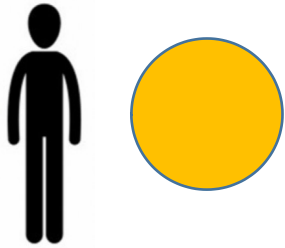


¿Tenemos que preocuparnos del aumento de peso asociado al tratamiento con inhibidores de la integrasa?

# Desafíos asociados al peso y grasa corporal en las personas con VIH

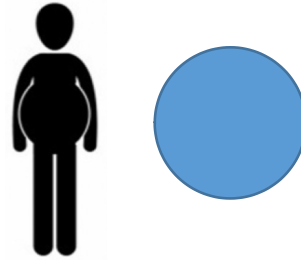
**Pérdida de peso,  
caquexia**



**1980-90**

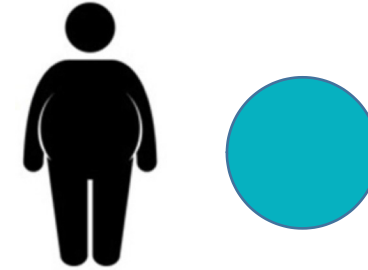
**Lipodistrofia:**

- Lipoatrofia periférica
- Obesidad central



**1990-00**

**Obesidad**



**Siglo XXI**



HIV-Wasting Syndrome



**Obesity among Patients with  
HIV: The Latest Epidemic**

USA 2004-05

Patients with HIV in the HAART era are commonly overweight and/or obese with rates like the general population.

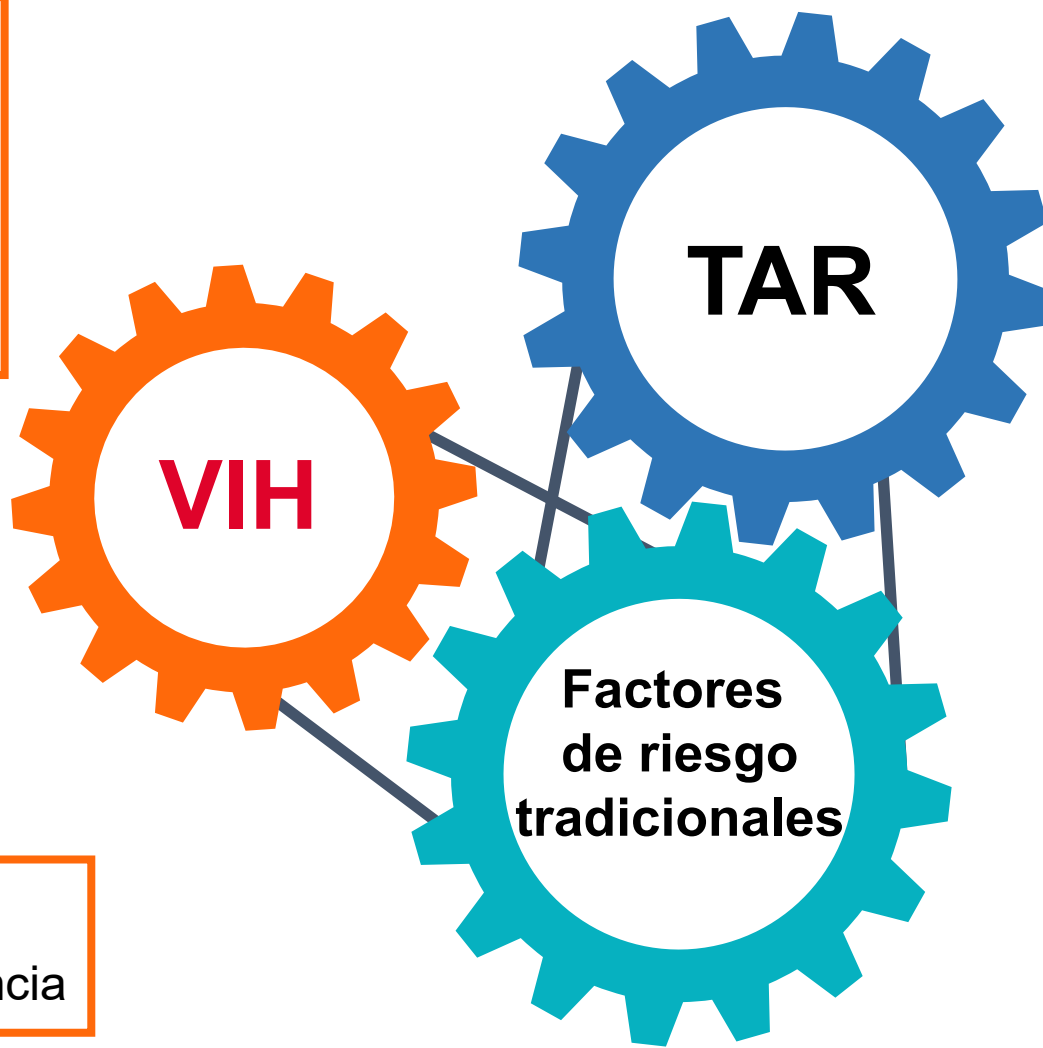
# ¿A qué se debe el aumento de peso/obesidad?

▪ **Aumento de peso =**  
Reversión de los efectos catabólicos de la infección por VIH (recuperación de la salud, retorno a la normalidad)

▪ **Mayor aumento de peso si:**

- ↓ CD4
- ↑ Carga viral
- Enf. Oportunistas
- ↓ previa de peso

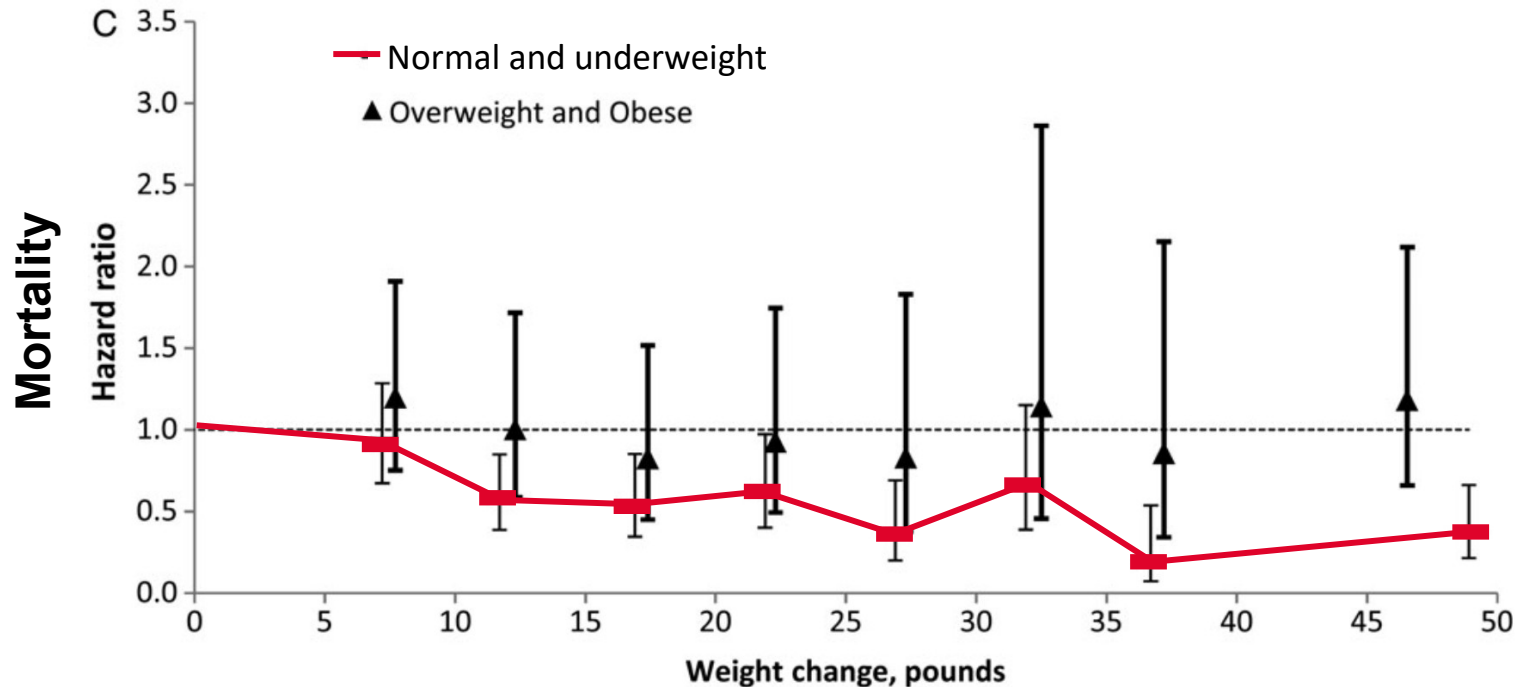
- **Aumento de peso:**
- Aumento de la supervivencia



IMC (peso/talla <sup>2</sup> )	Clasificación
< 18,50	Bajo peso
18,50 – 24,99	Normo peso
25,00 – 29,99	Sobrepeso
≥ 30,0	Obesidad

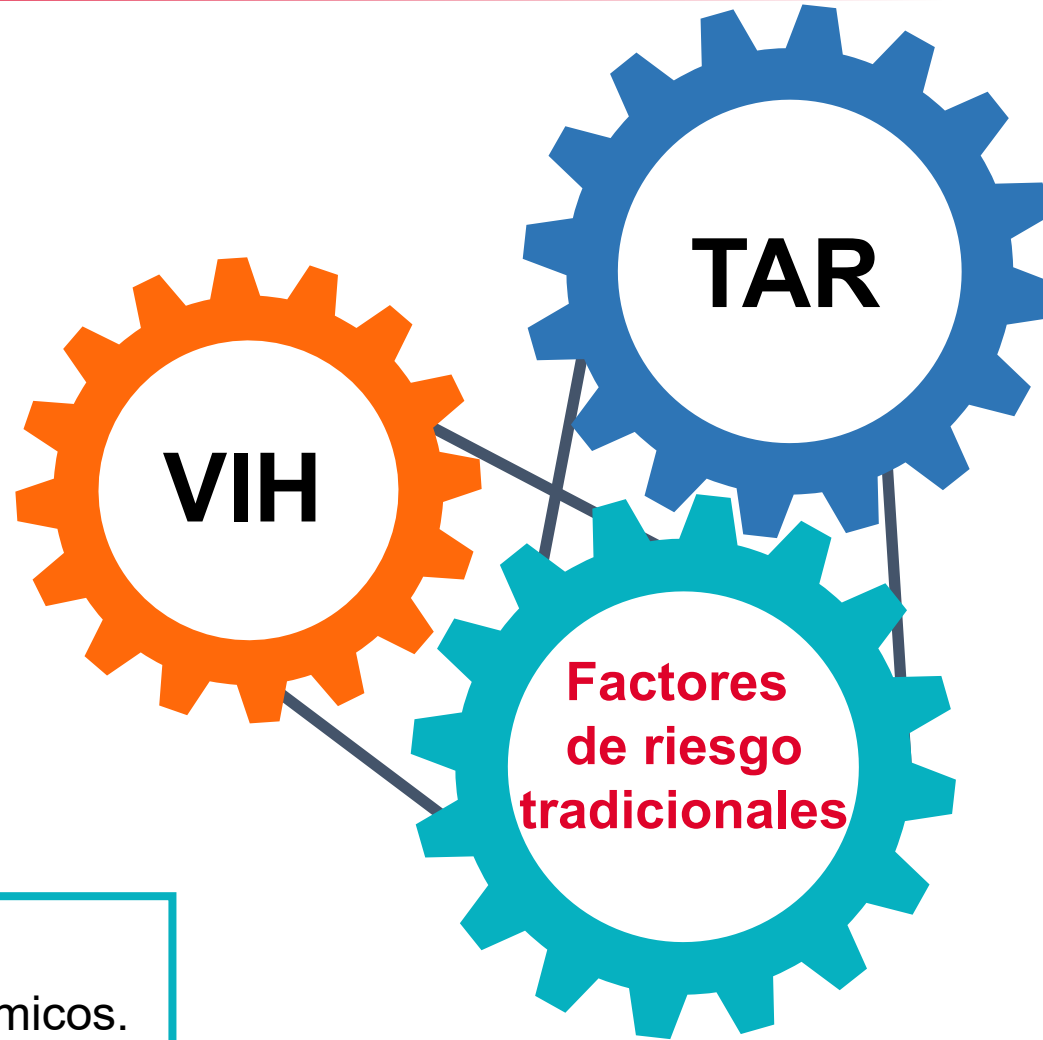
# VACS: Weight Change after Antiretroviral Therapy and Mortality

- N=4311 HIV-infected patients in VA care who initiated ART from 2000 to 2008.
- Mean age 48 yrs, men 97%, black 55%, BMI: underweight 6%, normal 52%, over 30%, obese 12.



- After 1 year of ART, median weight change was 2.7 kg: IQR−1.3 to 7.7 kg.
- During a median of 5 years of follow-up, 708 patients died.
- Weight gain after ART initiation was associated with lower mortality among underweight and normal-weight patients.
- Factors associated with weight gain included age, baseline low BMI, PI-based ART regimen, and baseline VACS Index (CD4 < 200, Hb<12).

