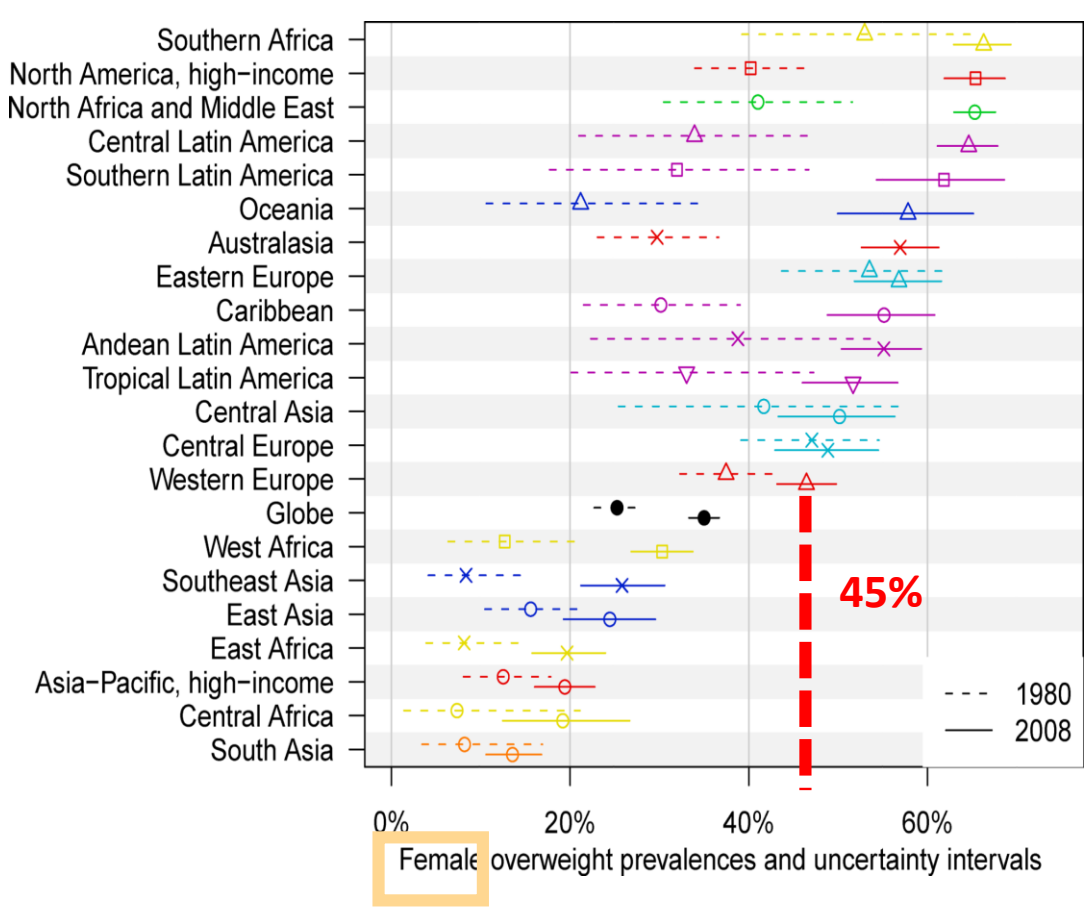
Weight over the first five-years of ART by regimen class (22,972 PLWH)

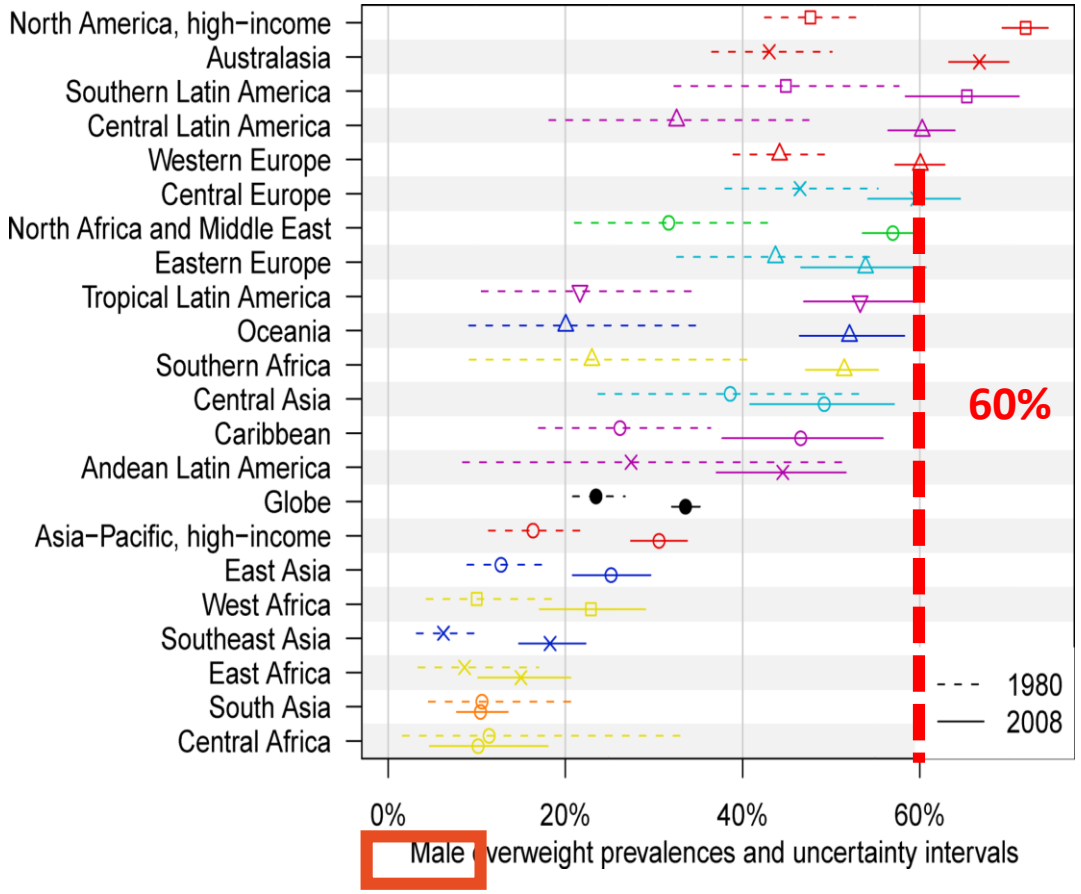


Mean change in bodyweight over time in all randomly assigned individuals (1,053 PLWH)



Bourgi K, et al., JIAS 2020, 23: e25484. Venter WDF, et al., Lancet HIV 2020; 7: e666–76.

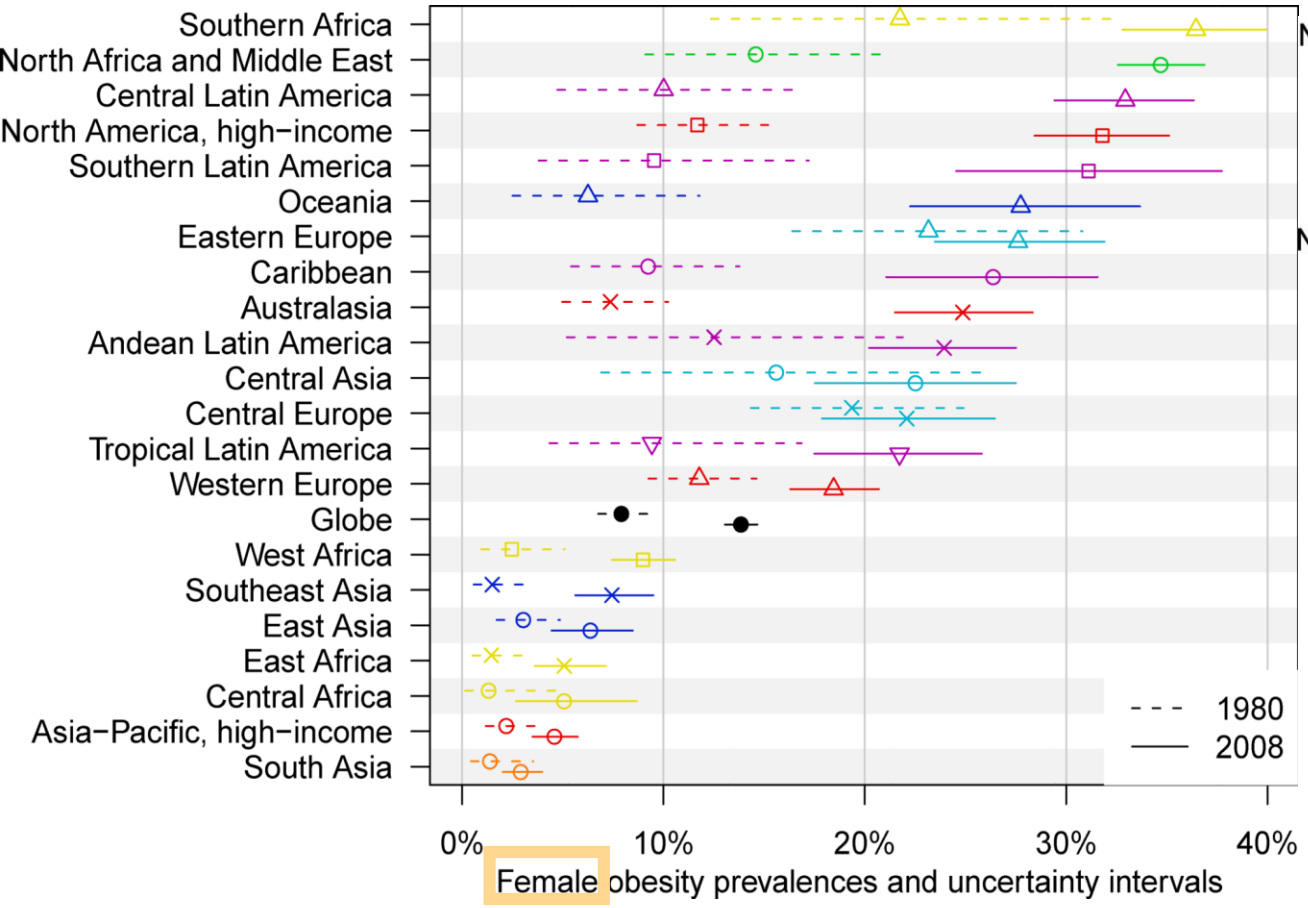


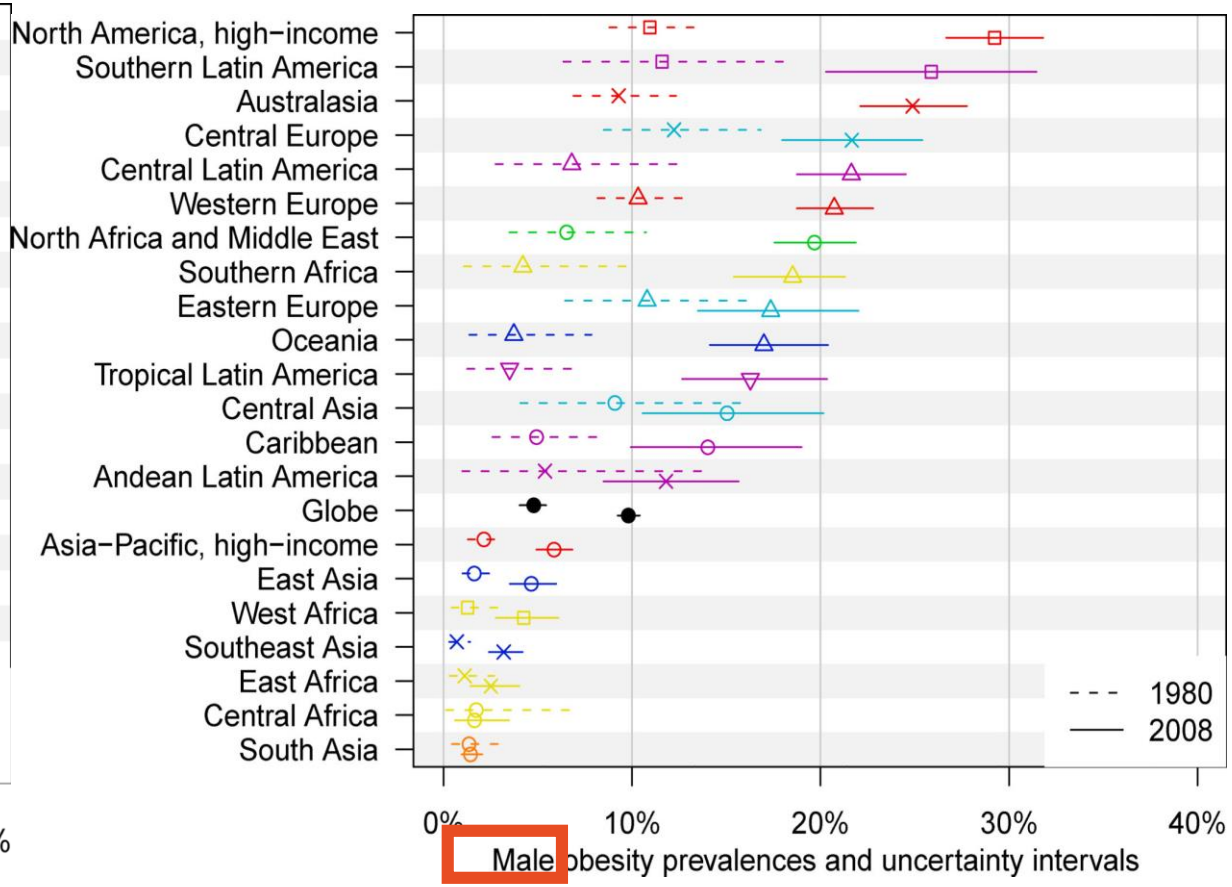


The epidemiology is changing...

OVERWEIGHT

Finucane M, et al. Lancet 2011;377:557–567





The epidemiology is changing...

OBESITY

Finucane M, et al. Lancet 2011;377:557–567

- DO INSTIs CAUSE WEIGHT GAIN OR SIMPLY A RETURN TO THE SAME QUALITY OF LIFE OF THE GENERAL POLUATION?

Cohort studies and weight gain

INSTI > OTHER ARV

- NA-ACCORD. USA, Canadá (N = 24001)[1]. Naive
- Bakal DR. Brasil (N=1794)[2]. Naive
- Menard A. France (N=462)[3]. Naïve o Switch
- Lake JE. ACTG A5001, A5322 (N=691)[4]. Switch
- Kerchberger AM. WIHS (N=1118)[5] .Switch
- Norwood J. USA (N=495)[6]. Switch
- Pallela F. USA (N=653)[7]. Switch
- Berstein A. USA (N=260)[17]. Switch

TAF > TDF

- Gomez M. Alemania. (N=241)[8]. Switch
- Schafer JJ. USA (N=110)[9]. Switch

INSTI = OTHER ARV

- Burns JE. London (N=378)[10]. Switch
- McComsey GA. TRIO. USA (N = 3468)[11]. Switch
- Taramasso L. SCOLTA. Italia (N=1118)[12]. Switch
- Mounzer K. OPERA. USA (N=10.653)[13]. Switch
- TSEPAMO. Botswana. EFV (N=621) < DTG (N=757) < HIV- (N=11280)[14]
- Hsu R. USA (N=6246)[15]. Switch DRV>INSTI>RPV
- Verboket S. AGE$_H$IV. Swiss (N=595)[16]. Switch (HIV-)