# ¿A qué se debe el aumento de peso/obesidad?



IMC (peso/talla <sup>2</sup> )	Clasificación
< 18,50	Bajo peso
18,50 – 24,99	Normo peso
25,00 – 29,99	Sobrepeso
≥ 30,0	Obesidad

## Entorno OBESOGÉNICO:

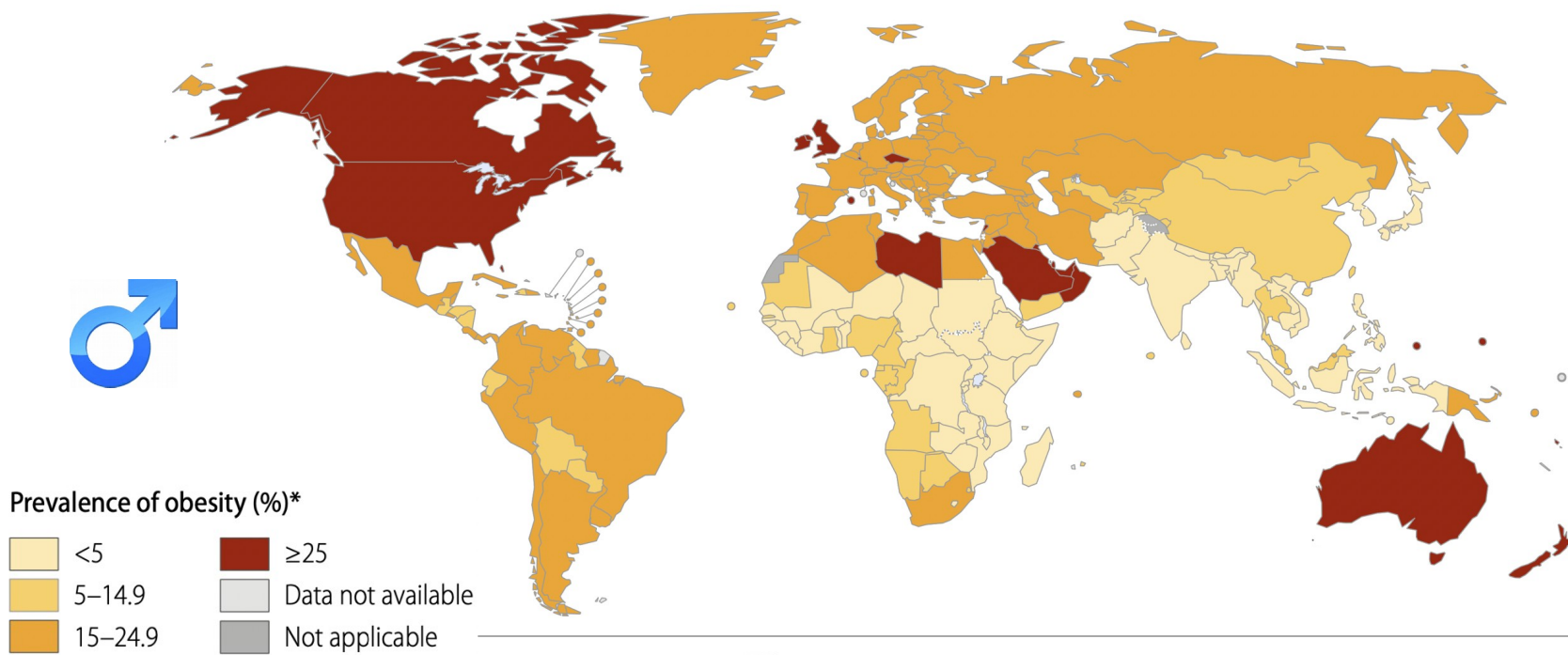
- Fc. socioculturales y económicos.
- Actitudes respecto a dieta saludable, nutrición, ejercicio.
- Hábitos: Internet, tabaco, alcohol...

Sobrepeso y obesidad en la población general y con VIH

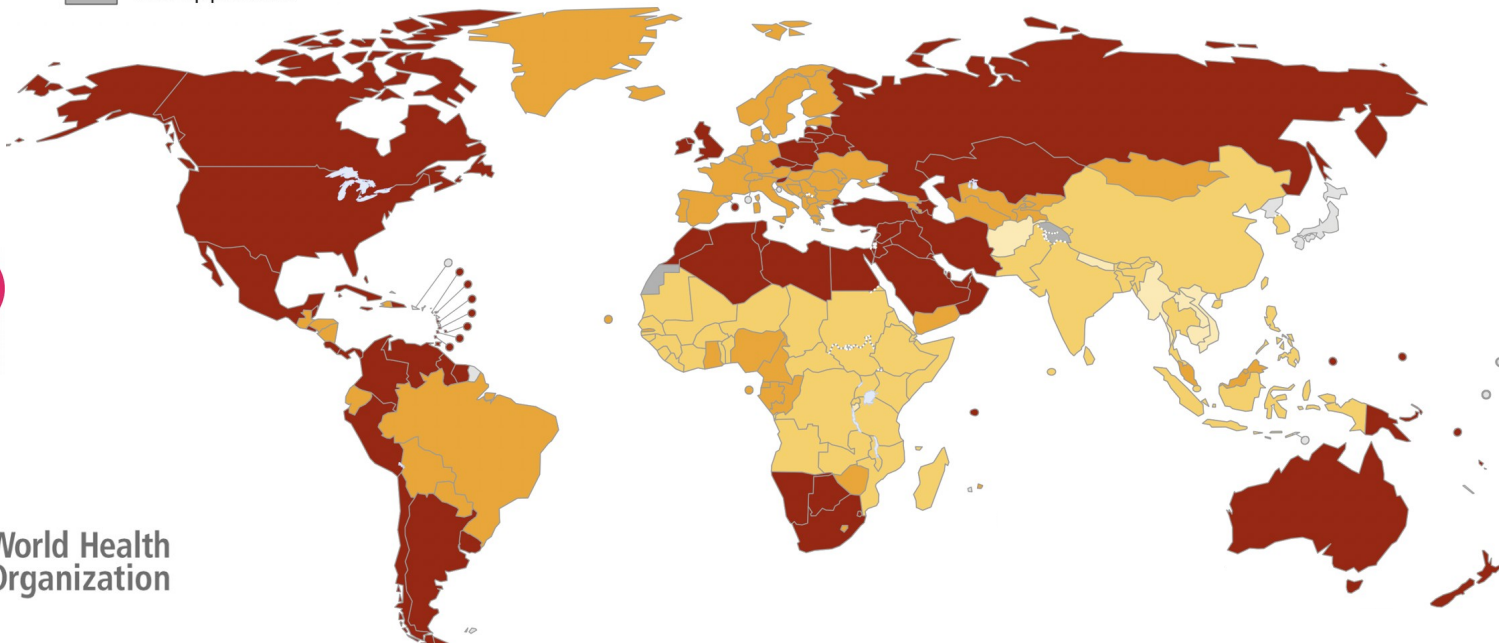
## Biología:

- Sexo, raza
- Factores Genéticos
- Inflamación
- Salud mental: antipsicóticos...

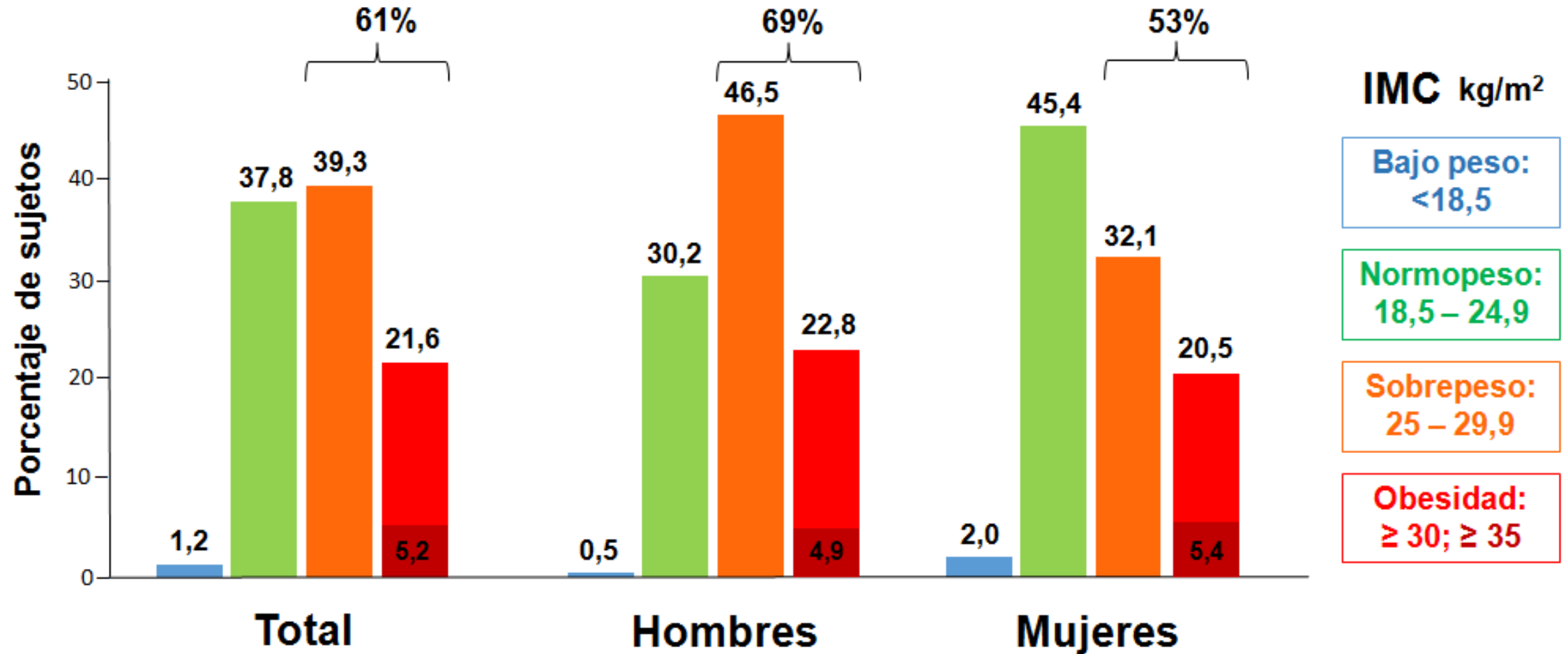
# Prevalencia de obesidad, 2014



- El importante aumento global de la obesidad (1980 a 2014 casi se ha duplicado) es uno de los retos más difíciles en salud pública que debe afrontar la sociedad actual.
- No solo afecta a los países con rentas más altas, sino que también está en aumento en los países con rentas medias y baja.
- En el mundo el sobrepeso y la obesidad se asocian con más muertes que el bajo peso.



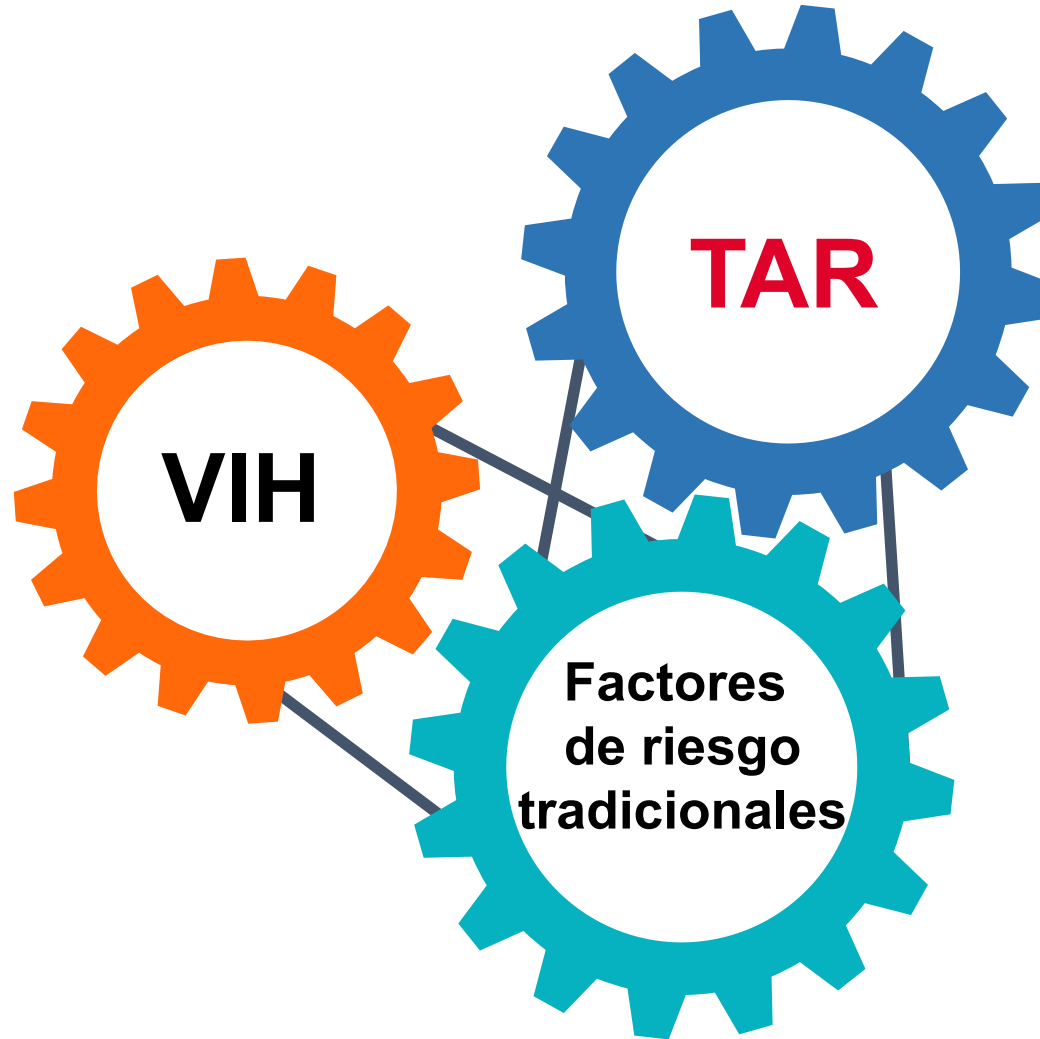
# Estudio ENPE: Elevada prevalencia de sobrepeso y obesidad en la población española (años 2014-15, edad 25 a 64 años)



**Obesidad (IMC ≥ 30) según nivel de estudios:**

Educación ≤ 1<sup>a</sup>: 27%, 2<sup>a</sup> primer ciclo: 19%, 2<sup>a</sup> segundo ciclo: 13%, Universitaria: 10%

# ¿A qué se debe el aumento de peso/obesidad?



- Lipoatrofia: ddC, d4T, AZT
- Obesidad central: IPs iniciales (IDV)

- Papel del TAR actual en el aumento de peso:
  - ¿INSTI?
  - ¿TAF?



# Cohortes VIH: Aumento de Peso con INSTI

## INSTI asociado a ↑ peso vs No-INSTI

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

## ↑ peso TAF > TDF

- Gomez M. Alemania. (N=241)<sup>8</sup>. Switch
- Schafer JJ. USA (N=110)<sup>9</sup>. Switch

## INSTI No asociado ↑ peso vs otros TARs

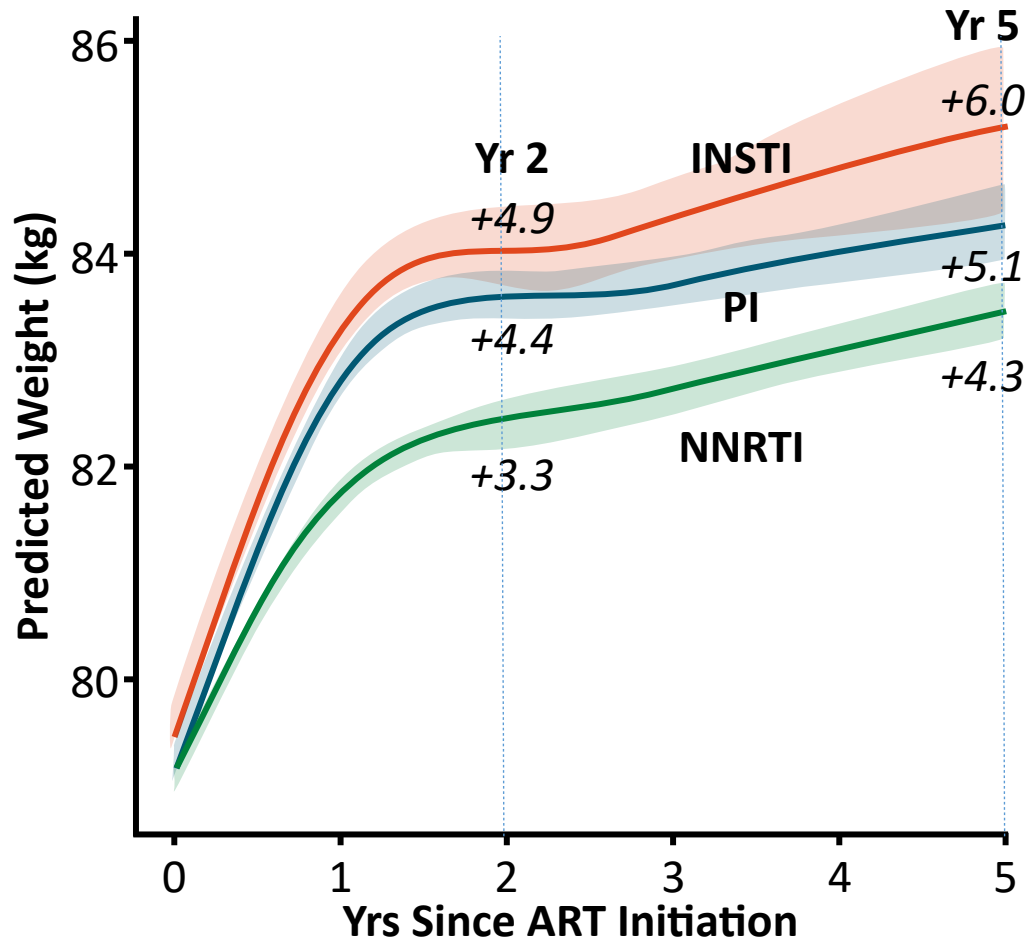
- Burns JE. London (N=378)<sup>10</sup>. Switch
- McComsey GA. TRIO. USA (N = 3468)<sup>11</sup>. Switch
- Taramasso L. SCOLTA. Italia (N=1118)<sup>12</sup>. Switch
- Mounzer K. OPERA. USA (N=10.653)<sup>13</sup>. Switch
- TSEPAMO. Botswana. EFV (N=621) < DTG (N=757) < HIV- (N=11280)<sup>14</sup>
- Hsu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

## ↑ peso IP/p < INSTI

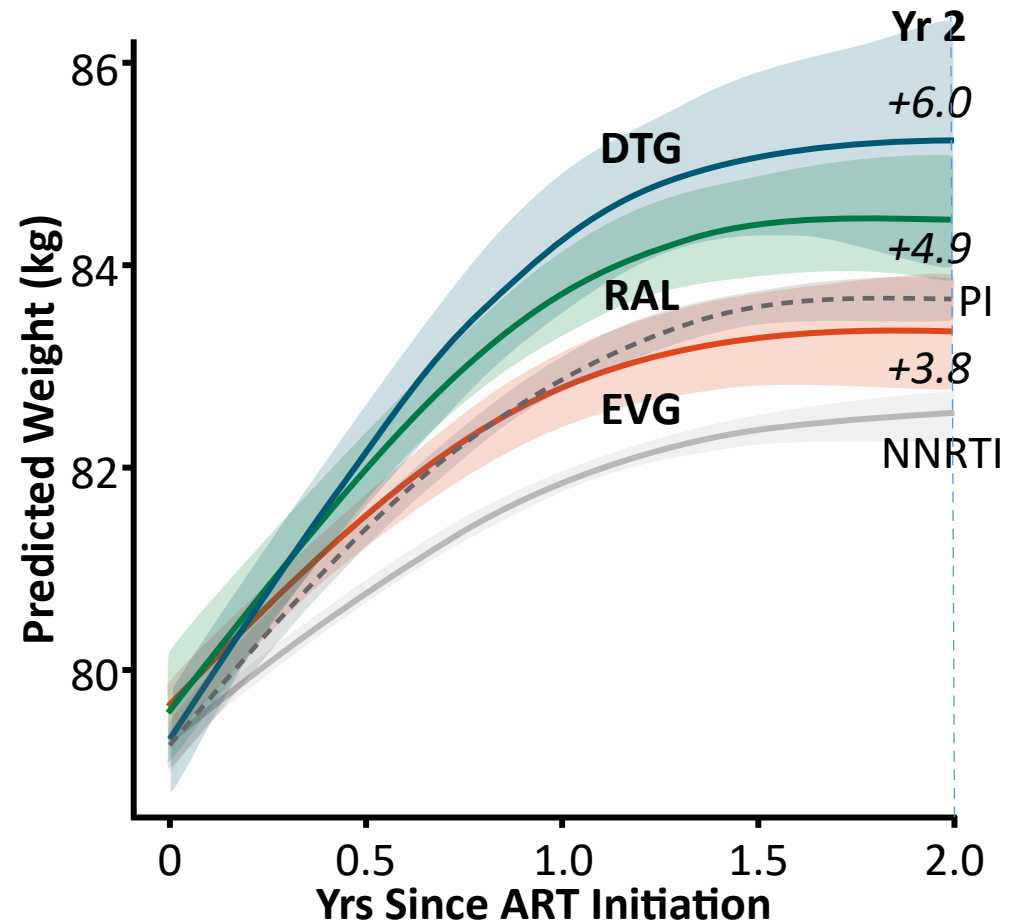
- Bakal DR. Brasil (N=1794)<sup>2</sup>. Naïve
- Norwood J. USA (N=495)<sup>6</sup>. Switch
- Mounzer K. OPERA. USA (N=10.653)<sup>13</sup>. Switch
- McComsey GA. TRIO. USA (N = 3468)<sup>11</sup>. Switch

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.

# NA-ACCORD: Weight Gain by Class or Specific INSTI



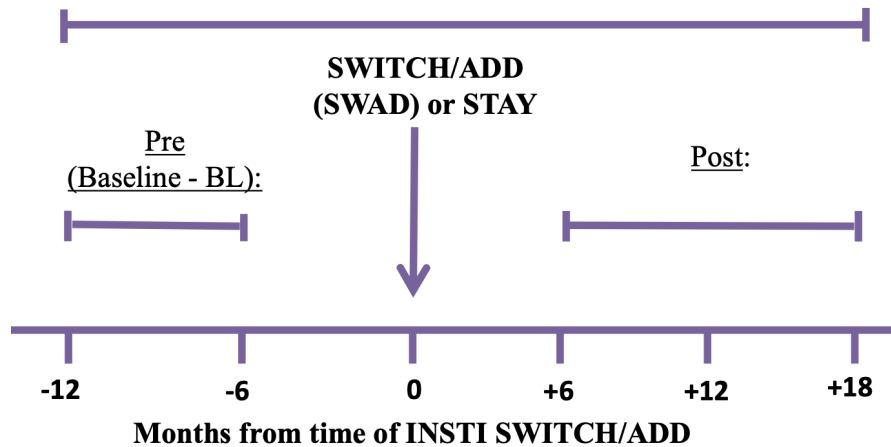
**N=24001**  
INSTI n=11825  
PI n=7436  
NNRTI n=4740



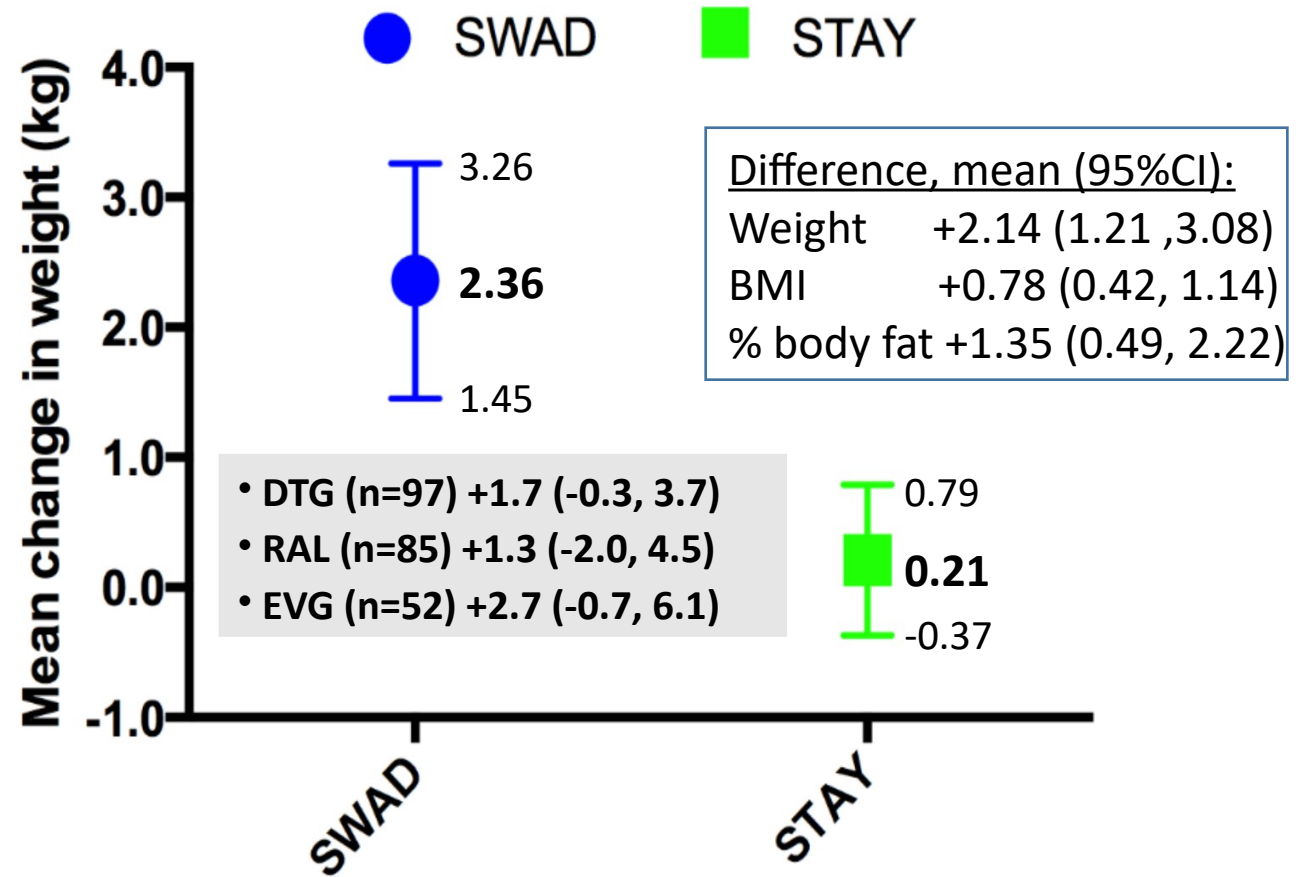
- Higher weight gain with **INSTI**- vs NNRTI-regimens.
- Weight gain with INSTIs did not vary by sex or race.