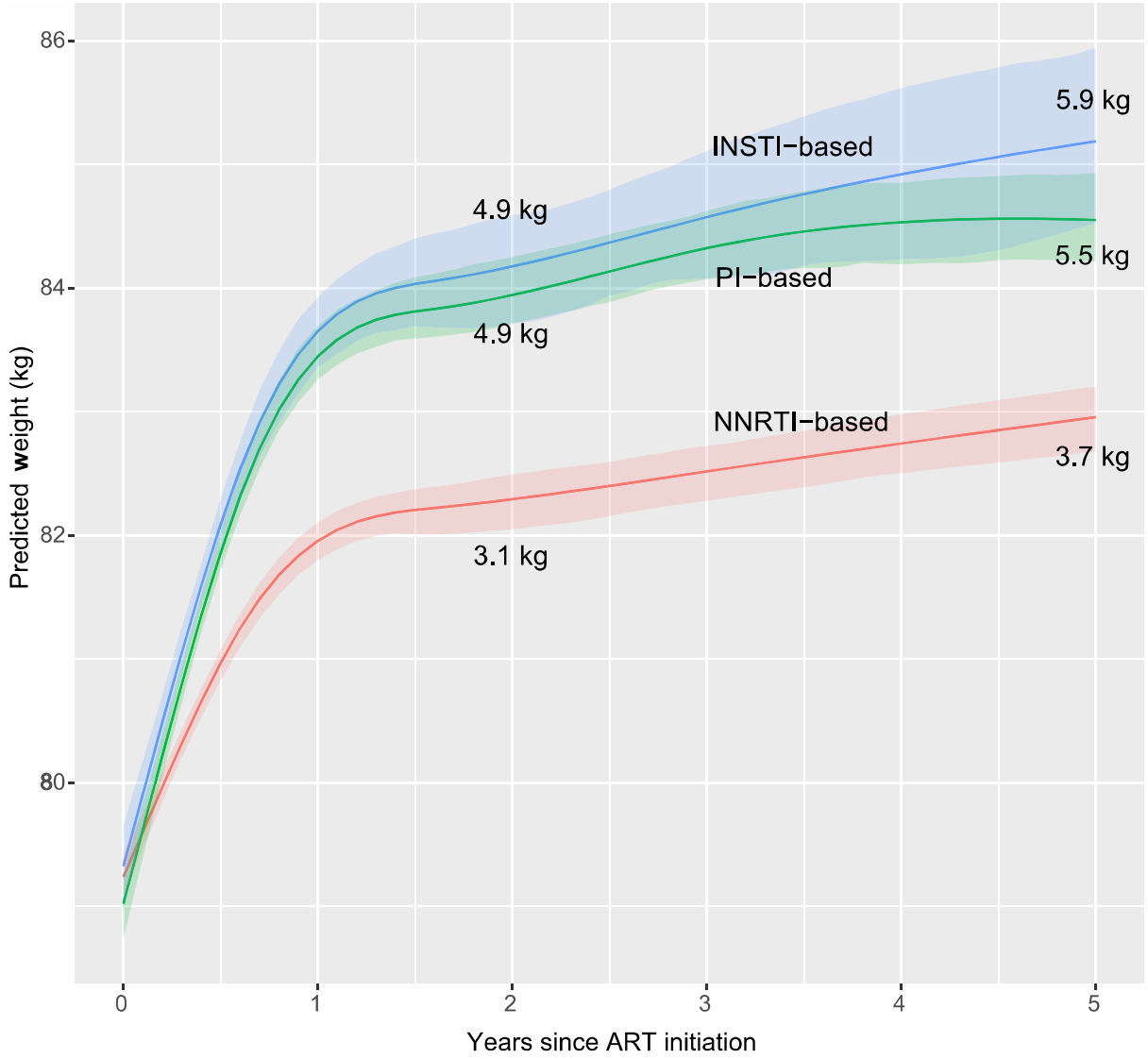
INSTI > PI

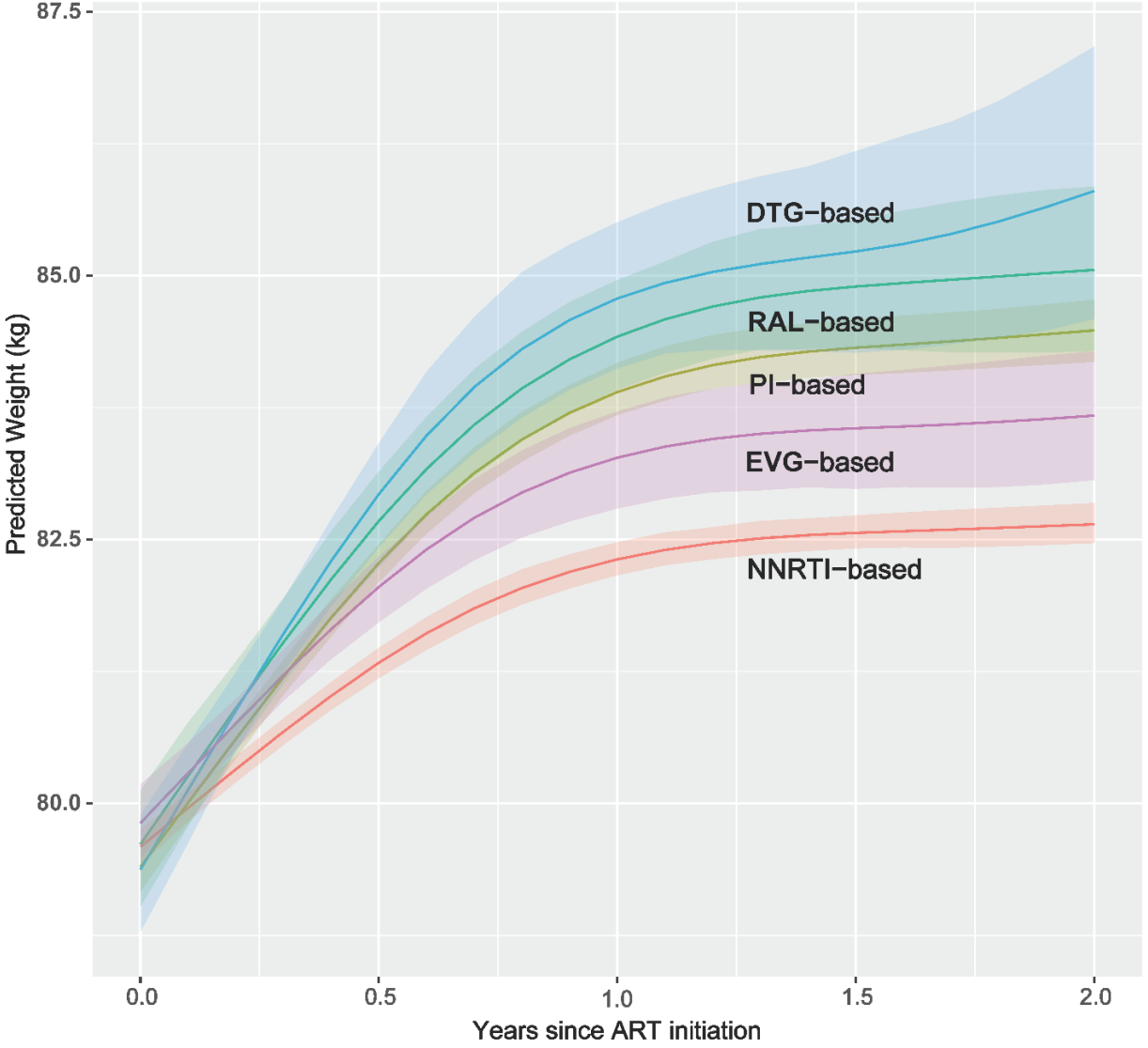
- Bakal DR. Brasil (N=1794)[2]. Naïve
- Norwood J. USA (N=495)[6]. Switch
- Mounzer K. OPERA. USA (N=10.653)[13]. Switch
- McComsey GA. TRIO. USA (N = 3468)[11]. Switch

1. Bourgi. CROI 2019 # 670. 2. Bakal DR, et al. JAC 2018;73:2177-2185. 3. Menard A, et al. AIDS 2017;31:1499-1500. 4. Lake. CROI 2019 #669. 5. Kerchberger AM, et al. CROI 2019 #672. 6. Norwood J et al. JAIDS 2017;5:527-31. 7. Pallela F, et al. CROI 2019. Seattle, WA # 674. 8. Gomez M, et al. Infection 2019;47:95–102. 9. Schafer JJ, et al. Open Forum Infect Dis 2019 (in press). 10. Burns JE, et al. AIDS 2019 (in press). 11. McComsey GA, et al. CROI 2019 #671. 12. Taramasso L, et al. Open Forum Infect Dis 2017;4:ofx239. 13. Mounzer K, et al. IDWeek 2019 #978. 14. Caniglia E, et al. IAS 2019 # MOPEB241. 15. Hsu et al. EACS 2019 # PE2/32. 16. Verboeket. EACS 2019. Abstr PS3/6. 17. Bernstein A. IDWEEK #334.

PROIEZIONI WEIGHT GAIN a 5 e 2 ANNI

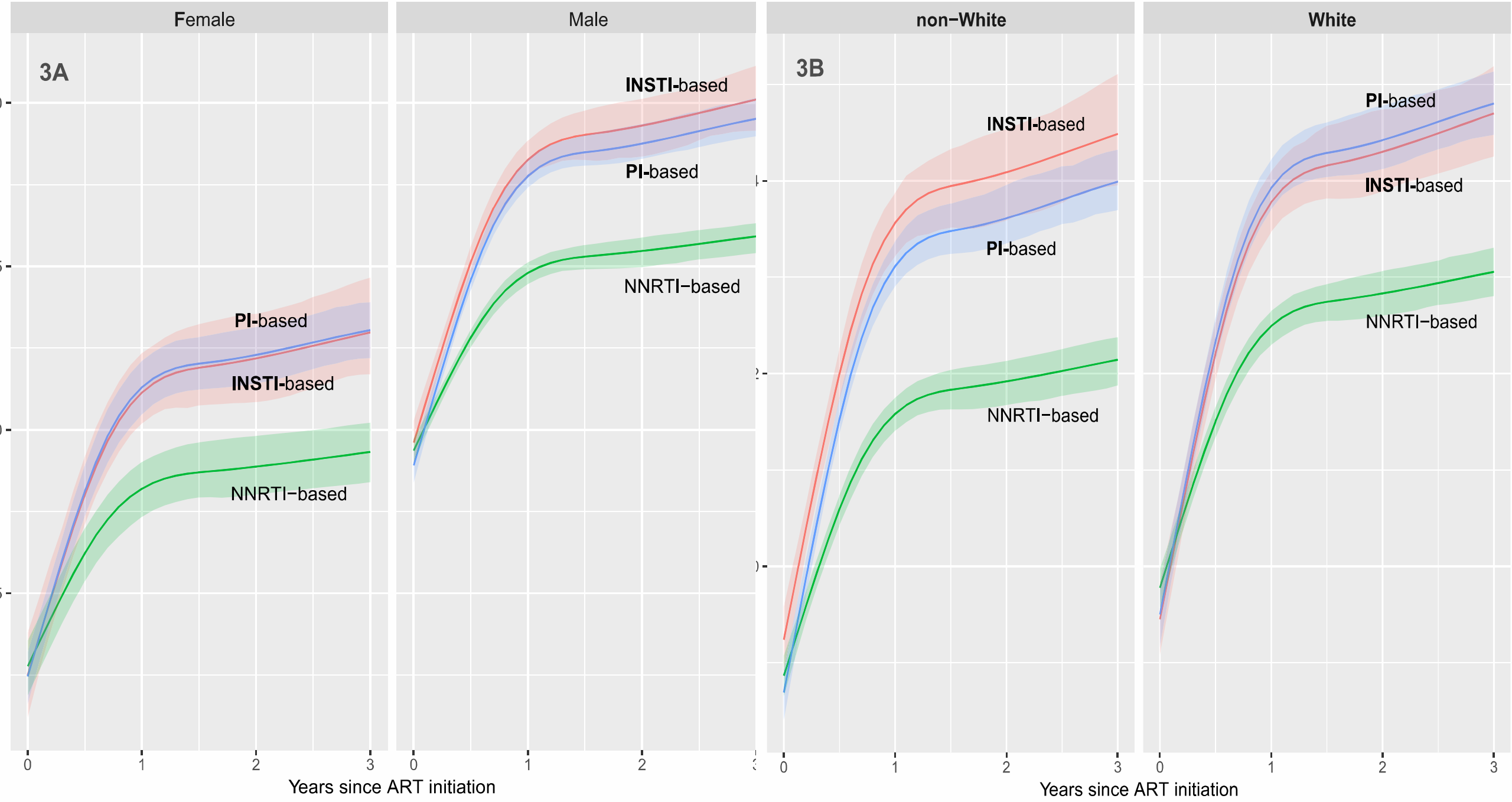
22,972 PLWH: 20% started INSTI-based regimens:1624 raltegravir (RAL). 2085 elvitegravir (EVG) and 929 dolutegravir (DTG)





BOURGI K et al JIAS 2020, 23: e25484

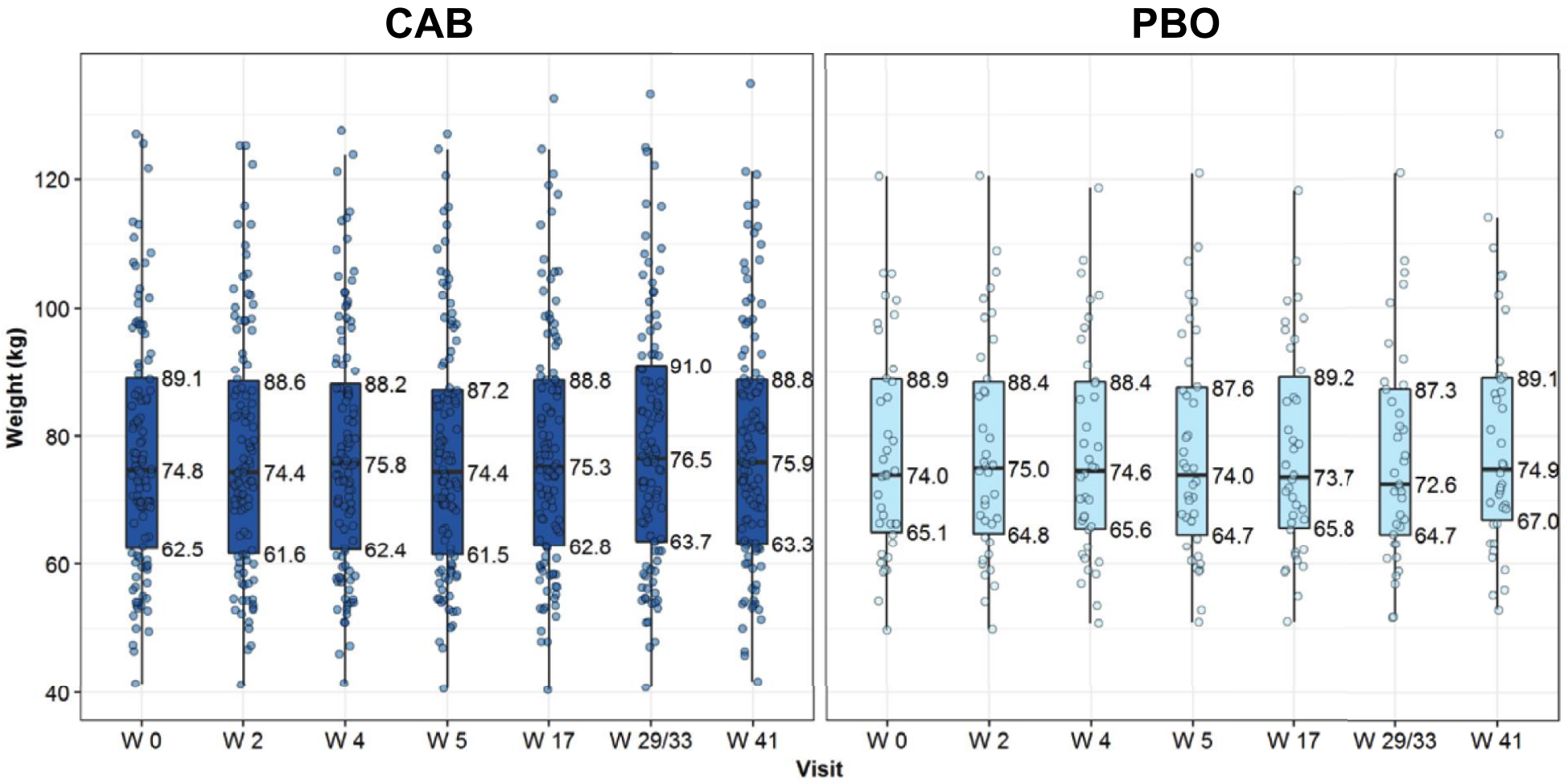
BOURGI K et al JIAS 2020, 23: e25484



Cabotegravir

INSTI										
RAL		Nausea			Myopathy, Rhabdomy - olysis		Sleep disturbance, Headache		**Weight gain**	Systemic hypersensitivity syndrome(viii)
DTG	Rash	Nausea				↓ eGFR(iv)	**Sleep disturbance, Headache**		**Weight gain**	Systemic hypersensitivity syndrome (< 1%) ↑ Risk of neural tube defects (pre-concep- tion)(ix)
EVG/c		**Nausea,** Diarrhoea				↓ **eGFR**(iv)	Sleep disturbance, Headache		**Weight gain**	
BIC						↓ eGFR(iv)	Sleep disturbance, Headache		**Weight gain**	
CAB	Injection site reac- tions(x)						Sleep disturbance, Headache			Pyrexia(xi)

Cabotegravir Is Not Associated With Weight Gain in Human Immunodeficiency Virus-uninfected Individuals in HPTN 077



Among the 146 participants with paired weights, between W0 and W41 the median increase in weight was:

- **CAB +1.1** (IQR, –0.9, +3.0) kg;
- **PBO +1.0** (IQR, –.2, +3.2) kg

(Δ = +0.1 kg, *P* = .66).

Landovitz et al, Clin Infect Dis 2020 2;70(2):319-322.