# WIHS: INSTI are associated with Weight Gain (Women, USA)

- N = 1,118 women from 2006 to 2017
- 884 STAY (NNRTI, PI or EI), 234 SWAD
- Mean follow-up time: 2 .0 yr



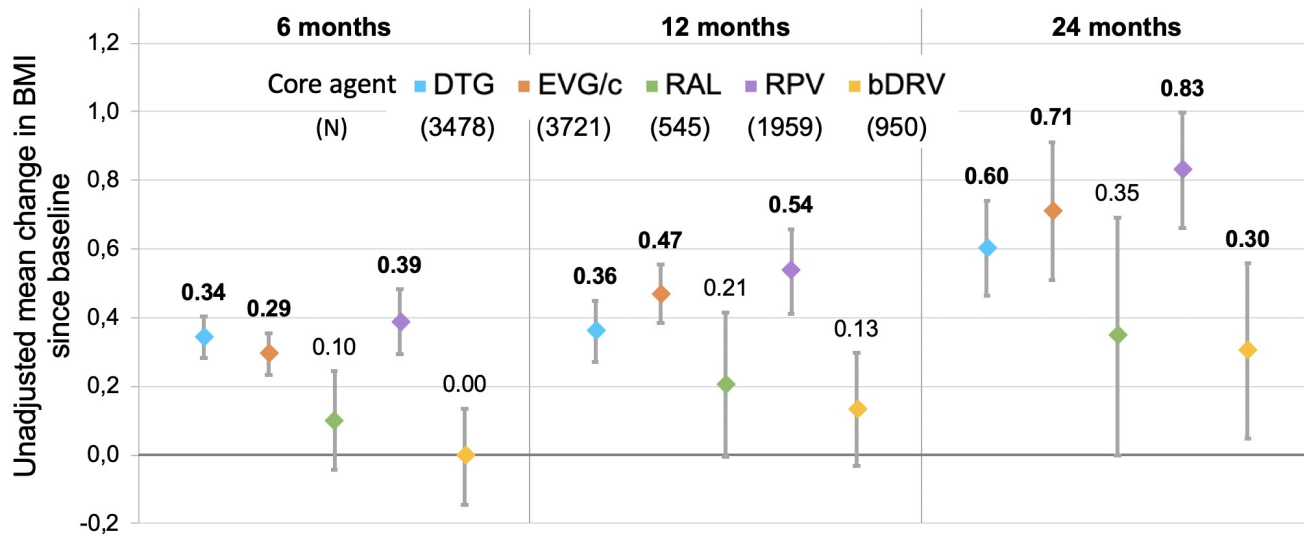
- Mean Age: 48.8 yrs.
- Black: 61%
- ART experienced
- Mean CD4: 669, VL < 1000 c/mL



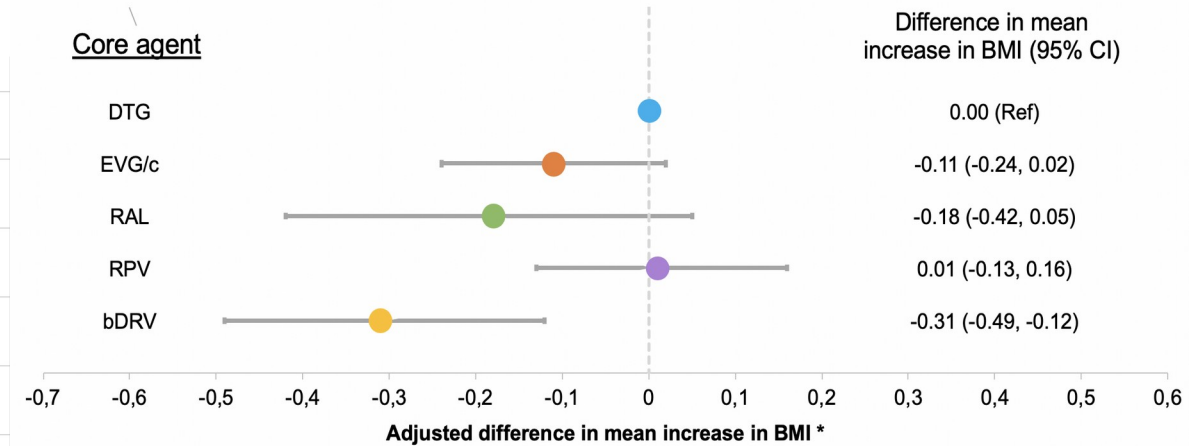
- In women on ART, a switch to **INSTI** was associated with increases in weight, BMI and % of fat.
- No differences in magnitude of these changes were observed by INSTI type

# OPERA: Changes in BMI with ART regimens in Suppressed Individuals

- OPERA USA Cohort: Prospectively captured, routine clinical data
- ART-experienced virologically suppressed N=10.653
- Switch between 1/8/2013 and 31/2/2017



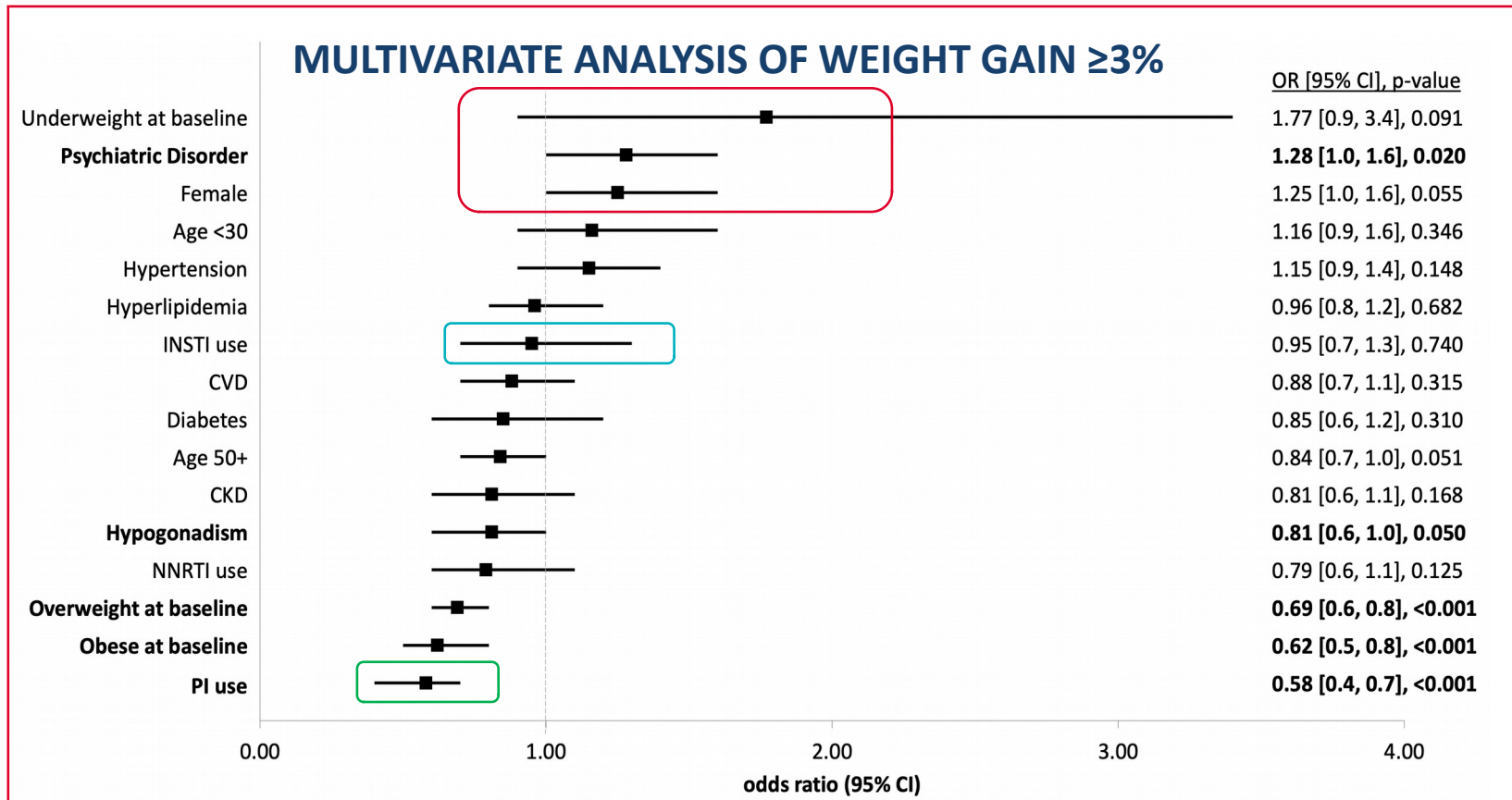
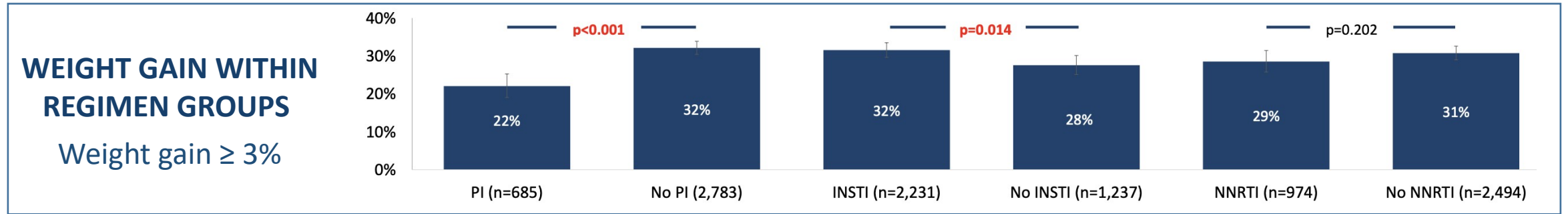
## 12-Month Adjusted Difference in Mean Increase in BMI From Baseline



\* Adjusted for baseline age, sex, race/ethnicity, BMI, lipodystrophy, endocrine disorders, hypertension, substance abuse, CD4 cell count, viral load, and TAF use.

- Increases in BMI persist in treatment-experienced, suppressed patients.
  - Return to health does not fully explain weight gain associated with ART
- Small absolute increases in BMI with all core agents (Lower increase with bDRV vs. DTG).
- Although both weight gain and weight loss were observed across all groups, the trend remains an increase in BMI over time.

# Weight gain among Tx-experienced adults with HIV (USA)



- N=4368. Switch to a new ART 2013-17.
- $\downarrow$  Peso  $> 3\%$ : **16%** (mean  $-5.4 \pm 3.3$  kg)
- No gain  $> 3\%$ : **54%** (mean  $0.2 \pm 1.4$  kg)
- $\uparrow$  Peso  $> 3\%$ : **30%** (mean  $5.2 \pm 3.1$  kg)

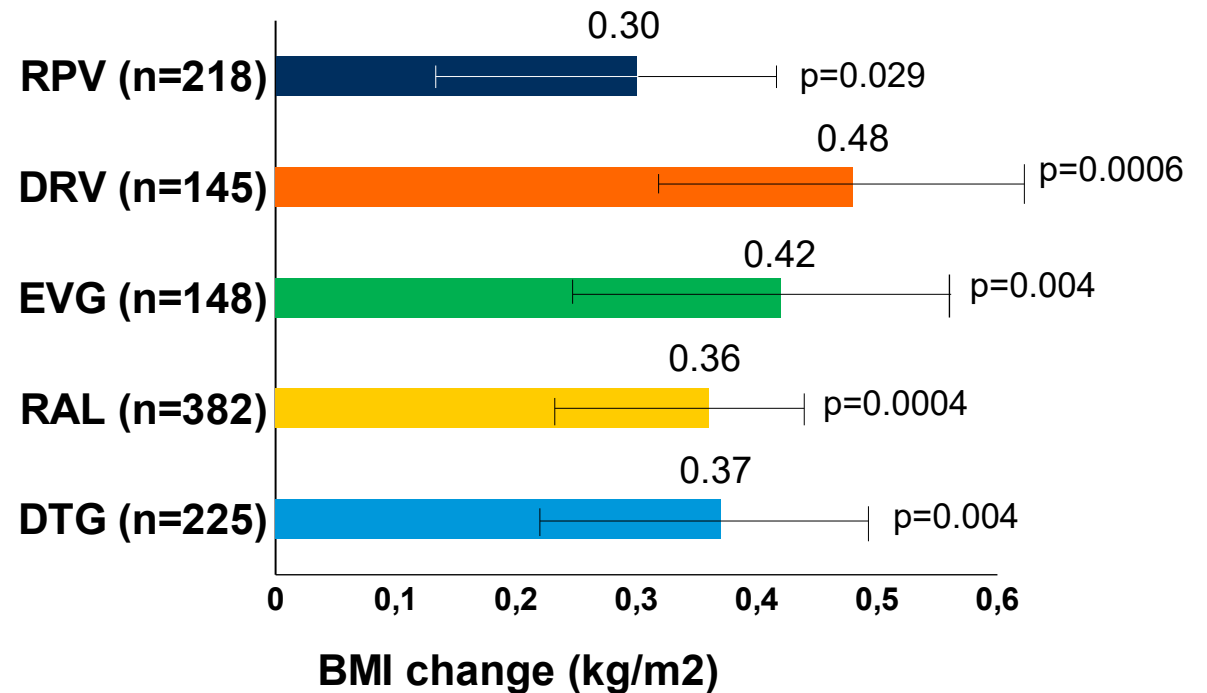
- The association **INSTI** and weight gain reached significance in bivariate analyses, but NS in multivariable logistic regression model, suggesting that in this population, **weight changes are primarily driven by other factors.**
- Absence of weight gain associated with hypogonadism, overweight or obese at baseline, and PI use

# SCOLTA (Italia): Weight Gain, a possible side effect of all ARV

## SCOLTA observational analysis (N=1,118)

- N = 1.118 on treatment
- Median Age 46 yrs.
- Male 71%
- CD4<200: 38%
- VL < 50 c/mL: 60%
- Median time on previous ART: 10.8 yrs.
- BMI at baseline:
  - Underweight 6%
  - Normal weight 60%
  - Overweight 27%
  - Obese 7%

## One-Year adjusted mean ( $\pm$ SE) BMI increase\*



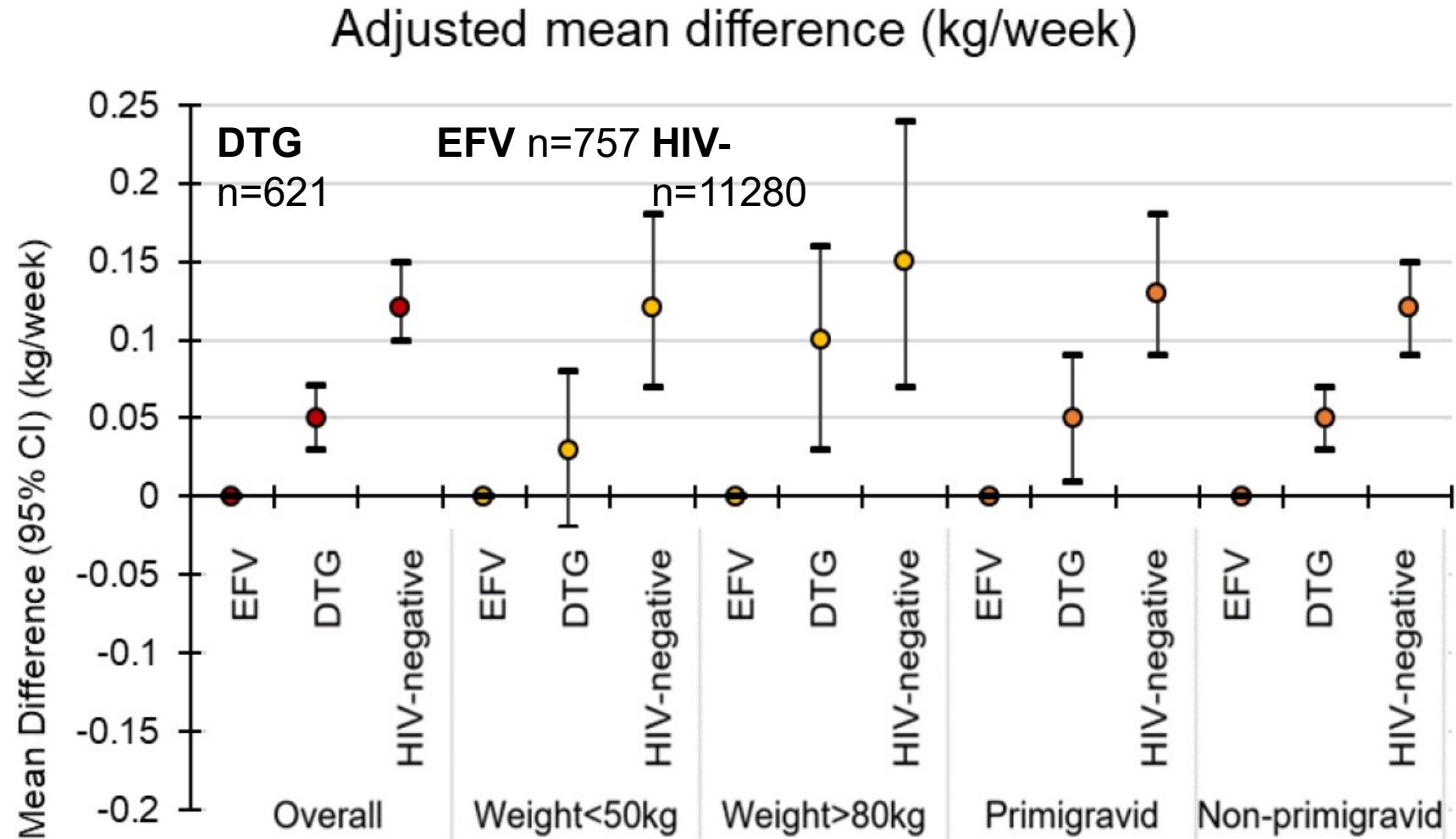
\*Adjusted for sex, age, CD4+, detectable viral load, CDC stage, duration of ART, lipodystrophy, and BMI at study entry.

- Switching to RAL-, DTG-, EVG-, DRV- or RPV-based regimens were associated with increases in BMI.
- **No INSTI** was significantly different from DRV or RPV in the adjusted analysis.
- Age, low BMI, and CD4 <200 cells/mL at study entry were significantly associated to BMI increase.

# Weight gain during pregnancy in Botswana (Tsepamo)

- Mean age 28 yr
- Pre-ART CD4 337,
- Pre-pregnancy weight 63 kg
- Weight ART initiation 66 kg

- Women initiating DTG gained more weight compared with EFV.
- Particularly those with higher pre-ART pregnancy weight.
- Neither group gained as much weight as HIV- negative women



Adjusted for: age, CD4, employment, education, parity, gravidity, marital status, site, smoking, alcohol, pre-pregnancy weight, weight at ART initiation (or first ANC), gestational age at ART initiation (or first ANC).

¿Aumento de peso con  
antirretrovirales?

Ensayos Clínicos Aleatorizados

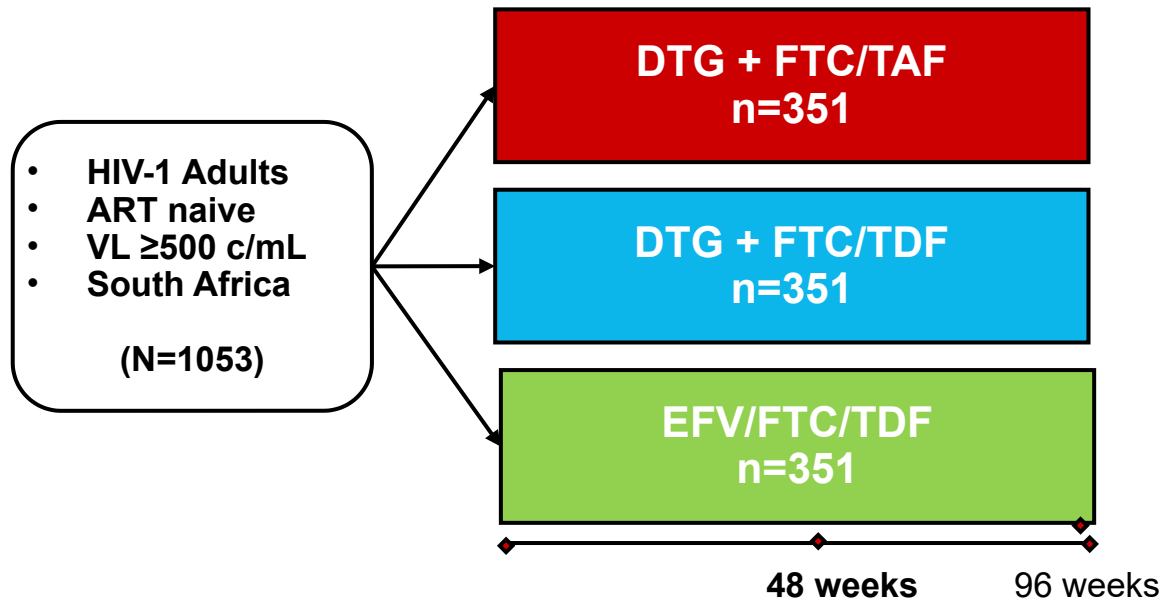


# IAS 2019: 2 EC aleatorizados con estudio de peso e IMC

## Evaluation of differences in the changes in body weight and body mass index (BMI), and lean/fat mass using DXA

### ADVANCE

- Open-label, randomized trial in South Africa



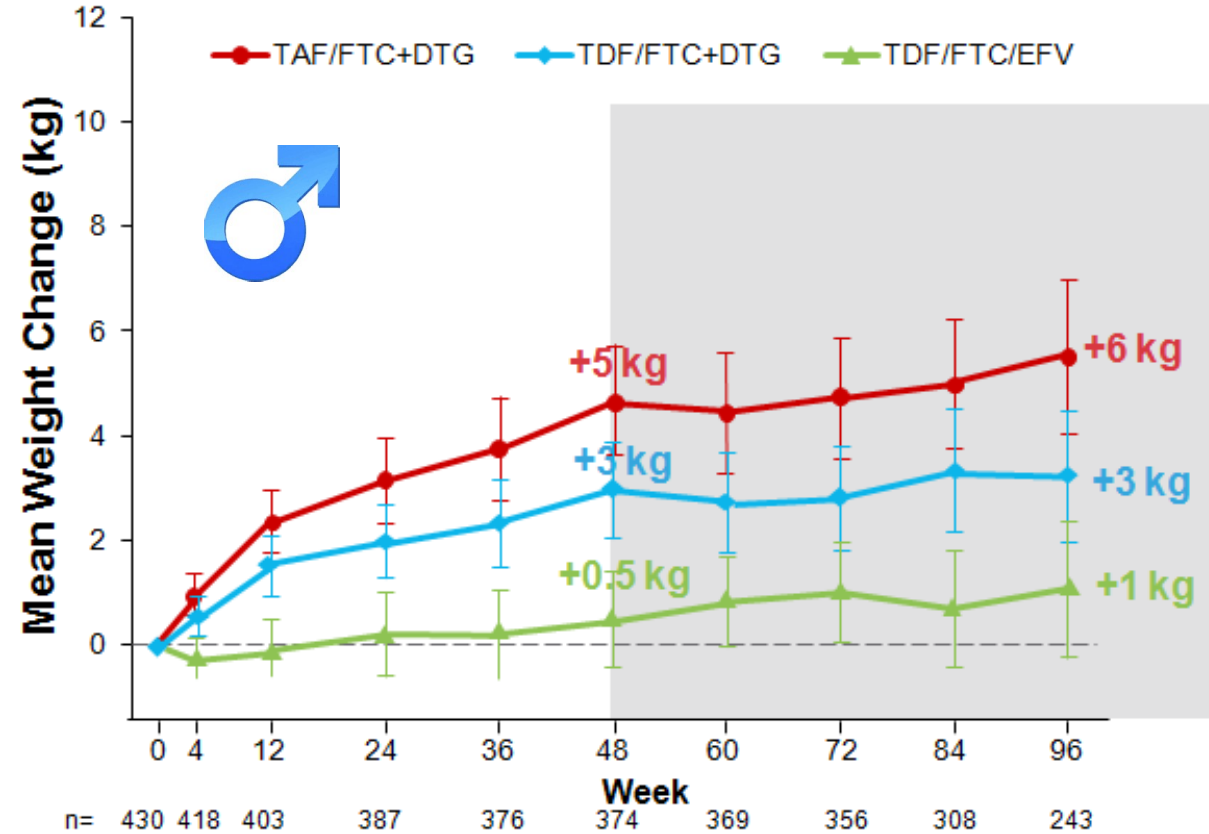
### Baseline Characteristics

Characteristic	DTG + FTC/TAF n=351	DTG + FTC/TDF n=351	EFV/FTC/TDF n=351
Age, mean (SD) years	33 $\pm$ 8	32 $\pm$ 8	33 $\pm$ 7
Female	61%	59%	57%
BMI, mean (kg/m <sup>2</sup> )			
• Male	21.7	21.6	21.8
• Female	25.6	26.1	26.1
BL HIV-1 $\geq 100,000$ - $500,000$ c/mL	19%	18%	21%
CD4+, cells/mm <sup>3</sup>	349 $\pm$ 225	323 $\pm$ 234	337 $\pm$ 222