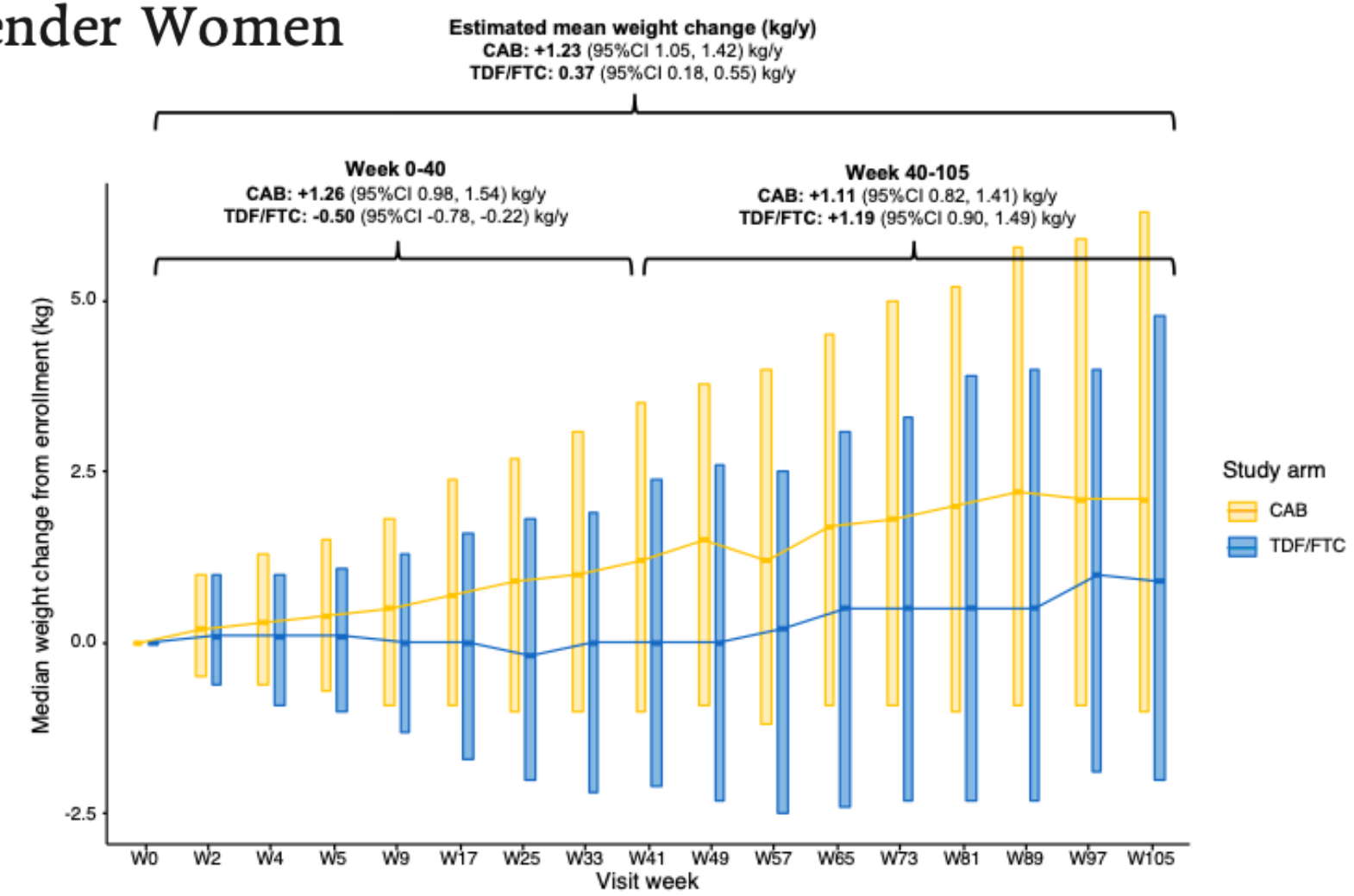
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

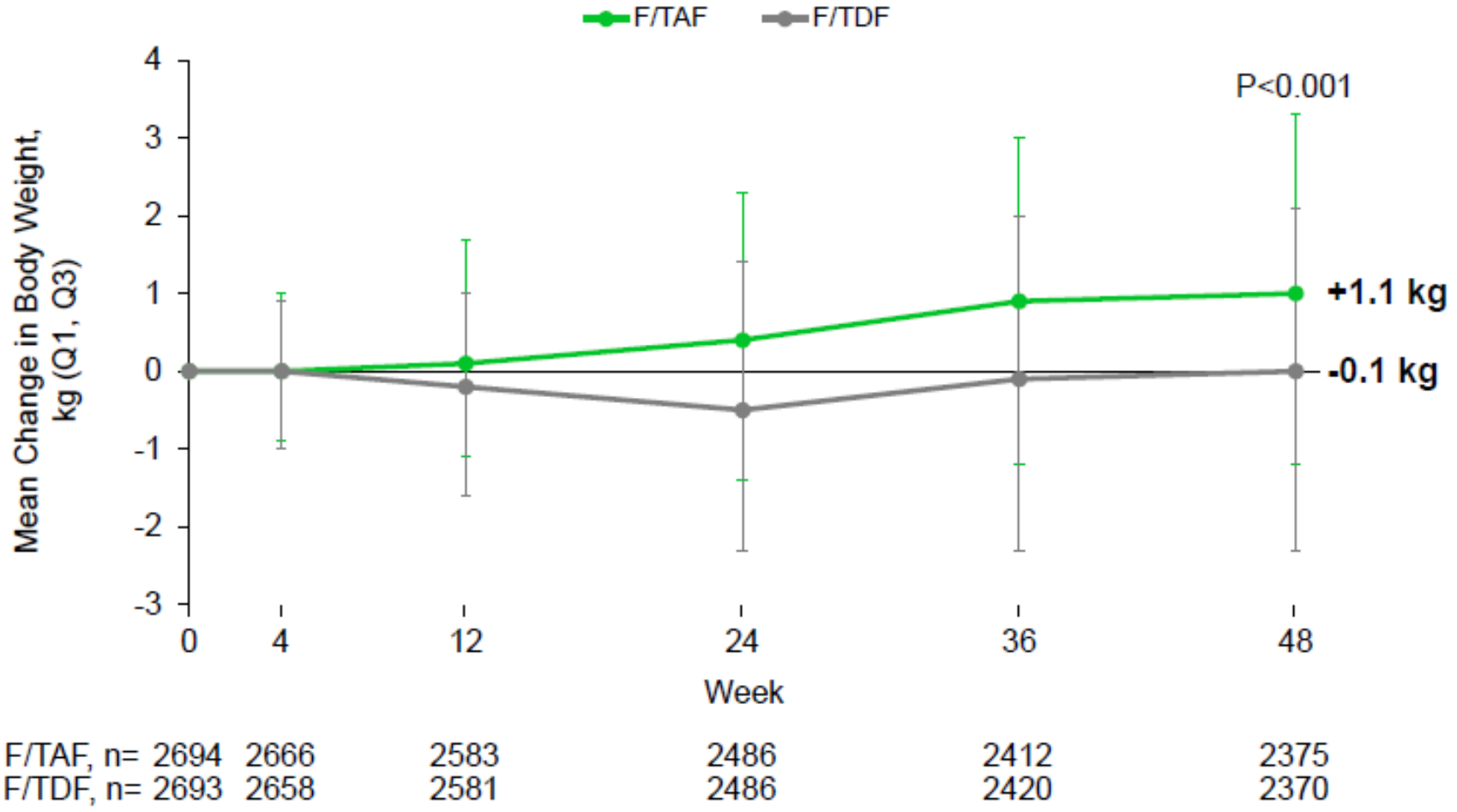
Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

In a post hoc analysis, a mean annualized increase 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.



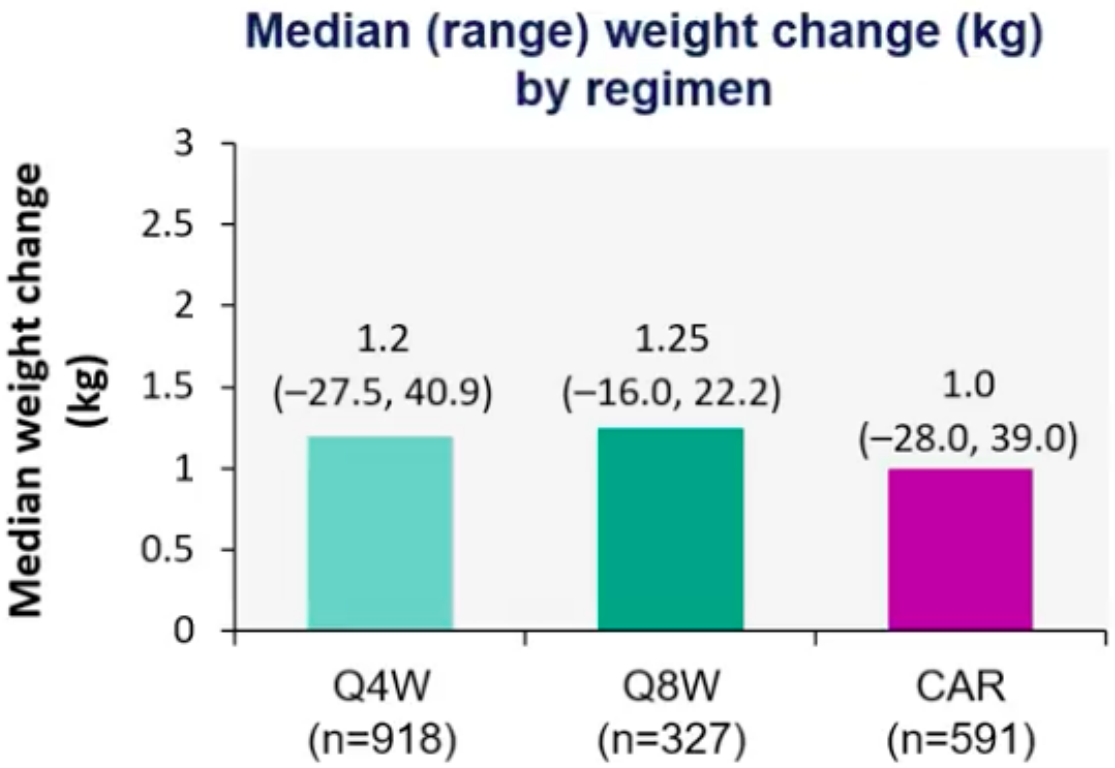
Kenneth H Mayer et al., Lancet 2020; 396: 239–54

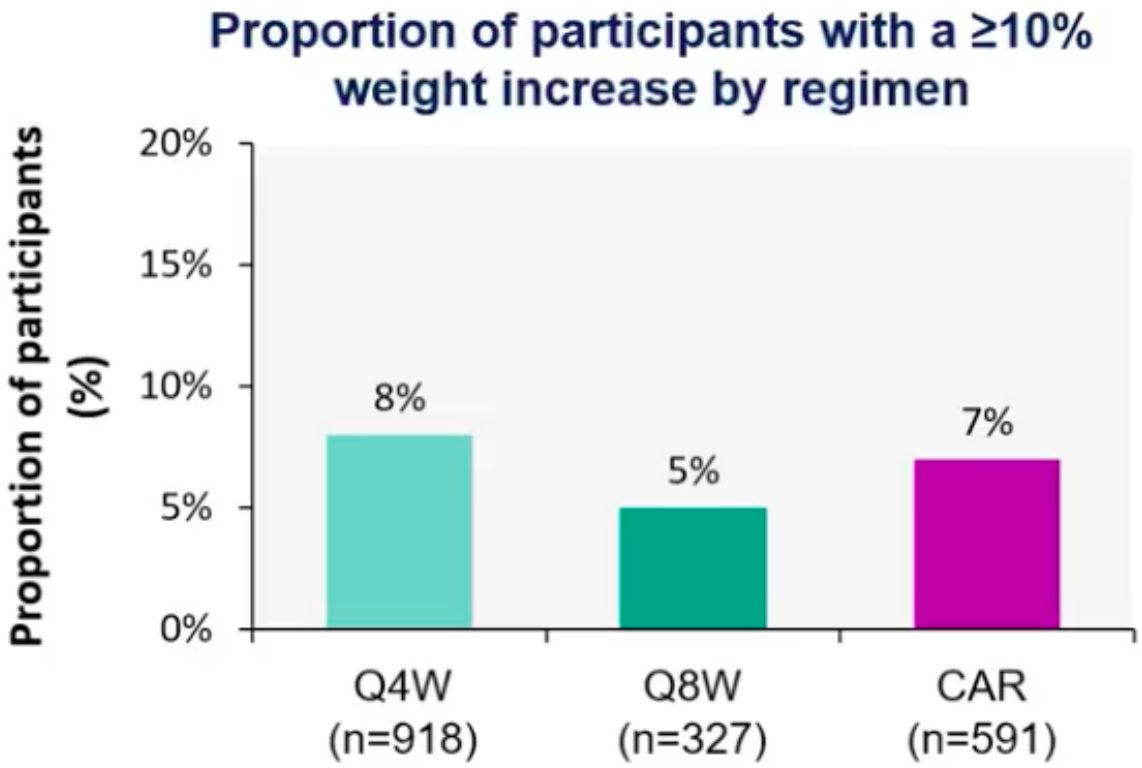
WEIGHT AND LIPID CHANGES IN PHASE 3 CABOTEGRAVIR AND RILPIVIRINE LONG-ACTING TRIALS

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

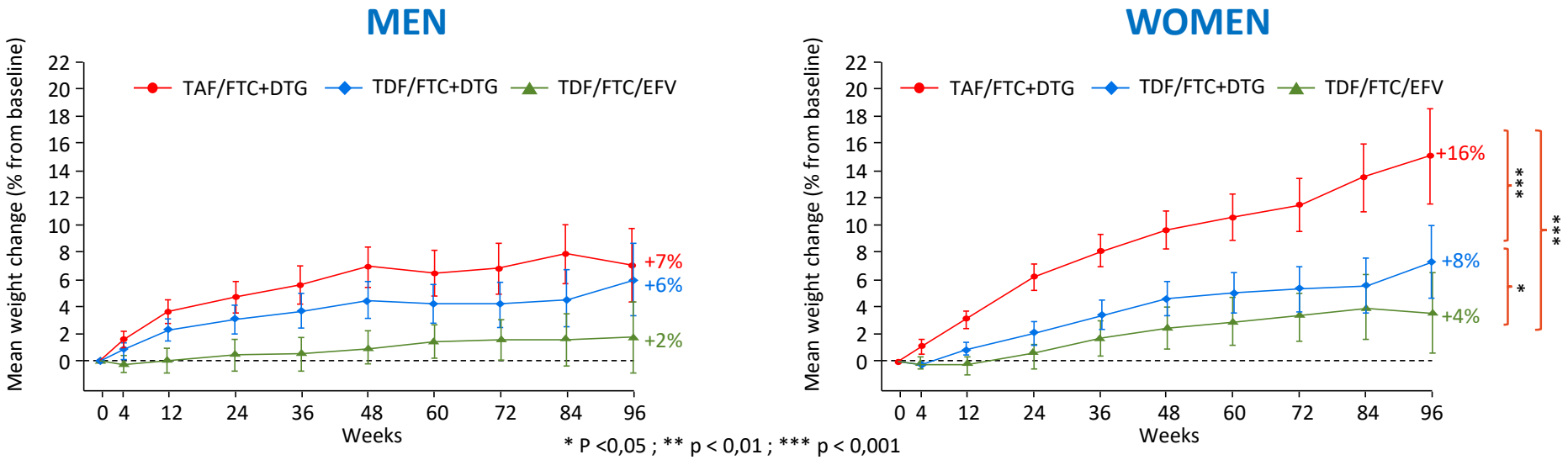
Patel et al., CROI 2021, Abstract 505

- Weight gain & INSTI
- **Weight gain & TAF**
- **Diabete & INSTI/TAF**
- **Rischio cardiovascolare & INSTI**
- **Popolazioni speciali ed aumento di peso (anziani, giovani, donne in gravidanza)**

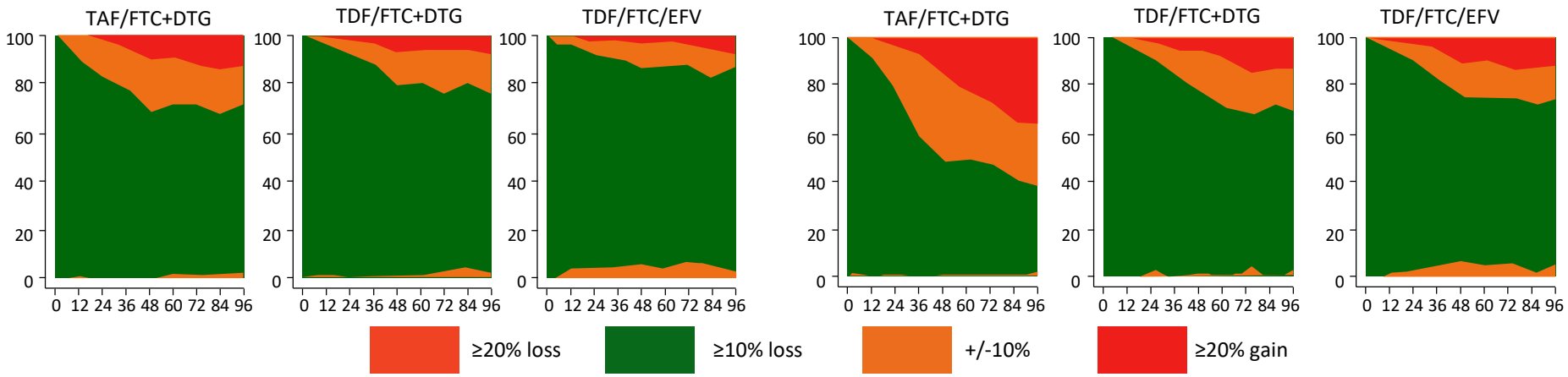
ADVANCE study: 1st line open-label randomized ART in Johannesburg

Percentage weight change (%) to w96 (incomplete data W48-W96)

- **TAF/FTC + DTG (N = 351) vs TDF/3TC + DTG (N = 351) vs TDF/3TC/EFV600 (N = 351)**



Percentage weight change over time



Hill A, IAS 2019, Abs. MOABX0102LB

Perceptions? Administered before weight gain information leaflet and consent

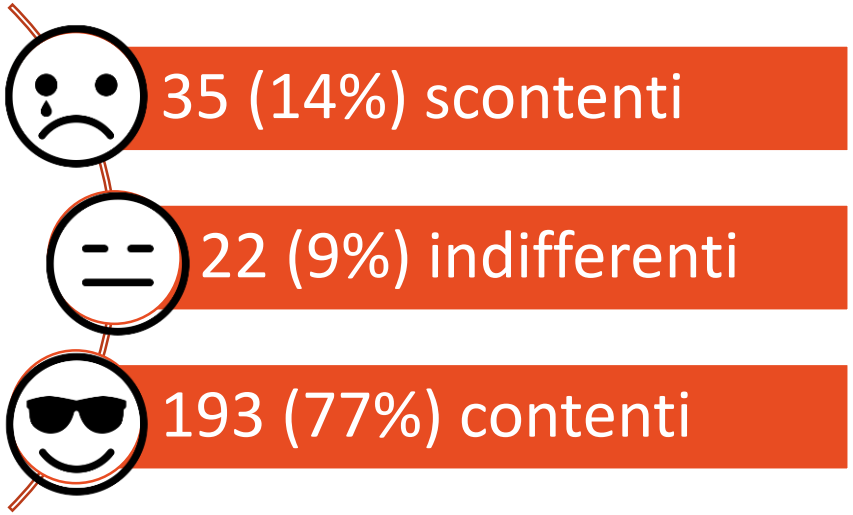
- 68 participants surveyed by 15 July 2019: 51 women, 17 men
- No discontinuations for weight gain; most participant's estimation of their weight gain was similar to the actual weight gain, with a few wild exceptions
- 8 women reported unhappiness with weight gain (one actually had lost 1.3 kg); 3 had actually gained < 5%, while 4 had > 10% weight gain. 2 of those who gained > 10% of their baseline weight expressed that they were very unhappy
- 6 women participants reported uneven weight gain: 3 abdominal, 2 upper body, 1 hip area, and 1 lower body
- 2 men reported unhappiness with weight loss (verified weight loss for both)
- Most participants were happy with the weight gain, even though they had to get new clothes as their pre-ART clothes could not fit anymore. Some viewed the weight gain as "return to health" although they had not reported weight loss at screening.

Source: **Dr Simiso Sokhela**

Presented at IAS 2019,
slides MOAX0102LB

ADVANCE: percezione dell'aumento di peso

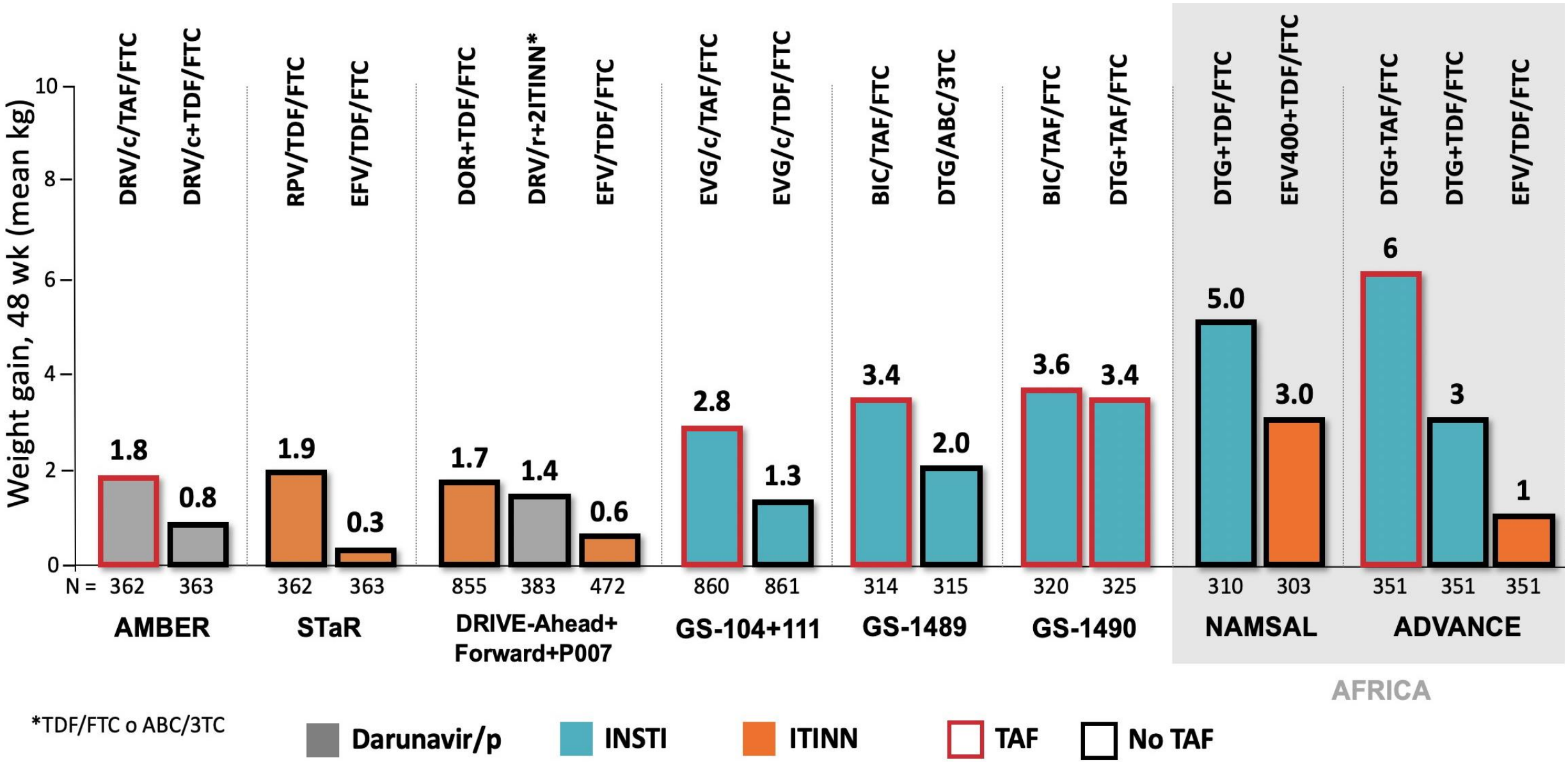
- 250 persone intervistate (150 femmine, 93 maschi)



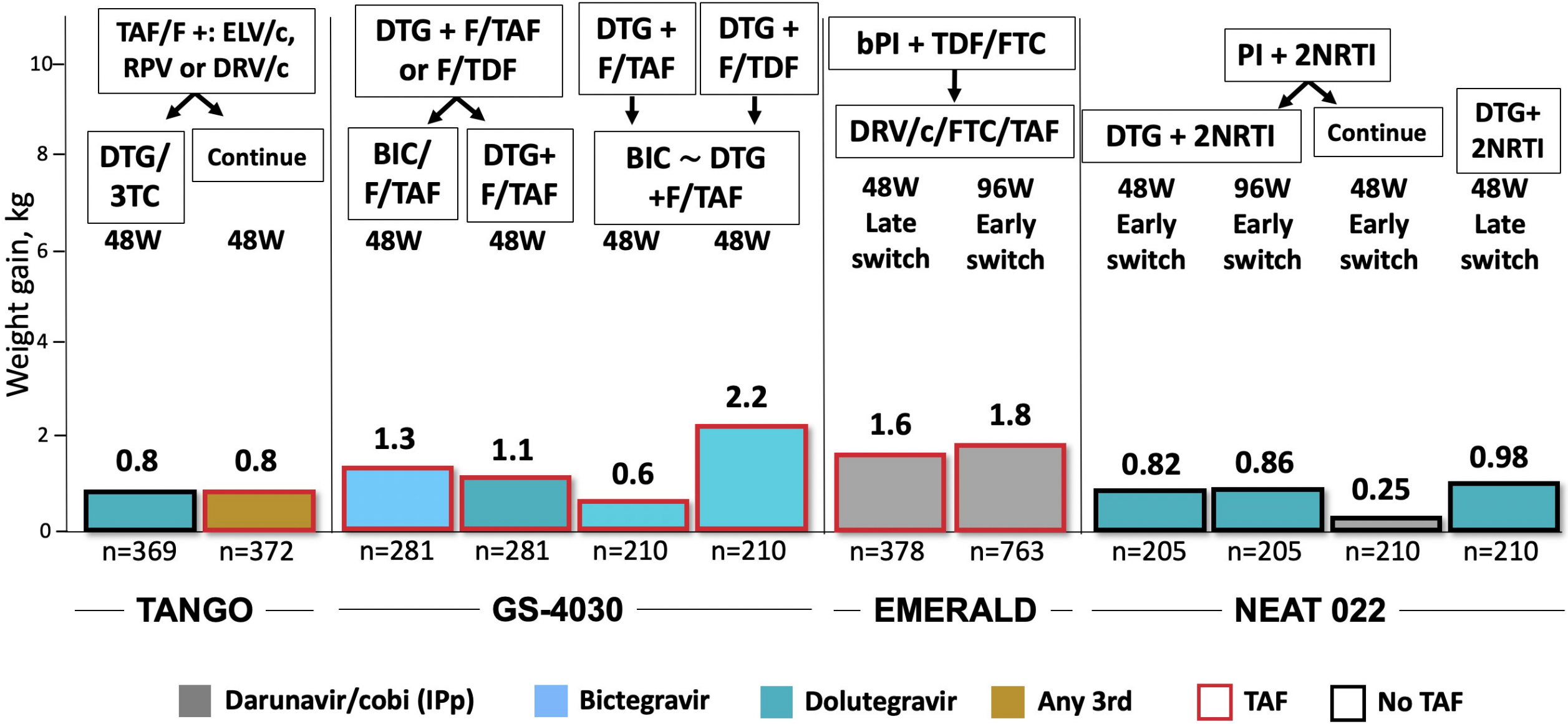
Su 20 persone intervistate con aumento di peso >20% solo 2 non erano soddisfatte
Nessuno ha rischiesto sospensione o variazione della ART per variazione di peso

Presented at IAS 2019,
slides MOAX0102LB

naive


Weight gain, 48 wk (mean kg)
10
8
6
4
2
0
DRV/c/TAF/FTC
DRV/c+TDF/FTC
RPV/TDF/FTC
EFV/TDF/FTC
DOR+TDF/FTC
DRV/r+2ITINN*
EFV/TDF/FTC
EVG/c/TAF/FTC
EVG/c/TDF/FTC
BIC/TAF/FTC
DTG/ABC/3TC
BIC/TAF/FTC
DTG+TAF/FTC
DTG+TDF/FTC
EFV400+TDF/FTC
DTG+TAF/FTC
DTG+TDF/FTC
EFV/TDF/FTC
1.8
0.8
1.9
0.3
1.7
1.4
0.6
2.8
1.3
3.4
2.0
3.6
3.4
5.0
3.0
6
3
1
N = 362 363 362 363 855 383 472 860 861 314 315 320 325 310 303 351 351 351
AMBER
STaR
DRIVE-Ahead+ Forward+P007
GS-104+111
GS-1489
GS-1490
NAMSAL
ADVANCE
AFRICA
*TDF/FTC o ABC/3TC
Darunavir/p
INSTI
ITINN
TAF
No TAF

switch


Weight gain, kg
0
2
4
6
8
10
TAF/F +: ELV/c, RPV or DRV/c
DTG/ 3TC
Continue
48W
48W
0.8
0.8
n=369
n=372
DTG + F/TAF or F/TDF
BIC/ F/TAF
DTG+ F/TAF
48W
48W
1.3
1.1
n=281
n=281
DTG + F/TAF
DTG + F/TDF
BIC ~ DTG +F/TAF
48W
48W
0.6
2.2
n=210
n=210
TANGO
GS-4030
bPI + TDF/FTC
DRV/c/FTC/TAF
48W Late switch
96W Early switch
1.6
1.8
n=378
n=763
EMERALD
PI + 2NRTI
DTG + 2NRTI
Continue
DTG+ 2NRTI
48W Early switch
96W Early switch
48W Early switch
48W Late switch
0.82
0.86
0.25
0.98
n=205
n=205
n=210
n=210
NEAT 022
Darunavir/cobi (IPp)
Bictegravir
Dolutegravir
Any 3rd
TAF
No TAF

The switch from tenofovir disoproxil fumarate to tenofovir alafenamide determines weight gain in patients on rilpivirine-based regimen

Lucia Taramasso[a,b], Marco Berruti[c], Federica Briano[c] and Antonio Di Biagio[c]

Table 1. Weight changes in the study population, according to sex, baseline CD4$^+$, BMI and history of illicit drug use.

	Weight 12_BEF	Weight 6_BEF	Weight 3_AFT	Weight 6_AFT	Weight change from 12_BEF to 6_BEF	Weight change from 6_BEF to 3_AFT	Weight change from 3_AFT to 6 AFT
Whole group ($n=252$)	73.8 (±14.3)	73.8 (±14.3)	77.7 (±42.3)	75.5 (±14.5)	0.0	+3.9	−2.2
		$P=0.000$			$P^*=1.000$	$P^*=0.717$	$P^*=1.000$
Male sex ($n=170$)	78.1 (±12.9)	78.0 (±13.1)	82.9 (±49.9)	79.1 (±13.6)	−0.1	+4.9	−3.8
		$P=0.004$			$P^*=1.000$	$P^*=1.000$	$P^*=1.000$
Female sex ($n=82$)	65.0 (±12.9)	65.0 (±12.6)	67.1 (±13.0)	68.1 (±13.7)	0.0	+2.1	+1.0
		$P=0.000$			$P^*=1.000$	**$P^*=0.000$**	**$P^*=0.008$**
BMI >25 ($n=122$)	83.7 (±11.8)	83.3 (±12.3)	84.9 (±12.6)	85.1 (±12.7)	−0.4	+1.6	+0.2
		$P=0.000$			$P^*=0.903$	**$P^*=0.000$**	$P^*=1.000$
BMI ≤ 25 ($n=130$)	64.6 (±9.4)	64.9 (±9.6)	71.1 (±56.9)	66.5 (±9.6)	+0.3	+6.2	−4.6
		$P=0.000$			$P^*=1.000$	$P^*=1.000$	$P^*=1.000$
CD4 >500 ($n=197$)	74.2 (±14.9)	74.3 (±14.9)	78.9 (±47.5)	76.0 (±15.1)	+0.1	+4.6	−2.9
		$P=0.000$			$P^*=1.000$	$P^*=0.908$	$P^*=1.000$
CD4 ≤ 500 ($n=55$)	72.5 (±11.7)	72.0 (±11.7)	73.4 (±12.1)	73.4 (±12.3)	−0.5	+1.4	0
		$P=0.012$			$P^*=0.878$	**$P^*=0.009$**	$P^*=1.000$
Previous IVDU ($n=95$)	74.2 (±12.8)	74.4 (±13.0)	75.8 (±13.8)	75.5 (±13.7)	−0.2	+1.4	−0.3
		$P=0.002$			$P^*=1.000$	$P^*=0.001$	$P^*=1.000$
Not previous IVDU ($n=157$)	73.6 (±15.1)	73.4 (±15.1)	78.9 (±52.5)	75.5 (±15.1)	−0.2	+5.5	−3.4
		$P=0.000$			$P^*=1.000$	$P^*=0.000$	$P^*=1.000$

Mallon PWG et al. *Journal of the International AIDS Society* 2021, **24**:e25702
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25702/full | https://doi.org/10.1002/jia2.25702

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

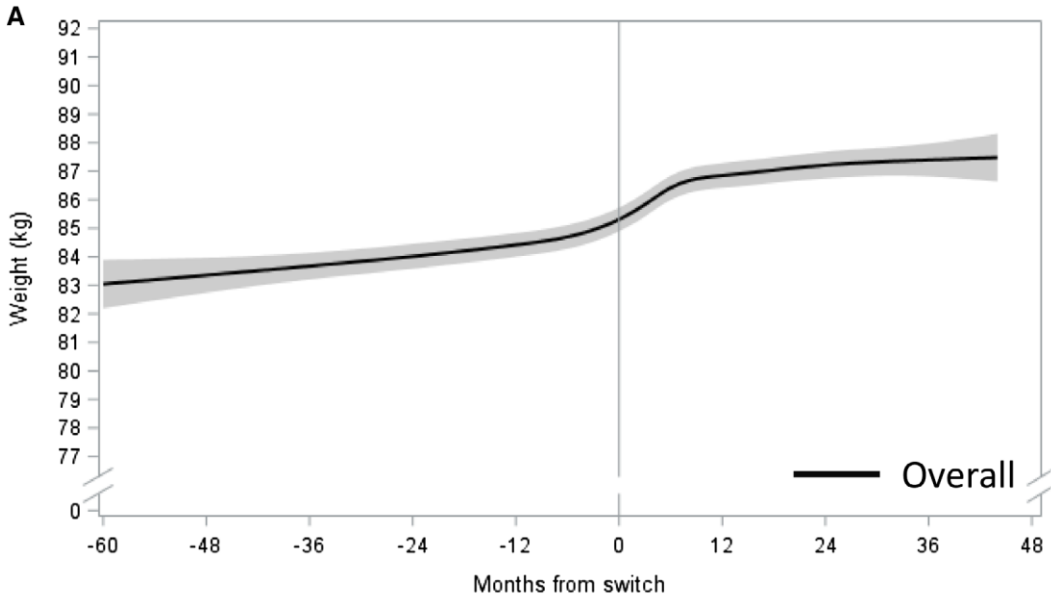
Weight gain before and after switch from TDF to TAF in a U.S. cohort study

Patrick WG Mallon[1,2], Laurence Brunet[3,§], Ricky K Hsu[4,5], Jennifer S Fusco[3], Karam C Mounzer[6], Girish Prajapati[7], Andrew P Beyer[7], Michael B Wohlfeiler[8] and Gregory P Fusco[3]

Antiretroviral-experienced, virologically suppressed PLWH in the U.S. OPERA cohort switched from TDF to TAF . Linear mixed models were used to assess weight changes before/after the switch to TAF, adjusted for age, sex, race, BMI, CD4 cell count, endocrine disorders and concurrent medications that could affect weight.