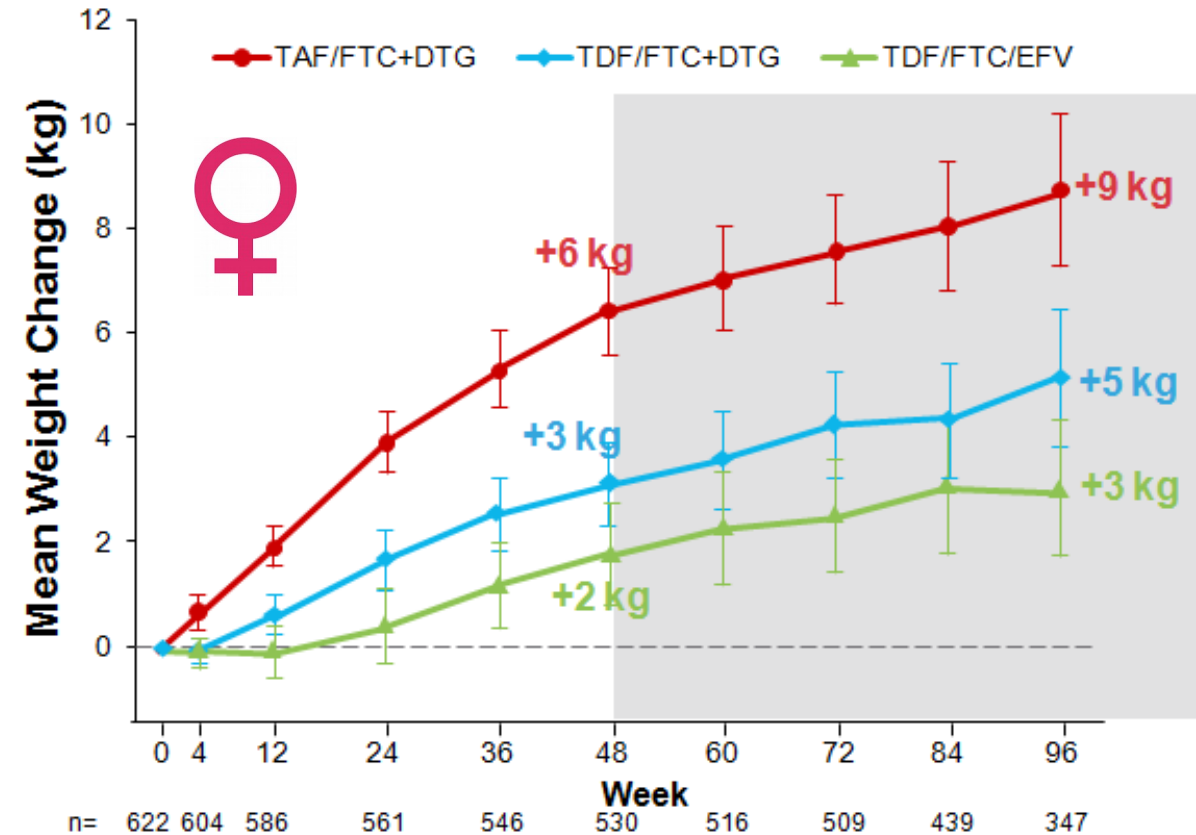
- At Week 48, both DTG arms non-inferior to EFV arm<sup>2,3</sup>  
 —Virologic suppression for DTG arms (84%-85%) vs. EFV (79%)

# ADVANCE: Mean change in weight from baseline by sex

## Mean Change in Weight (kg) in Men



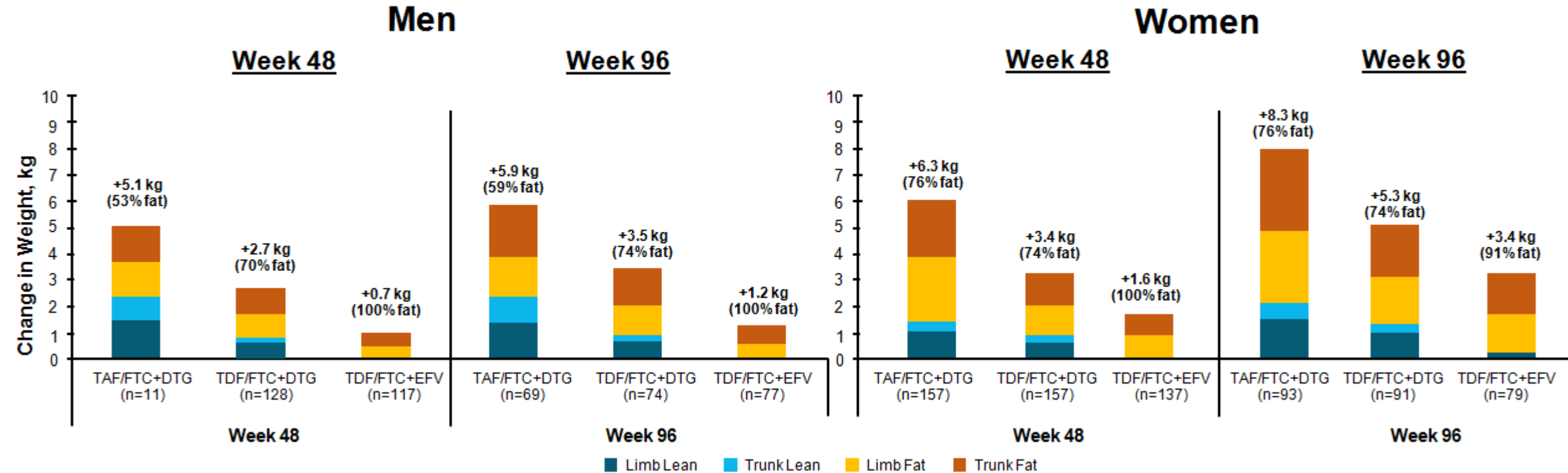
## Mean Change in Weight (kg) in Women



- We saw greater increases in weight in the 2 DTG arms compared to the EFV arm.
- These were higher in the TAF arm than the TDF-containing arms.
- Changes in weight plateauring after W48 in men but not in women.

**For this analysis, only 55% of study population had reached W96.**

# ADVANCE: Changes in body composition (DEXA) by sex



- DTG was associated with increased trunk and limb lean mass and fat vs. EFV, with greater increases with FTC/TAF in women than in men.
- There were contribution to weight gain from both lean body and fat, from both trunk and limbs

# ADVANCE: Factors Associated Obesity and Weight Gain

<b>Obesity</b>	Hazard ratio	95% CI	p-value
<b>Sex</b>			
male	ref		
female	1.66	0.95,2.88	0.073
<b>BMI (kg/m<sup>2</sup>)</b>			
continuous	<b>1.94</b>	<b>1.75,2.15</b>	<b>&lt;0.001</b>
<b>Treatment arm</b>			
TDF/FTC/EFV	ref		
<b>TAF/FTC+DTG</b>	<b>3.14</b>	<b>1.76,5.58</b>	<b>&lt;0.001</b>
TDF/FTC+DTG	1.69	0.91,3.13	0.094
<b>CD4+ cell count (/mm<sup>3</sup>)</b>			
/10cells/mm <sup>3</sup>	<b>0.98</b>	<b>0.97,1.00</b>	<b>0.032</b>
<b>Viral load (copies/mL)</b>			
median log <sub>10</sub> (IQR)	<b>2.04</b>	<b>1.50,2.78</b>	<b>&lt;0.001</b>

<b>10% weight gain</b>	Hazard ratio	95% CI	p-value
<b>Age (years) at baseline</b>			
continuous	<b>1.02</b>	<b>1.00,1.03</b>	<b>0.013</b>
<b>Sex</b>			
male	ref		
<b>female</b>	<b>1.49</b>	<b>1.18,1.89</b>	<b>0.001</b>
<b>Weight (kg)</b>			
continuous /10kg	<b>0.91</b>	<b>0.83,1.00</b>	<b>0.041</b>
<b>Treatment arm</b>			
TDF/FTC/EFV	ref		
<b>TAF/FTC+DTG</b>	<b>3.07</b>	<b>2.30,4.09</b>	<b>&lt;0.001</b>
TDF/FTC+DTG	1.34	0.97,1.83	0.072
<b>CD4+ cell count (/mm<sup>3</sup>)</b>			
/10cells/mm <sup>3</sup>	<b>0.98</b>	<b>0.97,0.99</b>	<b>&lt;0.001</b>
<b>Viral load (copies/mL)</b>			
median log <sub>10</sub> (IQR)	<b>1.46</b>	<b>1.23,1.72</b>	<b>&lt;0.001</b>

■ Mujer

- ↓ peso
- ↓ CD4
- ↑ CV

■ TAF/FTC + DTG

# ADVANCE: Percepción sobre el aumento de peso

250 personas encuestadas sobre el cambio de peso  
(150 mujeres, 93 hombres) (15/07/2019)

35 (14%)  
descontentas

22 (9%)  
indiferentes

193 (77%)  
**contentas**

11 (4.4%)  
descontentas  
por **perder** peso

24 (9.6%)  
descontentas  
por **augmentar** peso

- 20 ganaron más del 20% de peso y
- sólo 2 estuvieron descontentas

- Ninguno optó por cambiar DTG o TAF (tras asesoramiento)

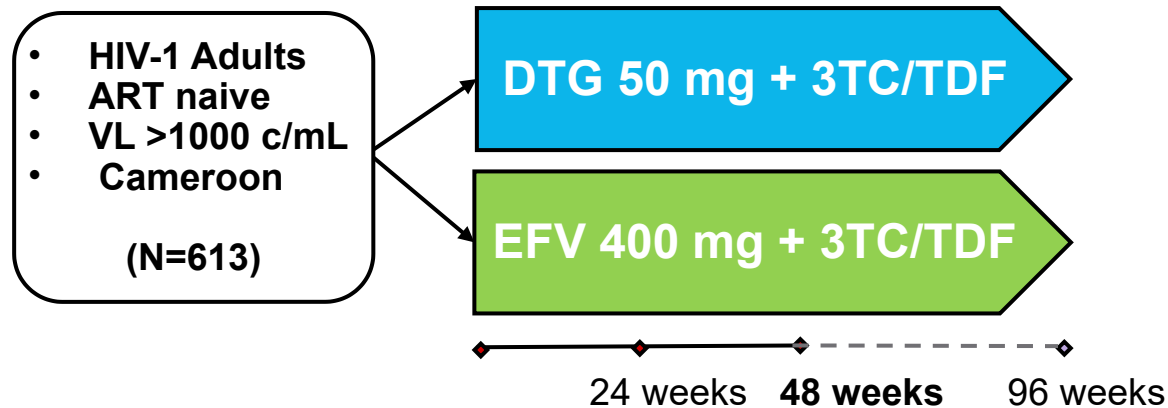
- La mayoría estaban contentos con el aumento de peso a pesar de tener que cambiarse la ropa.
- Muchos vieron el incremento de peso como un **“retorno a la salud”**

# IAS 2019: 2 EC aleatorizados con estudio de peso e IMC

## Evaluation of differences in the changes in body weight and body mass index (BMI)

### NAMSAL

- Open-label, randomized trial in 3 sites in Cameroon



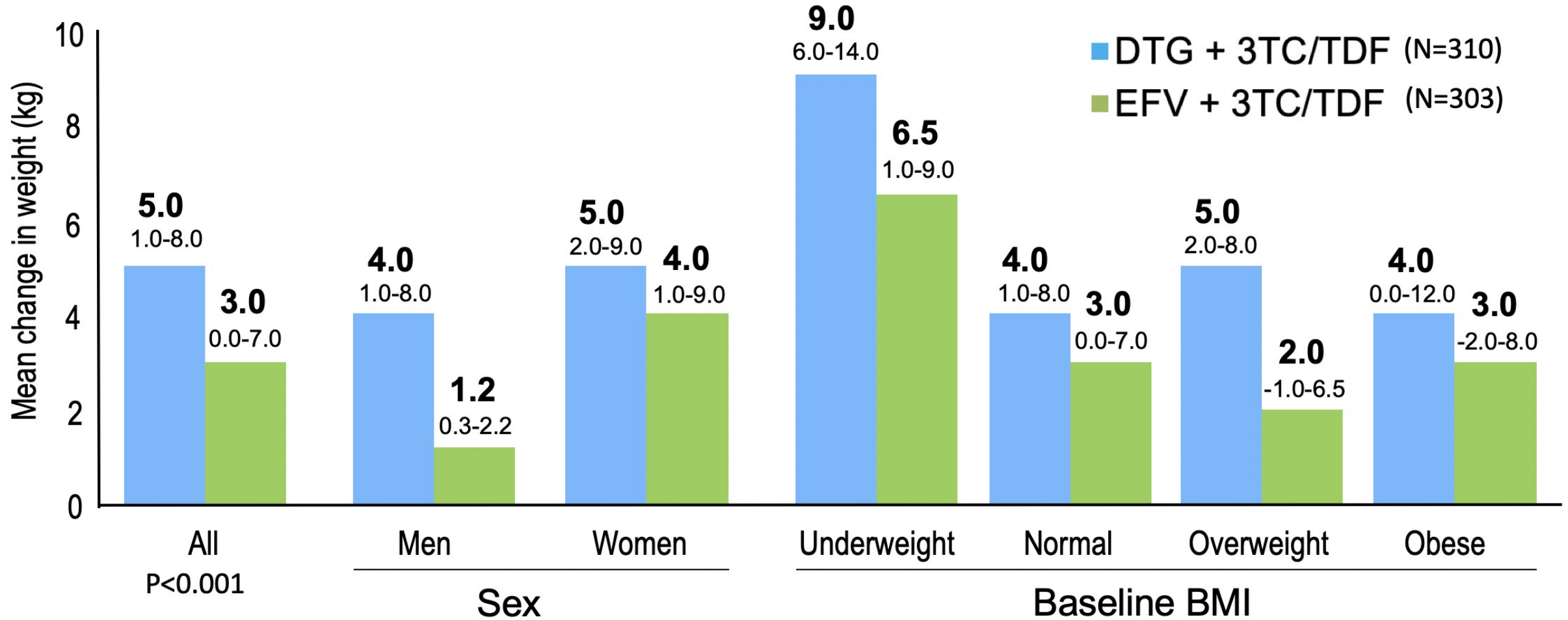
### Baseline Characteristics

Characteristic, median (IQR) unless stated	DTG + TDF/3TC (n=310)	EFV400 + TDF/3TC (n=303)
Age, years	38 (31-46)	36 (29-43)
Female, n (%)	197 (64)	207 (68)
BMI, kg/m <sup>2</sup>	23 (21-26)	23 (21-26)
BL HIV-1 ≥500,000 c/mL	93 (30)	95 (31)
CD4+, cells/mm <sup>3</sup>	289 (157-452)	271 (147-427)

# NAMSAL: Changes in Body Weight at Week 48

Cameroon

- Mean age 37 yr, female 66%, black 99%, mean CD4 281, VL>100k 67%, Median weight 64 kg, BMI 23 kg/m<sup>2</sup>.



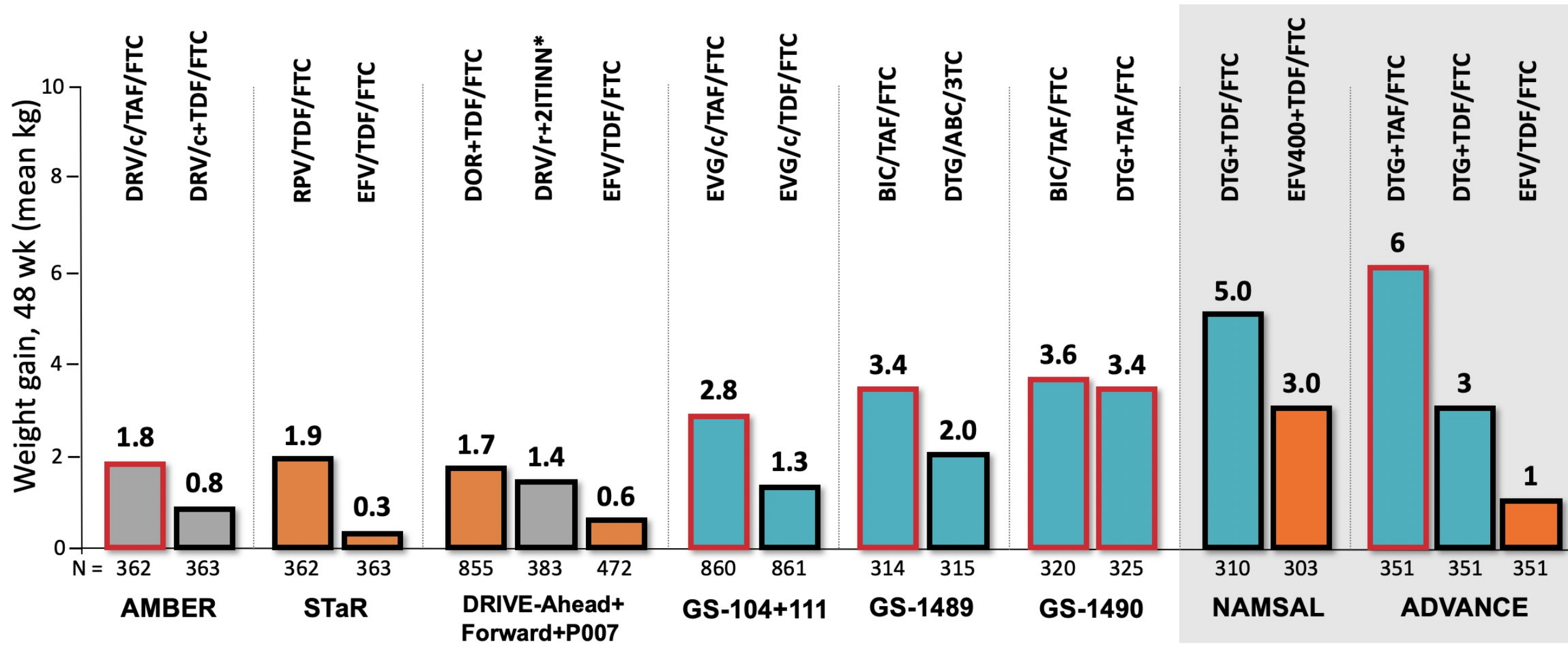
- A greater increase in body weight was observed in the DTG than in the EFV400 group.

Ensayos Clínicos Aleatorizados

¿Aumento de peso con INI o  
TAF en Occidente?



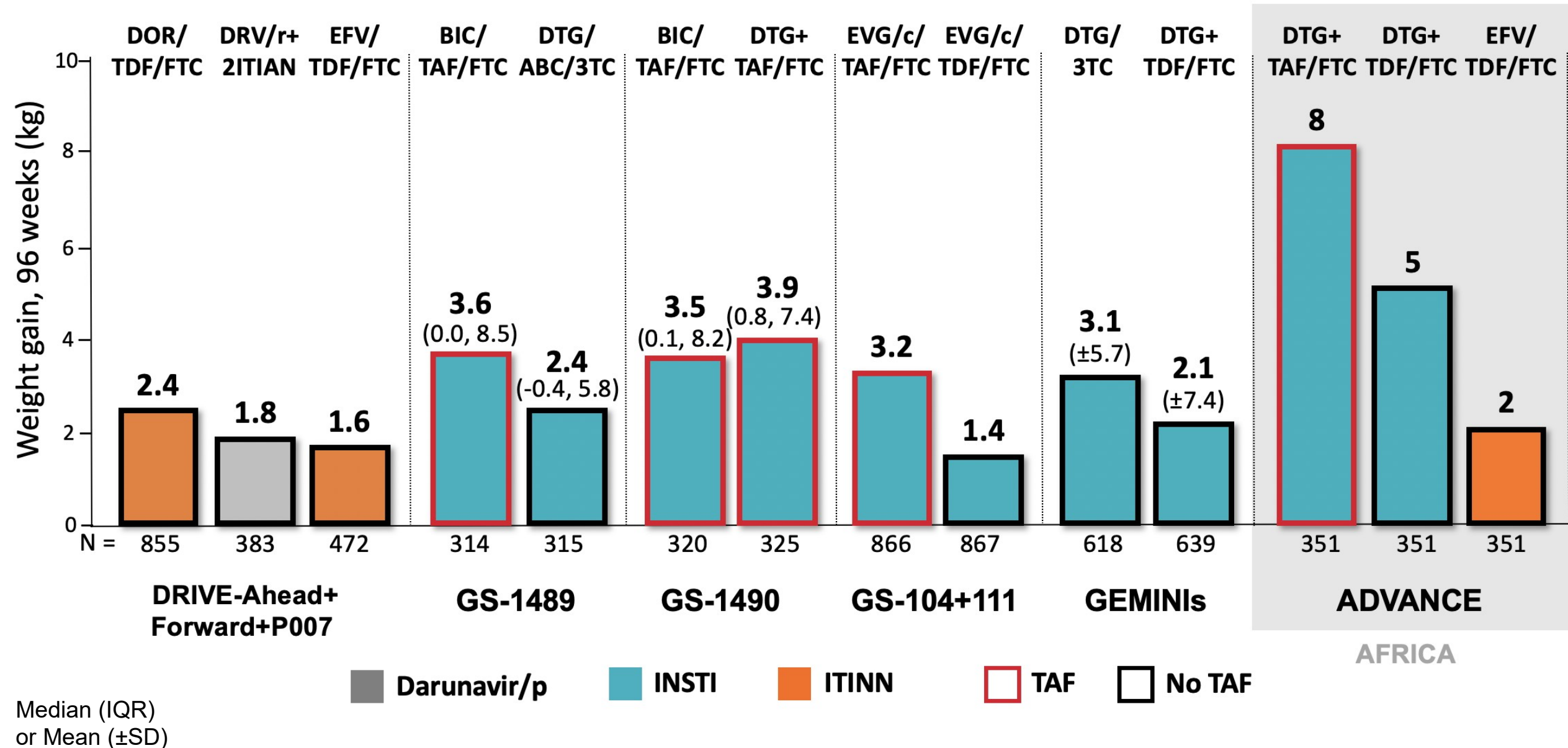
# Aumento de peso a 48 sem. en Ensayos Clínicos (naive)



\*TDF/FTC o ABC/3TC

Darunavir/p
  INSTI
  ITINN
  TAF
  No TAF

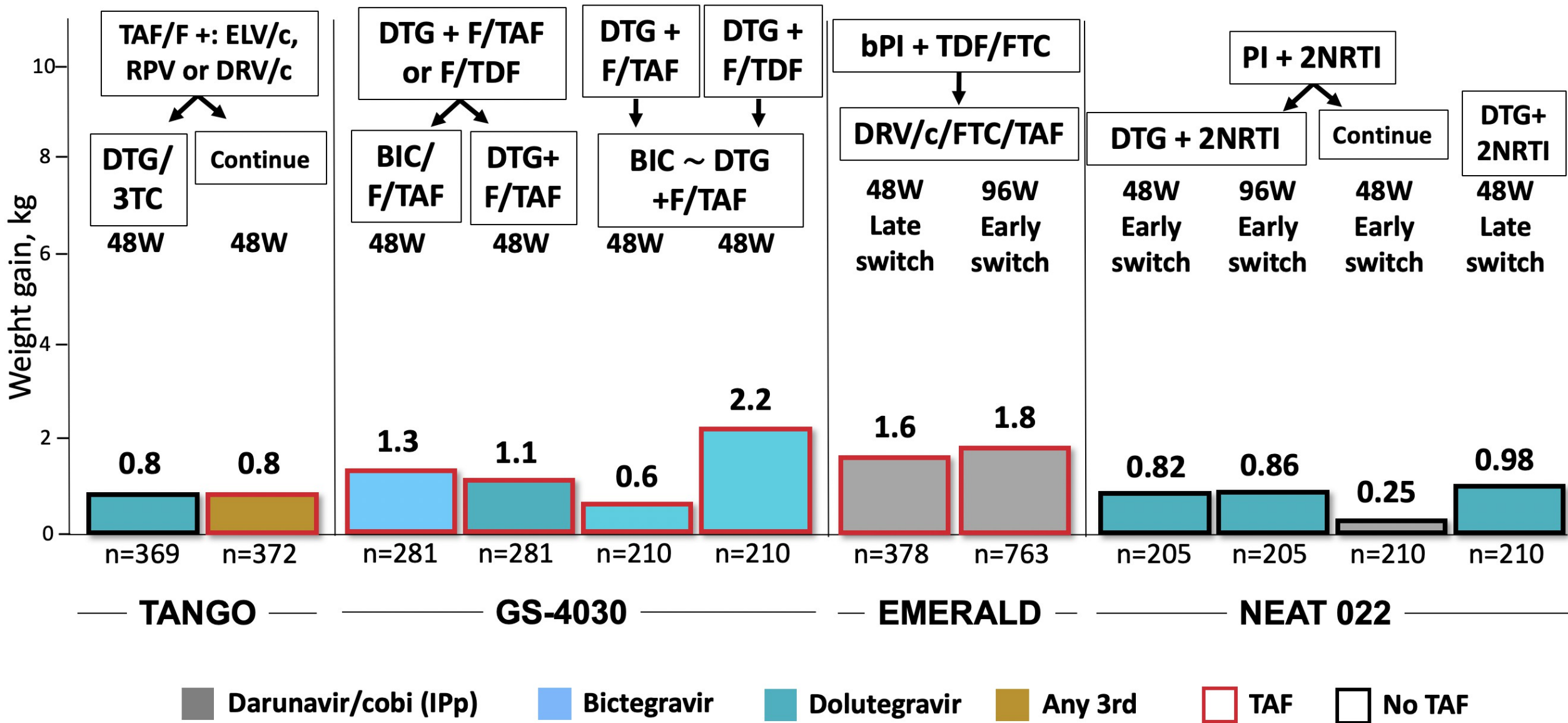
# Weight Gain in to week 96 in Clinical Trials (naive)



# Weight Gain (kg) to week 48 in Clinical Trials (*naive*)

	TAR ( <i>naive</i> )	Occidente	África
48 W	INSTI + TAF / NO-TAF	3.2 / 1.5	6 / 4
	DRV/p + TAF / NO-TAF	1.8 / 1.1	ND
	DOR o RPV + TDF	1.7	ND
96 W	INSTI + TAF / NO-TAF	3.5 / 2.1	8 / 5
	DRV/p + NO-TAF	ND / 1.8	ND
	DOR o RPV + TDF	2.4	ND
	EFV + TDF	1.6	2