6908 PLWH included:

- 5479 maintaining all other antiretrovirals (boosted protease inhibitor: 746, non-nucleoside reverse transcriptase inhibitor: 1452, InSTI: 3281)
- 1429 switching from a non-InSTI to an InSTI (elvitegravir/cobicistat: 1120, dolutegravir: 174, bictegravir: 129)



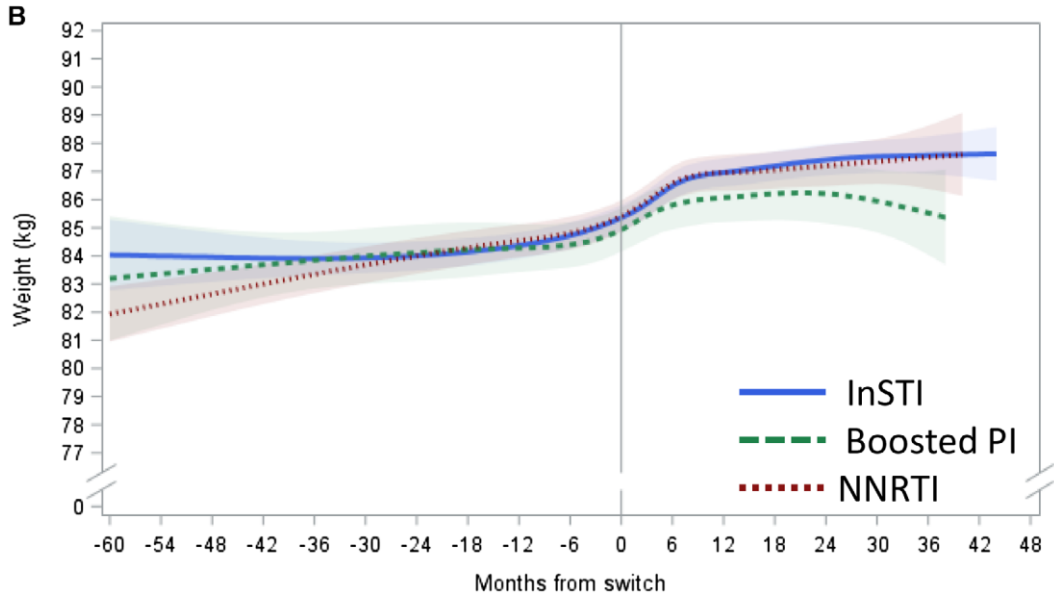


Table 2. Estimated rates of change in weight[a] before and after switch from TDF to TAF

	On TDF 60 to 0 months kg/year (95% CI)	On TAF 0 to 9 months kg/year (95% CI)	On TAF 9+ months kg/year (95% CI)
Maintained all other ARVs			
Overall	0.48 (0.37, 0.59)	2.43 (2.15, 2.71)	0.24 (0.07, 0.41)
NNRTI	0.66 (0.51, 0.81)	2.25 (1.78, 2.71)	0.20 (−0.14, 0.54)
Boosted PI	0.31 (−0.02, 0.64)	1.98 (1.13, 2.83)	−0.11 (−0.57, 0.35)
InSTI	0.42 (0.26, 0.59)	2.64 (2.26, 3.01)	0.29 (0.08, 0.51)
Maintained an InSTI			
Elvitegravir/cobicistat	0.71 (0.53, 0.90)	2.51 (2.05, 2.96)	0.36 (0.12, 0.61)
Dolutegravir	0.73 (0.34, 1.11)	2.38 (1.64, 3.13)	−0.18 (−0.64, 0.28)
Raltegravir	−0.44 (−0.79, −0.08)	1.80 (0.57, 3.03)	0.63 (−0.20, 1.46)
Switched from non-InSTI to InSTI			
Elvitegravir/cobicistat	0.24 (0.04, 0.43)	2.55 (1.86, 3.24)	0.26 (−0.10, 0.61)
Dolutegravir	0.22 (−0.08, 0.52)	3.09 (1.26, 4.93)	−0.23 (−1.62, 1.16)
Bictegravir[b]	0.01 (−0.38, 0.39)	4.47 (0.81, 8.13)	−9.97 (−23.79, 3.85)

- An early and pronounced weight gain was observed shortly after a switch from TDF to TAF, both in PLWH who maintained all other ARVs and in those who also switched to an InSTI-based regimen, followed by a flattening of the curve after nine months

Mallon PWG et al. *Journal of the International AIDS Society* 2021, **24**:e25702
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25702/full | https://doi.org/10.1002/jia2.25702

- Weight gain & INSTI
- Weight gain & TAF
- **Diabete & INSTI/TAF**
- **Rischio cardiovascolare & INSTI**
- **Popolazioni speciali ed aumento di peso (anziani, giovani, donne in gravidanza)**

J Acquir Immune Defic Syndr • Volume 86, Number 5, April 15, 2021

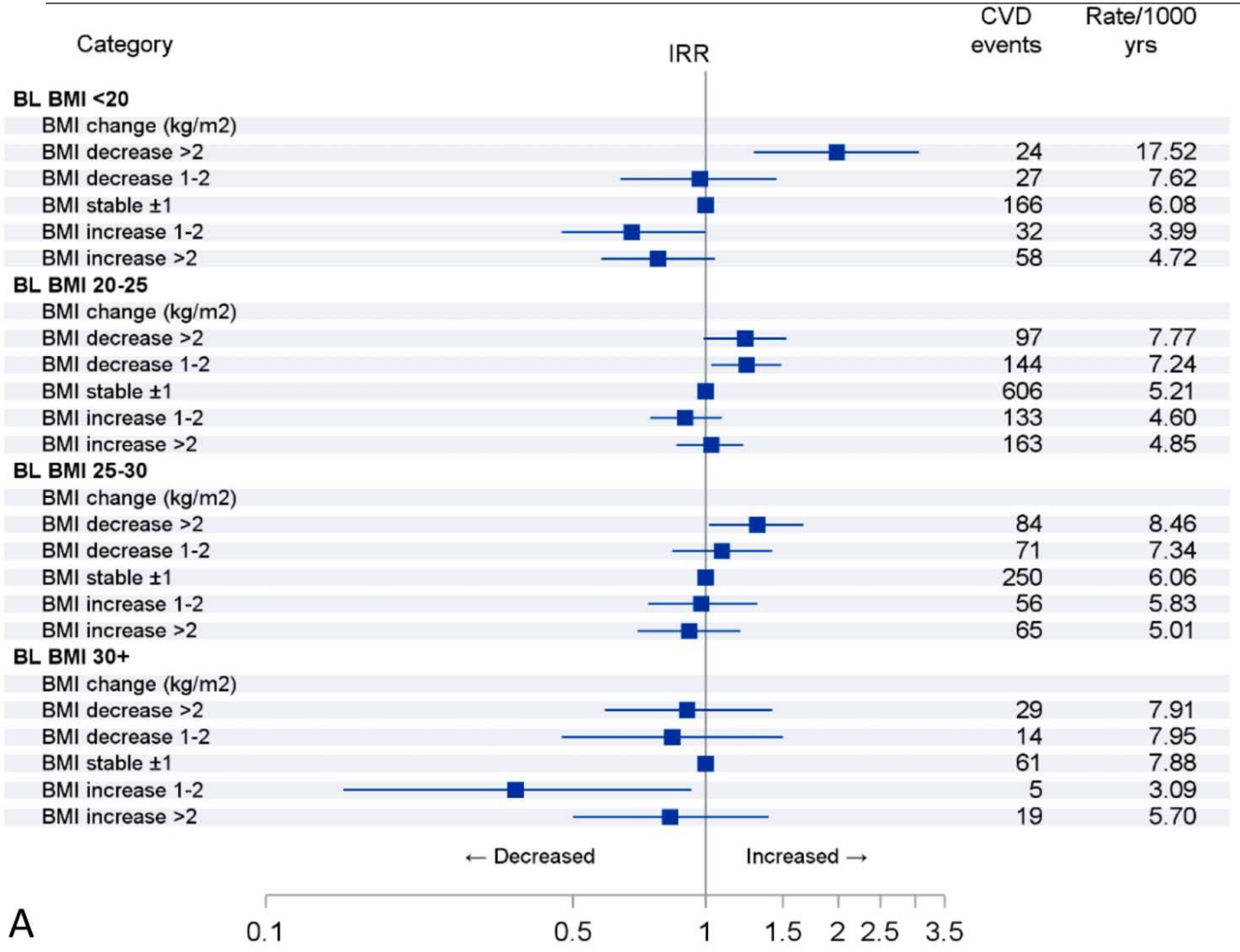
CLINICAL SCIENCE

Effect of Changes in Body Mass Index on the Risk of Cardiovascular Disease and Diabetes Mellitus in HIV-Positive Individuals: Results From the D:A:D Study

Kathy Petoumenos, PhD,[a] Locadiah Kuwanda, MMed Statistics,[a] Lene Ryom, MD, PhD,[b] Amanda Mocroft, PhD,[c] Peter Reiss, MD, PhD,[d,e] Stephane De Wit, MD,[f] Christian Pradier, MD,[g] Fabrice Bonnet, MD, PhD,[h] Andrew Phillips, PhD,[c] Camilla I. Hatleberg, MD, PhD,[b] Antonella d'Arminio Monforte, MD, PhD,[i] Rainer Weber, MD, DTM&H,[j] Caroline A. Sabin, PhD,[c] Jens Lundgren, MD, DMSc, PhD,[b] and Matthew G. Law, PhD,[a] for the D:A:D Study Group

NAIVE e EXPERIENCED
43,805 pazienti inclusi
365,287 PYFU

Background: Weight gain and diabetes, dangerous liaisons



Petoumenos et al., J Acquir Immune Defic Syndr. 2021;86(5):579-586

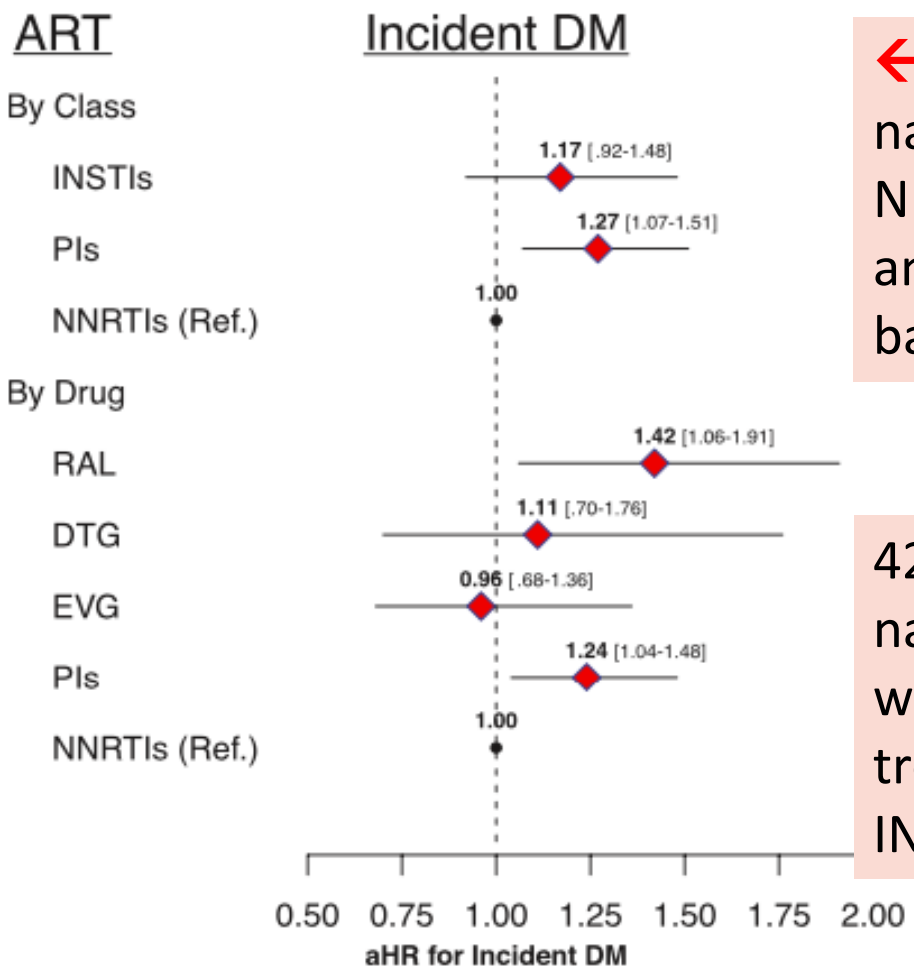
INSULIN RESISTANCE and INSTIs

Improvement: SPIRAL (Calza et al. J Antimicrob Chemother 2019; 74:731 – 738): TANGO (van Wyk et al. JAIDS 2021 Jun 1; 87(2): 794–800.

Indifferent: pooled analysis SPRING-2, STRIVING, SWORD-1 and SWORD- 2 (Lo J, Oyee J, Crawford M, et al. Dolutegravir and insulin resistance. CROI, 2019)

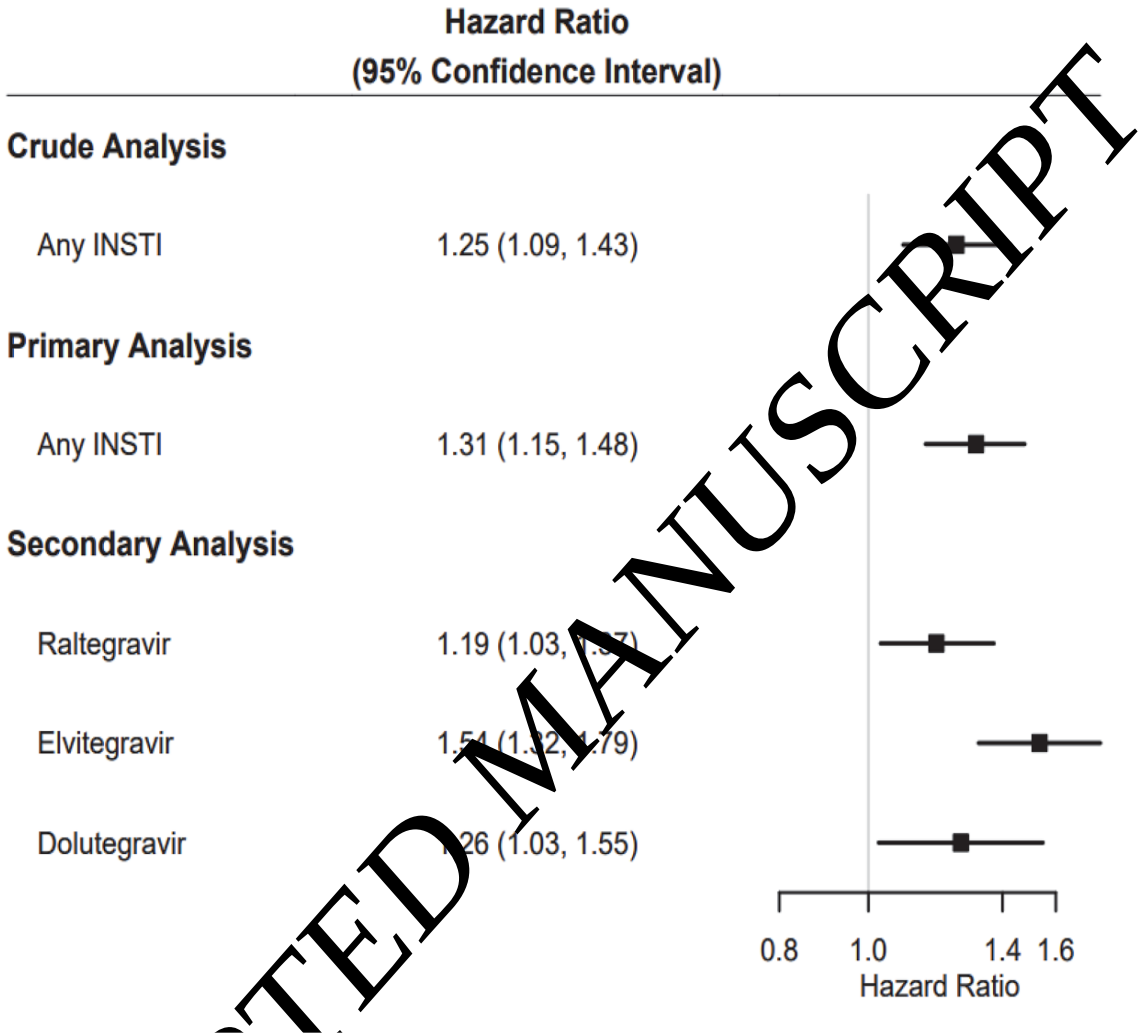
Worsening: Dirajlal-Fargo at al. OFID 2016; 3:ofw174; Gianotti et al. J Med Virol 2019; 91:1937 – 1943.

ART class and incident dabetes



← 22,884 cART-naive PWH: 47% NNRTI-, 30% PI-, and 23% INSTI-based cART

42,382 cART-naive PWH: 54% were treated with INSTI →



Rebeiro et al. Clin Infect Dis. 2021 Oct 5;73(7):e2234-e2242.

O'Halloran et al. Clin Infect Dis. 2022 Online ahead of print.

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14° CONGRESSO NAZIONALE

Incident diabetes in course of antiretroviral therapy

Lucia Taramasso*, Nicola Squillace, Elena Ricci, Barbara Menzaghi, Giancarlo Orofino, Giuseppe Vittorio De Socio, Chiara Molteni, Canio Vito Martinelli, Giordano Madeddu, Francesca Vichi, Laura Valsecchi, Benedetto Maurizio Celesia, Paolo Maggi, Federico Conti, Giovanni Francesco Pellicanò, Antonio Cascio, Eleonora Sarchi, Roberto Gulminetti, Giustino Parruti, Leonardo Calza, Katia Falasca, Antonio Di Biagio and Paolo Bonfanti on behalf of CISAI Study Group.

Infectious Diseases Clinic, IRCCS Policlinico San Martino Hospital, Genoa

4,111 PWH, 120 incident cases of DM	Hazard Ratio	Lower 95% CI	Higher 95% CI	P
Age (by 1 year)	1.04	1.02	1.07	0.0002
Risk factor for HIV acquisition (ref. MSM)				
Heterosexual	1.50	0.87	2.59	0.14
IDU	2.11	1.19	3.74	0.01
Other/Unknown	1.93	0.98	3.78	0.06
ART duration (by 1 year)	1.02	0.99	1.05	0.26
Detectable HIVRNA (ref. Undetectable)	1.91	1.26	2.91	0.002
Statin use (ref. no use)	1.81	1.09	3.01	0.02
Weight at T0 (by 1 Kg)	1.04	1.02	1.05	<0.0001
Study cohort (ref. dolutegravir)				
atazanavir	1.24	0.61	2.52	0.56
darunavir	1.15	0.64	2.07	0.64
rilpivirine	1.10	0.42	2.87	0.85
raltegravir	1.97	1.14	3.41	0.01
elvitegravir	1.79	0.87	3.69	0.12
bictegravir	1.43	0.62	3.32	0.40

Variables excluded by the backward selection methods because of p value >0.3 at univariate analysis: weight gain, sex, ethnicity, CDC stage, CD4 cell count, calendar year of enrollment, triglycerides/HDL ratio.

During the follow up, 120 incident cases of DM occurred, with an estimated incidence of 1.26 cases/100 person years-follow up (95% CI 1.05-1.50).

The mean weight increase was 0.9 and 1.4 Kg at 1- and 2-year follow-up (n=2,988 and n=1,711), different across ART (Table).

Mediation analysis

For each Kg of baseline weight the DM risk increased by 4%.

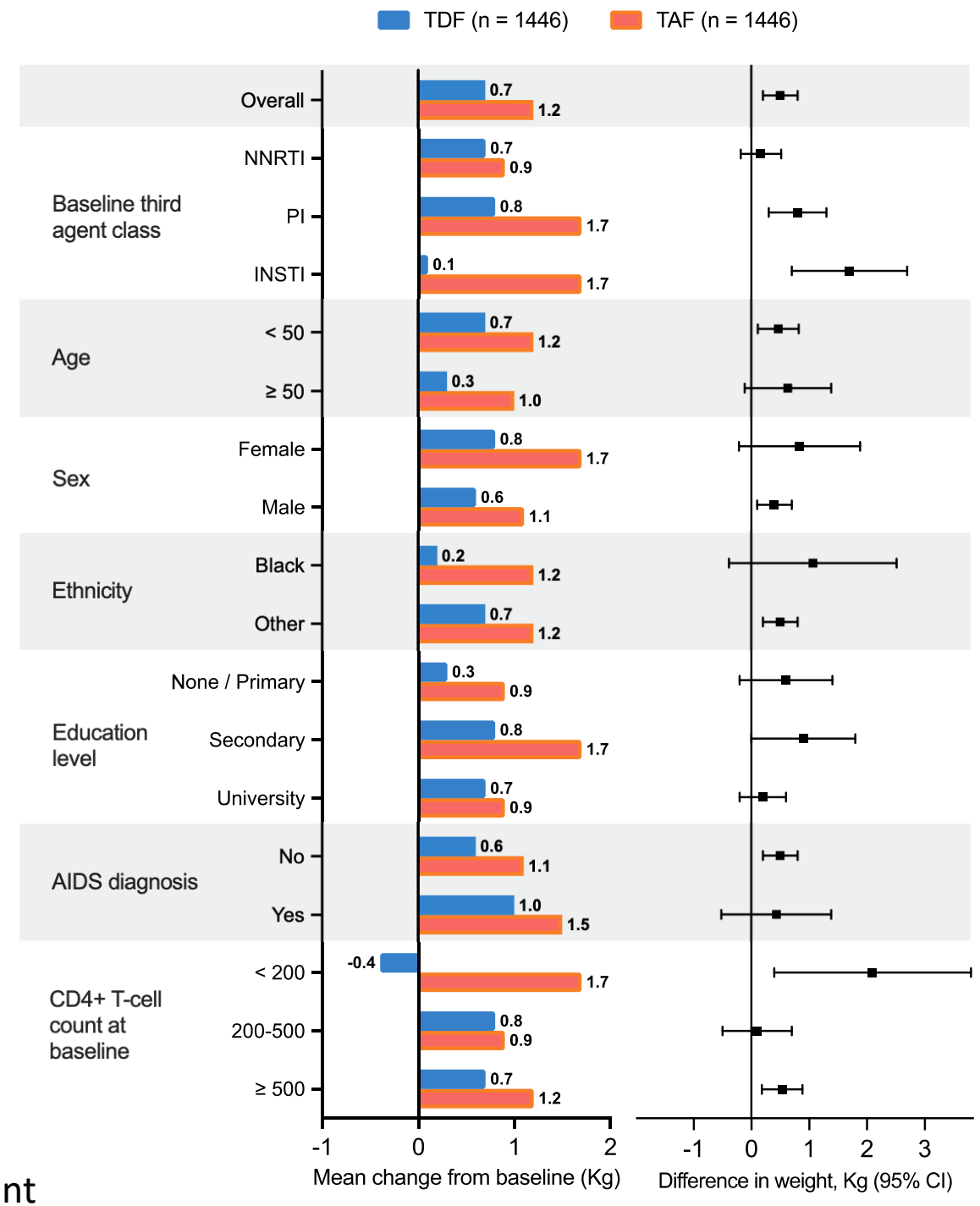
The mediation analysis investigated the relationship between basal weight and diabetes, weight gain and diabetes, and basal weight and weight gain, concluding that the true effect is that of basal weight.

Clinical Infectious Diseases

MAJOR ARTICLE

Metabolic-Related Outcomes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Adults With Human Immunodeficiency Virus (HIV): A Multicenter Prospective Cohort Study

- Virologically suppressed PWH, receiving TDF for more than 12 months who either switched to TAF or maintained TDF, with no changes in the core agent.
- 1,446 participants in each group (38 years, 85% male)
- In TAF mean weight increase of +0.5 kg at 144 weeks over those who maintained TDF
- No difference in the occurrence of overweight, obesity, hypertension, diabetes, or lipid-lowering drug use.



Martinez-Sanz et al., Clin Infect Dis. 2022 Jul 29; online ahead of print

Effects of antiretroviral combination therapies F/TAF, E/C/F/TAF and R/F/TAF on insulin resistance in healthy volunteers: the TAF-IR Study

Table 2. Changes in insulin sensitivity and lipid metabolism parameters after 14-day antiretroviral treatment[a]

	F/TAF (*n*=9)			E/C/F/TAF (*n*=10)			R/F/TAF (*n*=9)		
Parameter	Day 1	Day 14	*P*-value	Day 1	Day 14	*P*-value	Day 1	Day 14	*P*-value
Insulin sensitivity[b]									
M_{BW} [mg glucose/(min×kg)]	11.43 (3.23)	11.42 (3.04)	0.4947	10.95 (4.26)	10.04 (2.49)	0.2957	13.01 (4.11)	11.03 (1.96)	0.1284
$M_{BW/I}$ [mg glucose/(min×kg×μIU)]	0.08 (0.03)	0.07 (0.02)	0.2524	0.08 (0.03)	0.07 (0.02)	0.6401	0.09 (0.04)	0.07 (0.02)	0.2634
M_{CR} [dl/(min×kg)]	0.13 (0.03)	0.13 (0.03)	0.9940	0.12 (0.05)	0.11 (0.03)	0.6253	0.15 (0.04)	0.12 (0.02)	0.2864
Lipid metabolism[c]									
Total cholesterol, mg/dl	147.0 (136–175)	134.0 (116–178)	0.8037	172.0 (156–208)	180.5 (148–201)	0.2754	146 (140–155)	161 (157–167)	**0.0370**
Triglycerides, mg/dl	85 (76–98)	88 (60–90)	0.2903	83 (68–155)	122.5 (81–150)	0.5952	69 (50–87)	93 (80–98)	0.4846
LDL-cholesterol, mg/dl	99 (92–111)	86.0 (72–103)	0.8864	109.5 (88–138)	120 (89–137)	0.2422	88 (83–91)	108 (86–110)	**0.0108**
HDL-cholesterol, mg/dl	53 (47–55)	49 (46–51)	0.9335	54.5 (49–74)	55 (50–72)	0.9696	58 (48–64)	58 (53–73)	0.5704

Short-term treatment for F/TAF, E/C/F/TAF or R/F/TAF did not increase IR in healthy male volunteers.

Spinner et al., Antivir Ther. 2018;23(7):629-632

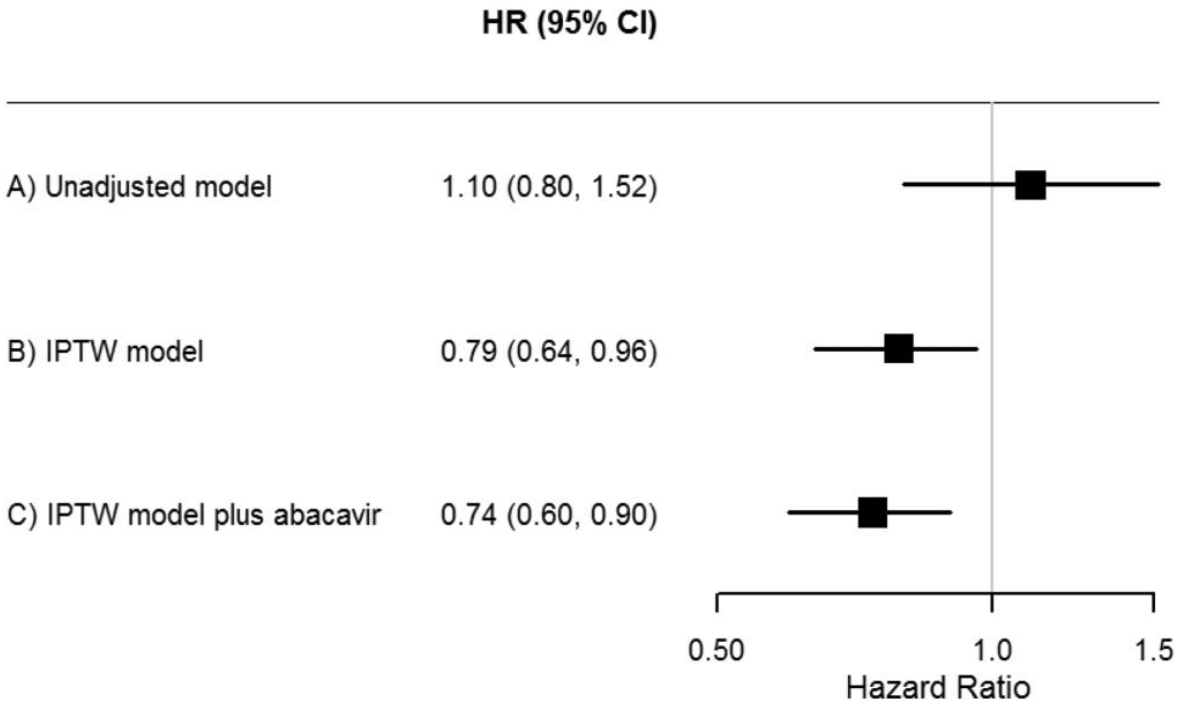
- Weight gain & INSTI
- Weight gain & TAF
- Diabete & INSTI/TAF
- **Rischio cardiovascolare & INSTI**
- **Popolazioni speciali ed aumento di peso (anziani, giovani, donne in gravidanza)**

Integrase Strand Transfer Inhibitors Are Associated With Lower Risk of Incident Cardiovascular Disease in People Living With HIV

IBMMarketScan databases for U.S. commercially insured and Medicaid covered adults

20,242 new ART initiators, (25% INSTI) between January 1, 2008 and December 30, 2015.

Major adverse cardiac event (MACE), a composite of **acute MI, ischemic stroke, coronary artery bypass grafting, and percutaneous coronary intervention** was the primary outcome.



In this cohort, INSTI-based regimens were associated with a 21% decreased risk of incident cardiovascular disease.

O'Halloran et al., JAIDS 2020; 84(4):396-399

J Acquir Immune Defic Syndr • Volume 86, Number 5, April 15, 2021

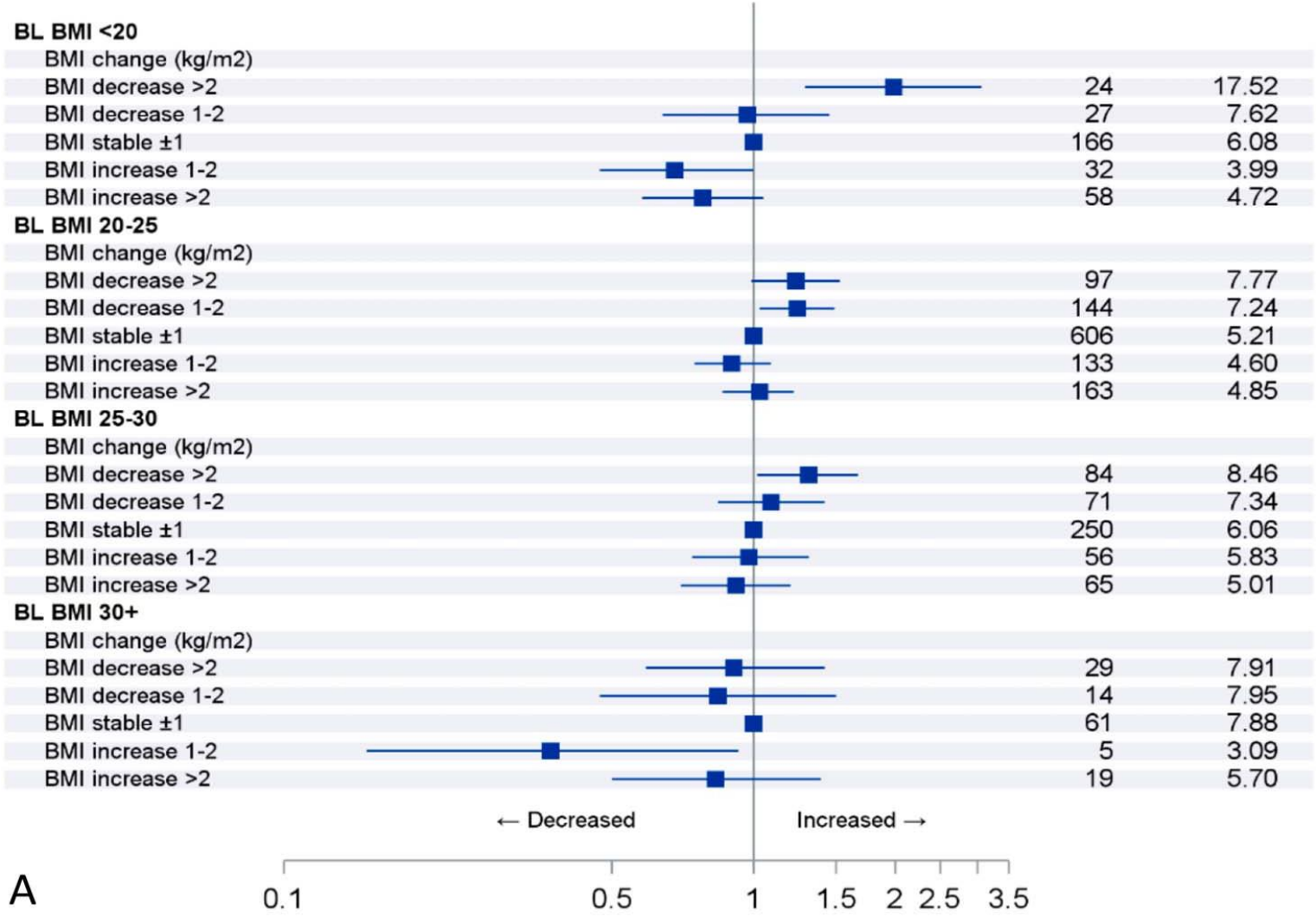
CLINICAL SCIENCE

Effect of Changes in Body Mass Index on the Risk of Cardiovascular Disease and Diabetes Mellitus in HIV-Positive Individuals: Results From the D:A:D Study

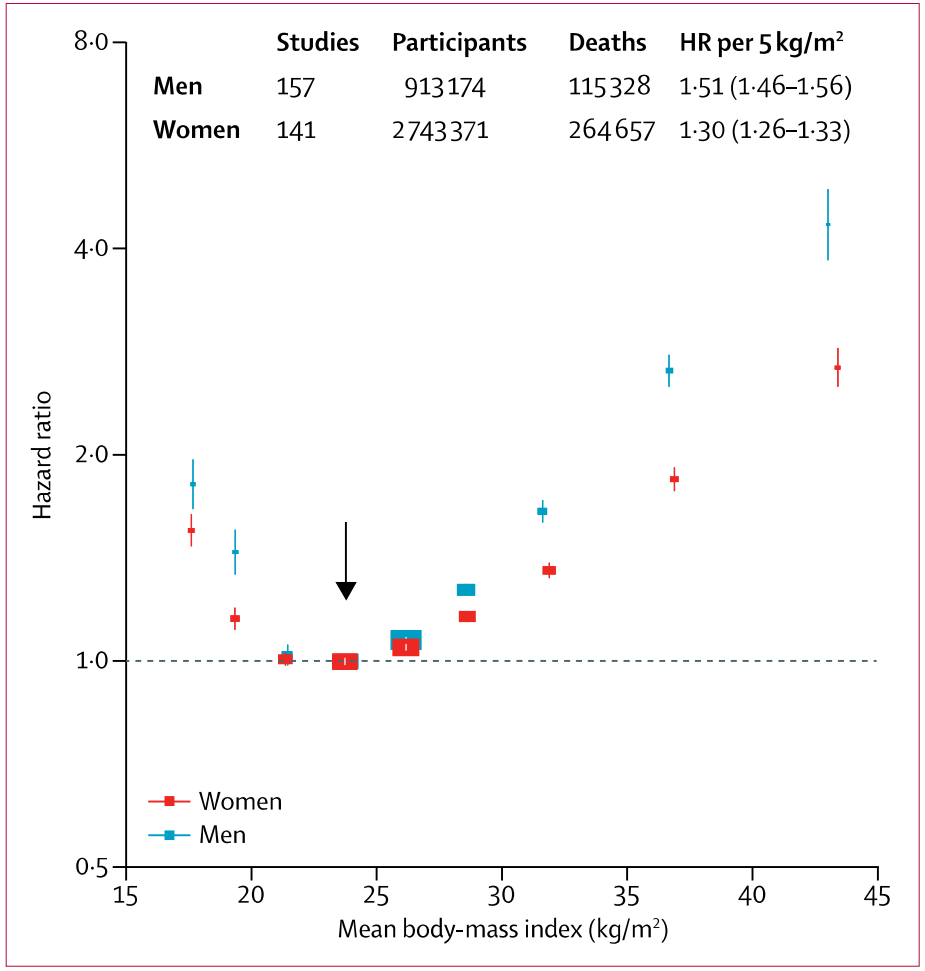
Kathy Petoumenos, PhD,[a] Locadiah Kuwanda, MMed Statistics,[a] Lene Ryom, MD, PhD,[b] Amanda Mocroft, PhD,[c] Peter Reiss, MD, PhD,[d,e] Stephane De Wit, MD,[f] Christian Pradier, MD,[g] Fabrice Bonnet, MD, PhD,[h] Andrew Phillips, PhD,[c] Camilla I. Hatleberg, MD, PhD,[b] Antonella d'Arminio Monforte, MD, PhD,[i] Rainer Weber, MD, DTM&H,[j] Caroline A. Sabin, PhD,[c] Jens Lundgren, MD, DMSc, PhD,[b] and Matthew G. Law, PhD,[a] for the D:A:D Study Group

NAIVE e EXPERIENCED
43,805 pazienti inclusi
365,287 PYFU

Effect of changes in BMI (kg/m$_2$) on the risk of CVD in PLWH



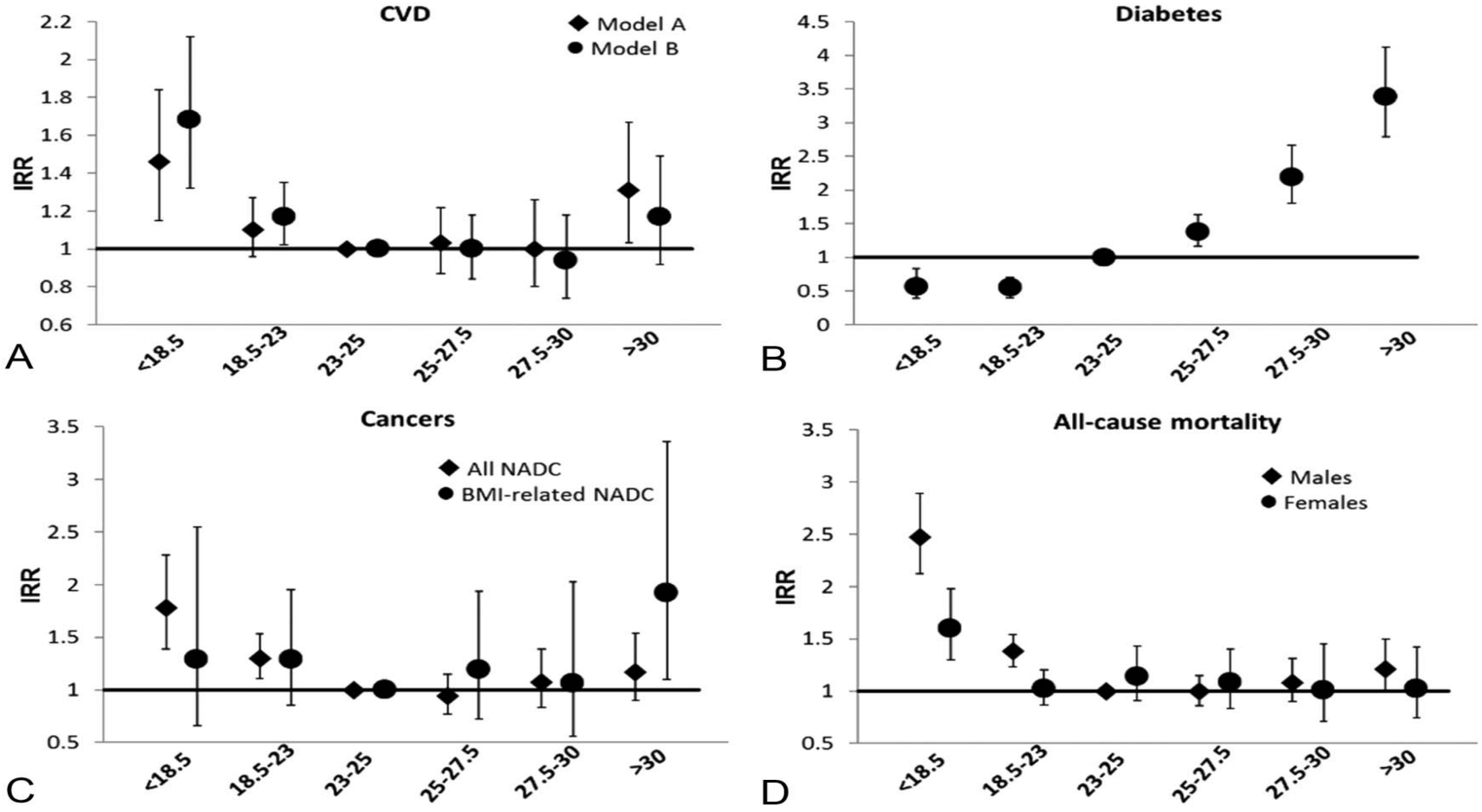
Association of BMI with all-cause mortality, by sex, general population



Petoumenos K et al., JAIDS. 2021; 86(5):579-586. The Global BMI Mortality Collaboration. Lancet. 2016; 388(10046):776-86.

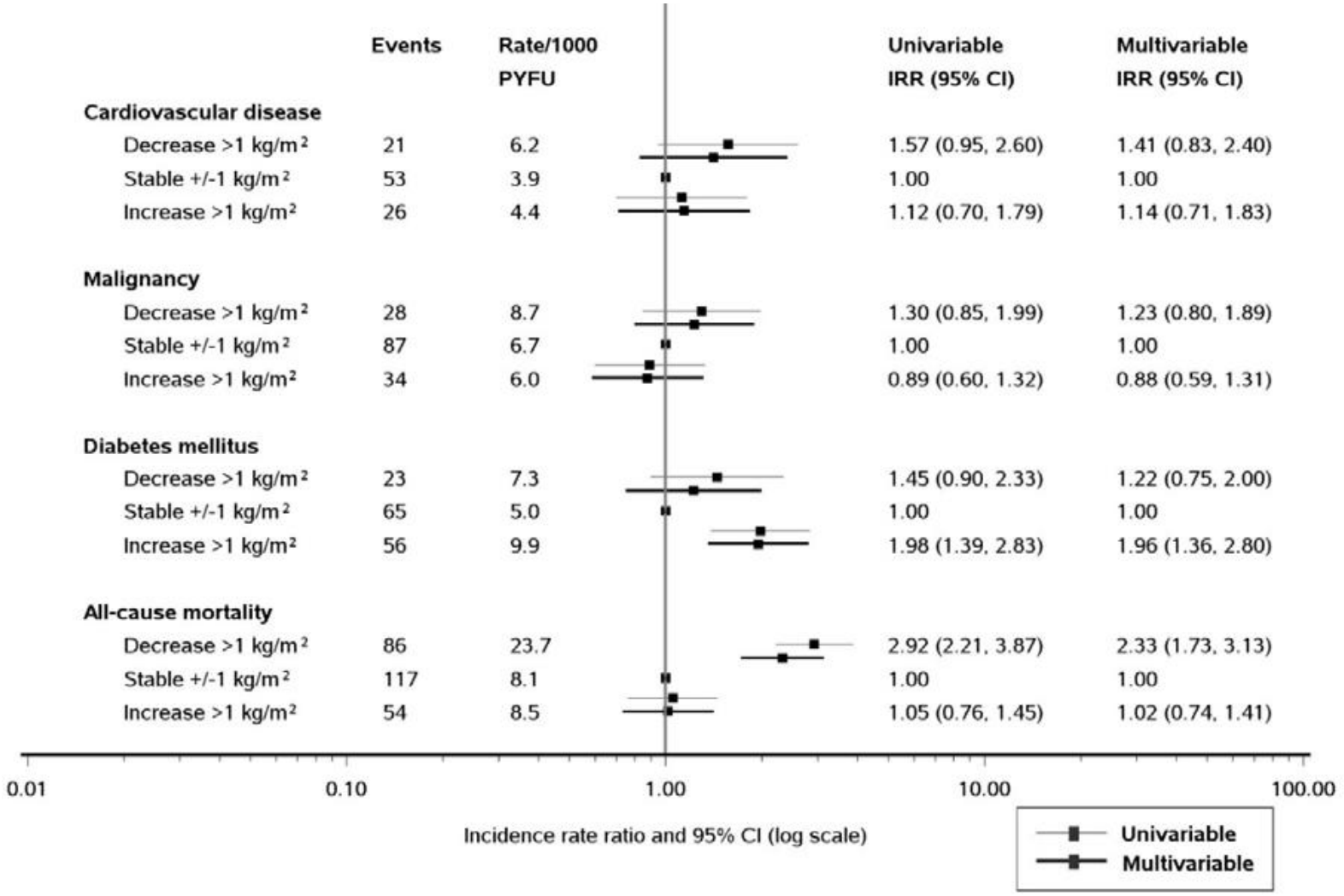
Body Mass Index and the Risk of Serious Non-AIDS Events and All-Cause Mortality in Treated HIV-Positive Individuals: D:A:D Cohort Analysis

Amit C. Achhra, MBBS, MPH, PhD,† Caroline Sabin, PhD,‡ Lene Ryom, MD, PhD,§ Camilla Hatleberg, MD, PhD,§ Monforte Antonella d'Aminio, MD, PhD,‖ Stephane de Wit, MD,¶ Andrew Phillips, PhD,‡ Christian Pradier, MD,# Rainer Weber, MD,** Peter Reiss, MD, PhD,††‡‡ Wafaa El-Sadr, MD, PhD,§§ Fabrice Bonnet, MD,‖‖ Amanda Mocroft, PhD,‡ Jens Lundgren, MD, PhD,§ and Matthew G. Law, PhD,* for the D:A:D Study Group*



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

Figure 3 Incidence rate ratios (IRRs) for clinical outcomes according to changes from baseline in BMI



- PWH who started a new ARV during 2010-2019
- 6721 PWH included; 8.4% naïve
- **>1 kg/m2 increase** was associated with increased risk of **DM** (**IRR: 1.96, 95% CI: 1.36-2.80**) and **>1 kg/m2 decrease** with increased risk of **death** (adjusted **IRR: 2.33, 95% CI: 1.73-3.13**).

AIDS, Publish Ahead of Print

- Weight gain & INSTI
- Weight gain & TAF
- Diabete & INSTI/TAF
- Rischio cardiovascolare & INSTI
- **Popolazioni speciali ed aumento di peso (anziani, giovani, donne in gravidanza)**

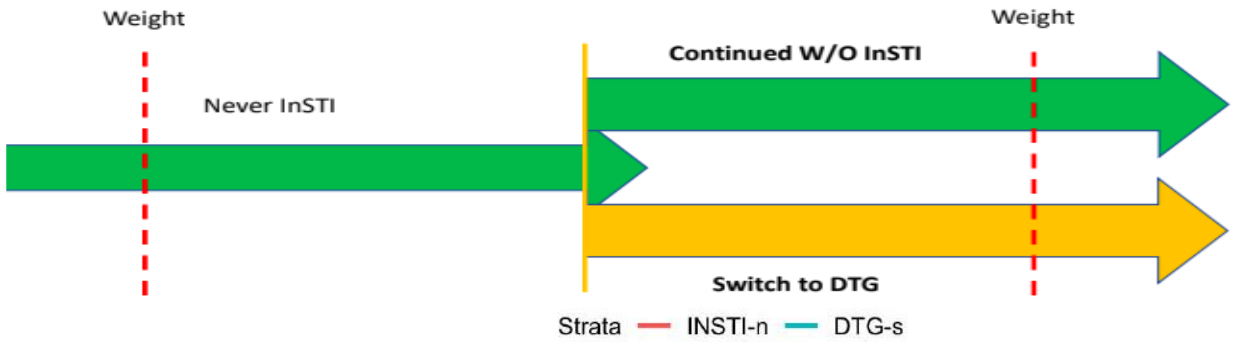
DTG prescribing patterns in PLWH ≥ 65 years: the impact of 2DR and weight gain

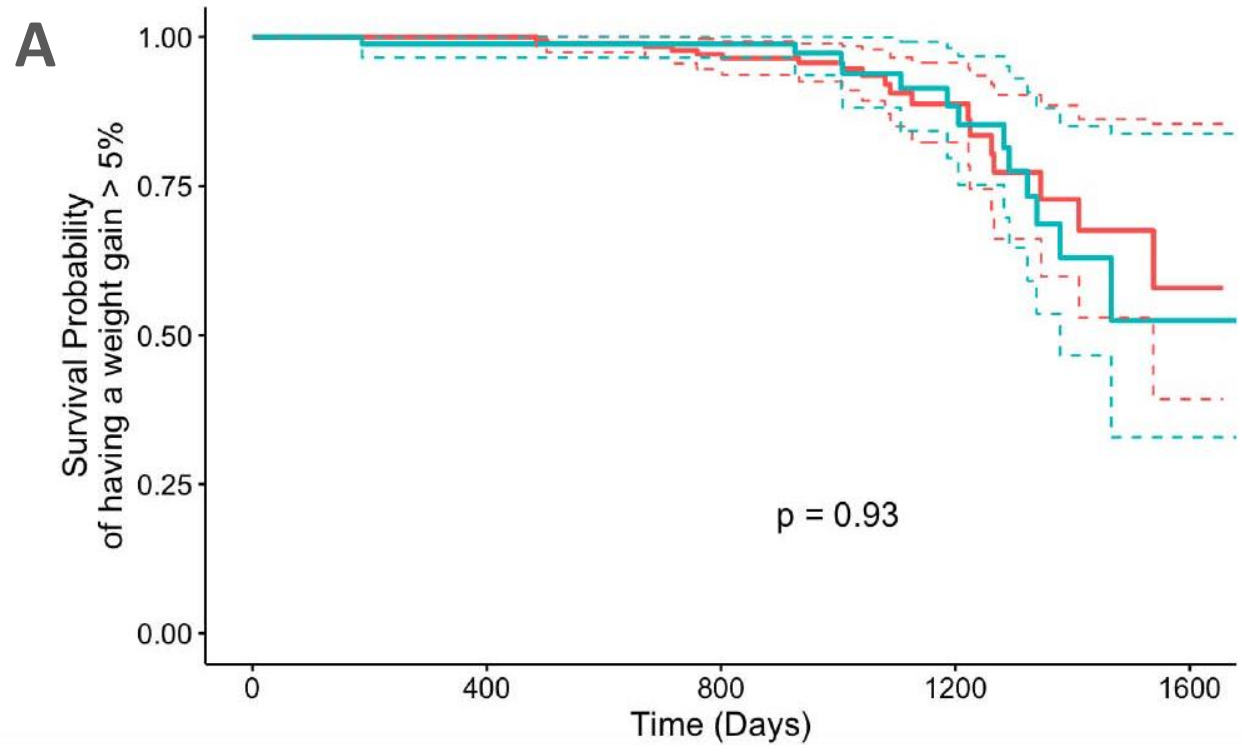
679

Guaraldi G[1], Calza S[2], Calcagno A[3], Milic J[1], Focà E[2], Rota M[2], Celotti A[2], Celesia BM[4], Piconi S[5], De Socio GV[6], Cattelan AM[7], Orofino G[8], Riva A[9], Nozza S[10], Di Perri G[3]

[1] University of Modena and Reggio Emilia, Italy; [2] University of Brescia, Italy; [3] University of Torino, Italy; [4]ARNAS 'Garibaldi' UOC Malattie Infettive Catania, Italy; [5] First Division of Infectious Diseases Unit, University of Milan, Ospedale L. Sacco,, Italy; [6] Department of Infectious Diseases, Azienda Ospedaliero-Universitaria di Perugia, Italy; [7] Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera-Universitaria di Padova, Italy; [8] Unit of Infectious Diseases, Division A, Ospedale Amedeo di Savoia, Turin, Italy; [9] Third Division of Infectious Diseases, University of Milan, Ospedale L. Sacco, Milano, Italy; [10] Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy

«Out of 568 PLWH (16.9% females), 141 were in the DTG and 427 in the INSTI-n group. After an average follow up of 2.6 (±0.8) years, we did not observe significant difference in CD4 (673 vs 663 cell/microL, p=0.8) or virologic suppression (96.3% vs. 96.2%, p=0.99).»





microorganisms

MDPI

Article

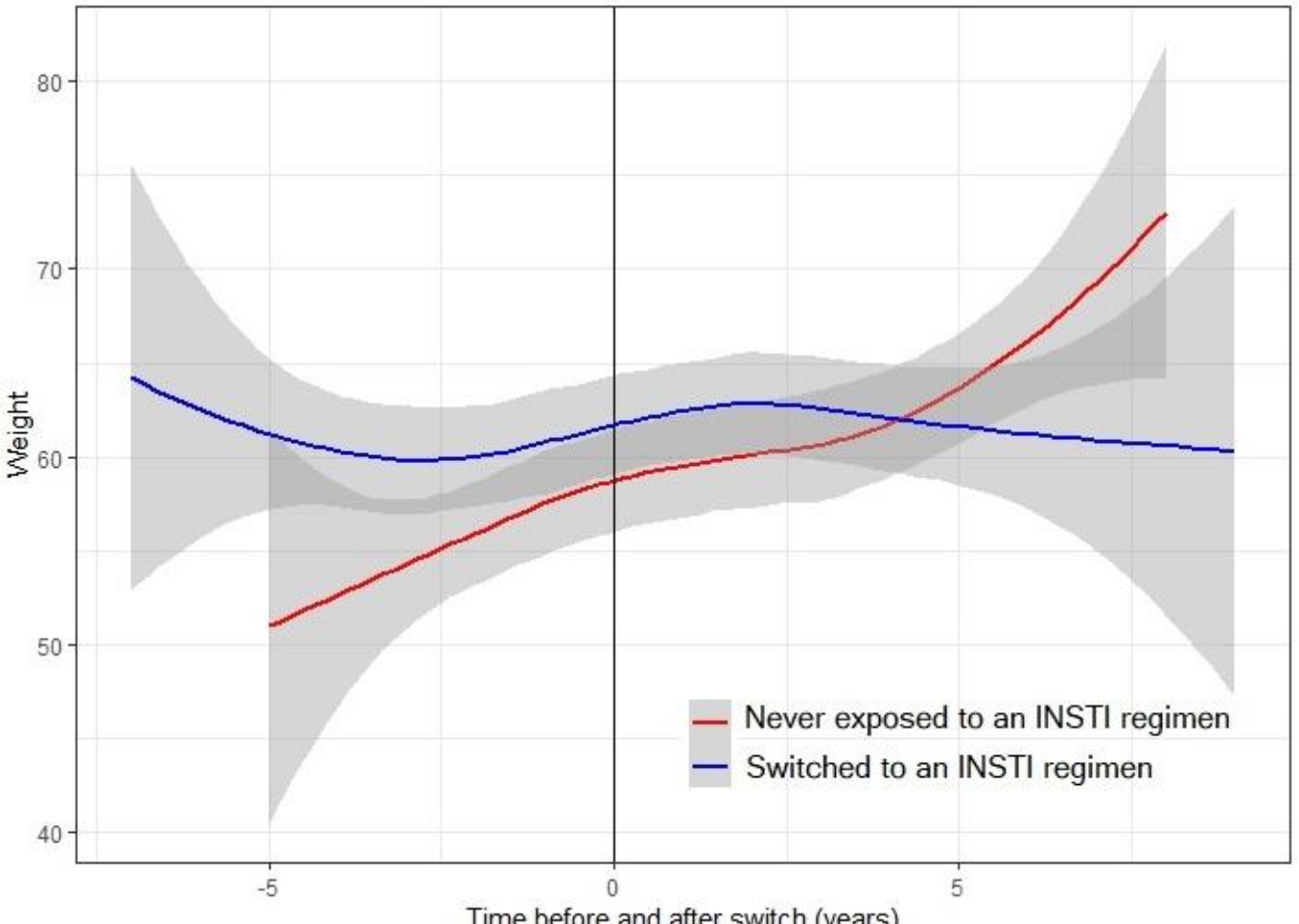
Switching to Integrase Inhibitors Unlinked to Weight Increase in Perinatally HIV-Infected Young Adults and Adolescents: A 10-Year Observational Study

Lucia Taramasso [1,2,†], Antonio Di Biagio [2,*,†], Francesca Bovis [3], Federica Forlanini [4], Elena Albani [4], Rebecka Papaioannu [2] and Vania Giacomet [4]

Microorganisms **2020**, *8*, 864; doi:10.3390/microorganisms8060864

Weight trend during the 10 year follow up in people perinatally infected with HIV, treated with or without integrase strand transfer inhibitors (INSTI)-based antiretroviral regimens.

Participants on the INSTI regimen gained slightly less weight compared to the non-INSTI group after T0 (-0.09 kg/year), but this difference was not significant (p for interaction between time and treatment regimen=0.868).



- The 45 INSTI-treated patients gained slightly more weight after switching to an INSTI regimen compared to the time before the switch (+0.28 kg/year. 95%CI -0.29;0.85), but this weight gain was not significant (p=0.337).
- We did not find a diffence in weight gain in patients switched for virologic failure (HIV RNA >50 copies/mL, N=12) compared to people who switched for other reasons (-0.59 kg/year, [95% CI -1.77;0.59], p=0.318).

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Weight gain during pregnancy among women initiating dolutegravir in Botswana

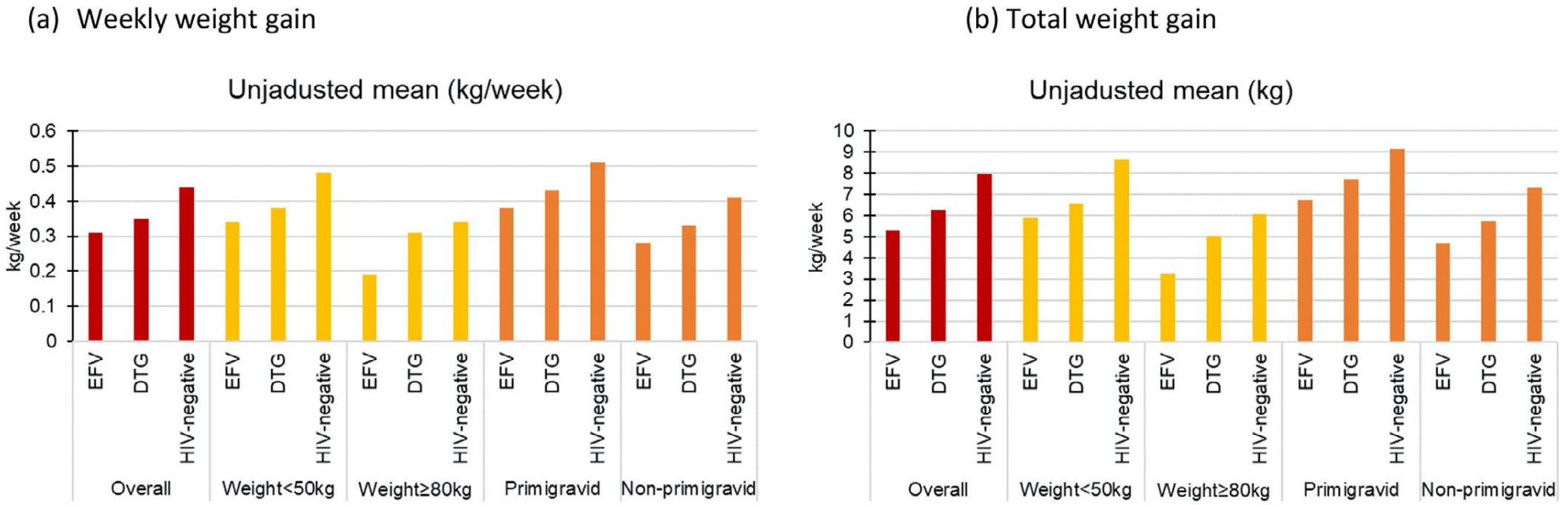
Ellen C. Caniglia[a,b,*], Roger Shapiro[b,c], Modiegi Diseko[c], Blair J. Wylie[d], Chloe Zera[d], Sonya Davey[e], Arielle Isaacson[c], Gloria Mayondi[c], Judith Mabuta[c], Rebecca Luckett[d], Joseph Makhema[c], Mompati Mmalane[c], Shahin Lockman[c,f], Rebecca Zash[c,d]

The Tsepamo Study captured data at delivery sites in Botswana from 2014 to 2019.

HIV-positive women initiating DTG or EFV-based ART and HIV-uninfected women

Of 28,686 HIV-positive women included in Tsepamo surveillance, 3262 (11%) initiated ART between conception and 17 weeks gesta- tion. Of these, 1464 initiated DTG (45%), 1683 (52%) initiated EFV, and 115 (4%) initiated other ART or an unknown regimen.

Were evaluated: weekly weight gain, total 18-week weight gain, excess weight gain (>0.59 kg/week), insufficient weight gain (<0.18 kg/week), and weight loss between 18±2 and 36±2 weeks gestation



Compared with EFV, mean weekly weight gain between 18 and 36 weeks gestation was 0.05 (95% CI 0.03, 0.07) kg/week higher for women initiating DTG and 0.12 (0.10, 0.14) kg/week higher for HIV-uninfected women.

Mean 18-week weight gain was 1.05 (95% CI 0.61, 1.49) kg higher for women initiating DTG and 2.31 (1.85, 2.77) kg higher for HIV-uninfected women, compared with EFV.

Women initiating DTG were more likely to gain excess weight but less likely to gain insufficient weight or lose weight than women initiating EFV.

defined by baseline weight in pregnancy and gravidity.

Clinical Infectious Diseases

MAJOR ARTICLE

CID; 2022 Sep 10; online ahead of print

The Effect of Antiretroviral Therapy for the Treatment of Human Immunodeficiency Virus (HIV)-1 in Pregnancy on Gestational Weight Gain

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- 303 pregnant women were included in the analysis.
- 53% of the entire cohort had initiated ART before pregnancy
- Excess gestational weight gain occurred in 29% of the cohort.
- Compared with non–INSTI or TAF–exposed women, receipt of INSTI+TAF showed a 1.7-fold increased RR of excess gestational weight gain (95% CI: 1.18–2.68; $P < .01$)
- Women who received TDF had a 0.64-fold decreased RR (95% CI: .41–.99; $P = .047$) of excess gestational weight gain.
- **INSTI alone was not significantly associated with excess weight gain in this population. The effect of TAF without INSTI could not be inferred from our data. There was no difference in neonatal, obstetric, or maternal outcomes between the groups.**

Conclusions. Pregnant women receiving ART with a combined regimen of INSTI and TAF have increased risk of excess gesta- tional weight gain.

Table 5 Weight gain in pregnant women with INSTIs

Study	Study design	Arms of trial/ study	Weight gain observed (kg)
Thokozile et al. [54] DolPHIN-2 South Africa, Uganda	Phase III RCT		At week 72:
		2 NRTI + DTG ($n = 125$)	+ 2.8
		2 NRTI + EFV ($n = 125$)	− 0.6
Chinula et al. [55] IMPAACT 2010 African	Phase III RCT		Weekly weight gain up to week 67:
		TAF/FTC + DTG ($n = 213$)	+ 0.38
		TDF/FTC + DTG ($n = 213$)	+ 0.32
		TDF/FTC + EFV ($n = 213$)	+ 0.29
Jao et al. [47]	Observational cohort		Weekly weight gain from week 14 to 28:
		TDF/FTC/DTG ($n = 170$)	0.3
		TDF/FTC/EFV ($n = 114$)	0.2
Caniglia et al. [46] Tsepamo cohort Botswana	Observational cohort		Weekly weight gain:
		DTG ($n = 1464$)	0.35 (+ 6.3 from 18 to 36 weeks)
		EFV ($n = 1638$)	0.31 (+ 5.3 from 18 to 36 weeks)

3TC lamuvidine, *BIC* bictegravir, *DTG* dolutegravir, *EFV* efavirenz, *FTC* emtricitabine, *INSTIs* integrase strand transfer inhibitors, *NRTI* nucleoside reverse transcriptase inhibitors, *RCT* randomised controlled trial, *TDF* tenofovir disoproxil fumarate, *TAF* tenofovir alafenamide

- Weight gain & INSTI
- Weight gain & TAF

→ associazione provata non noto meccanismo

- Diabete & INSTI/TAF

→ associazione con WG, non con INSTI (?)

- Rischio CV & INSTI

→ nessuna associazione con INSTI

- Popolazioni speciali

→ INSTI safe in anziani, giovani e gravidanza