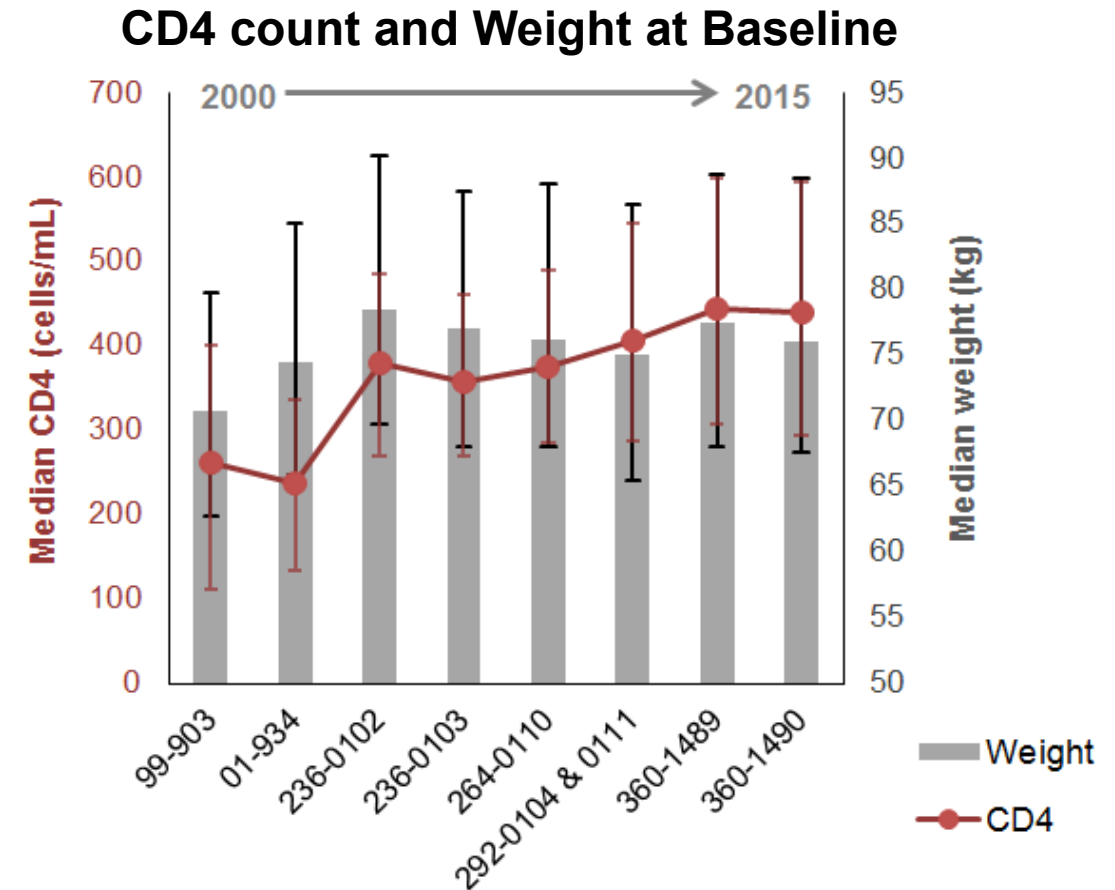
# Weight Gain in Clinical Trials (switch)



# Weight Gain with ART: Risk Factors in Gilead Randomized Trials

**Integrated analysis of 8 Phase 3 randomized, active-controlled studies of PLHIV initiating ART from 2003-2015 (N=5,680) with >10,000 PY of follow-up**

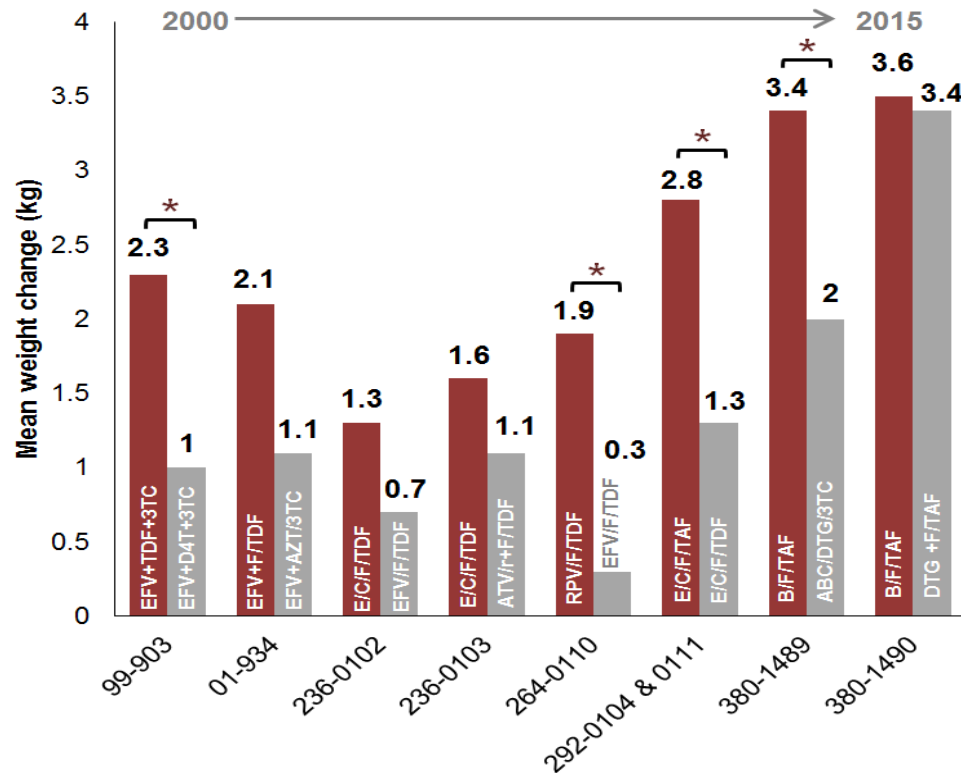
Study Number	Treatment Arms	Weeks
01-934	EFV+ F/TDF vs EFV +AZT/3TC	144
236-0102	E/C/F/TDF vs EFV/F/TDF	144
236-0103	E/C/F/TDF vs ATV/r + F/TDF	144
264-0110	RPV/F/TDF vs EFV/F/TDF	144
292-0104	E/C/F/TAF vs E/C/F/TDF	96
292-0111	E/C/F/TAF vs E/C/F/TDF	144
380-1489	B/F/TAF vs ABC/DTG/3TC	144
380-1490	B/F/TAF vs DTG+F/TAF	96



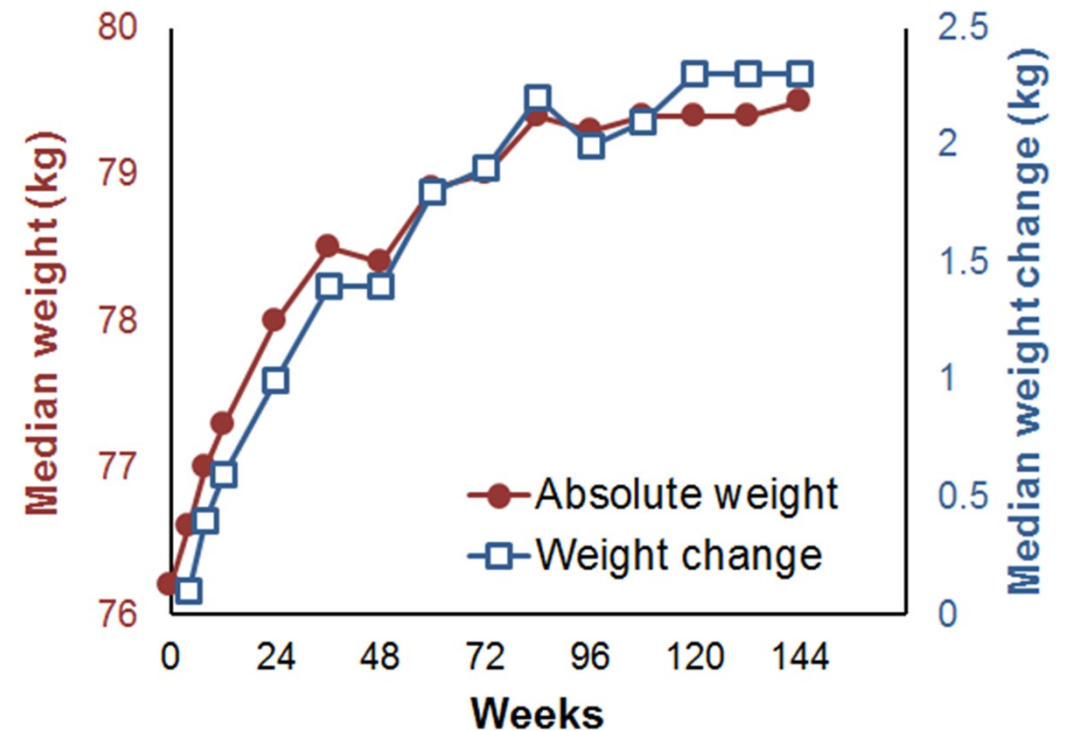
- Baseline CD4 and weight were higher in the more recent trials

# Weight Trends in Participants Initiating ARV Therapy

Mean Weight Change at Week 48



Median Weight and Weight Changes through 144 Weeks

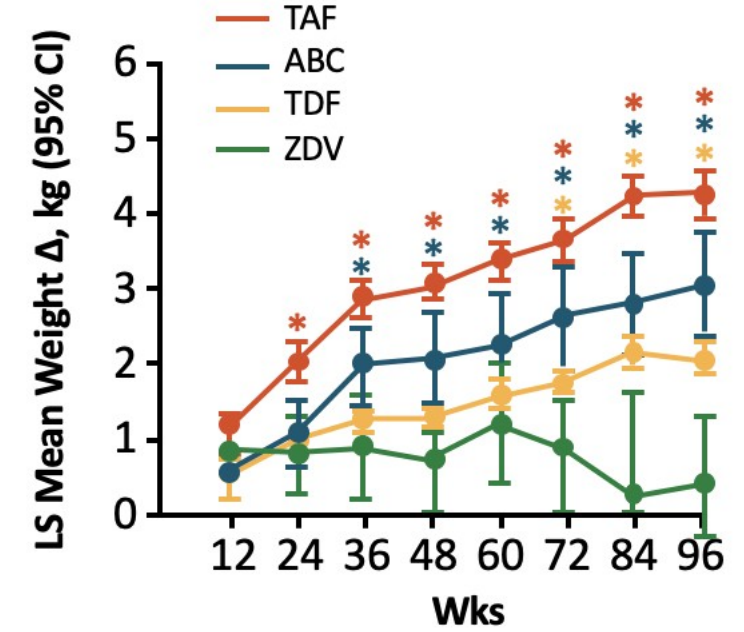
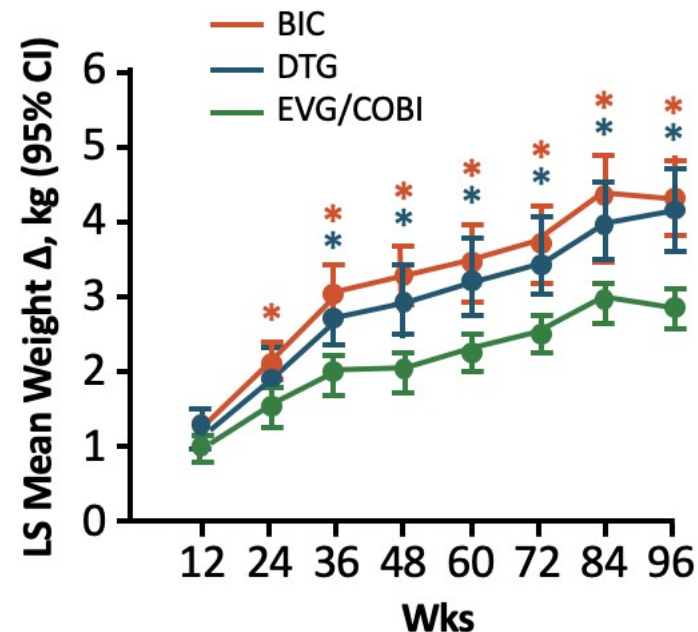
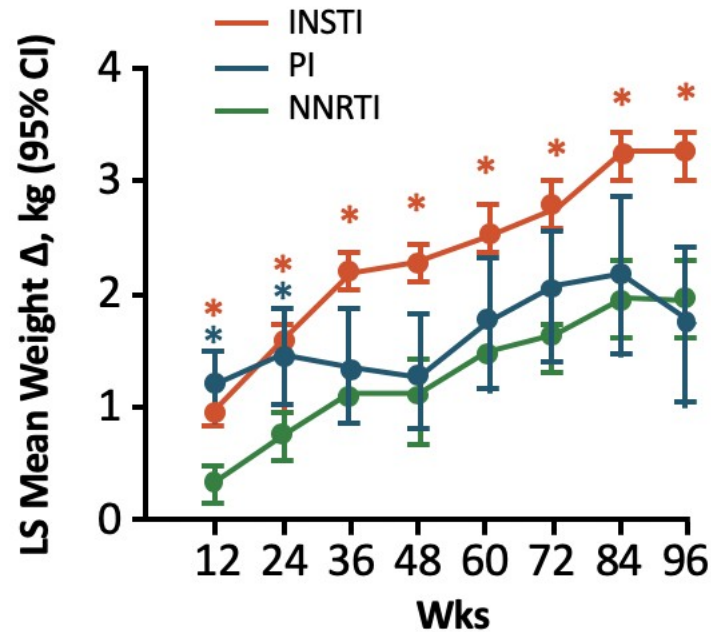


- Weight gain occurred in all study arms
- Investigational regimen was consistently associated with more weight gain than the comparator
- Magnitude of weight gain was larger in the more recent trials

- Median weight gain was 2.0 kg at Wk 96 (IQR -1.0, 5.8)
  - Greatest rate of weight gain occurred during the initial 48 wks, and plateaued from Wks 72-144
- Through Wk 96, 48.6% gained  $\geq 3\%$ , 36.6% gained  $\geq 5\%$ , 17.3% gained  $\geq 10\%$ , and 30.2% lost weight

# Effect of Baseline ARV on Weight Increase

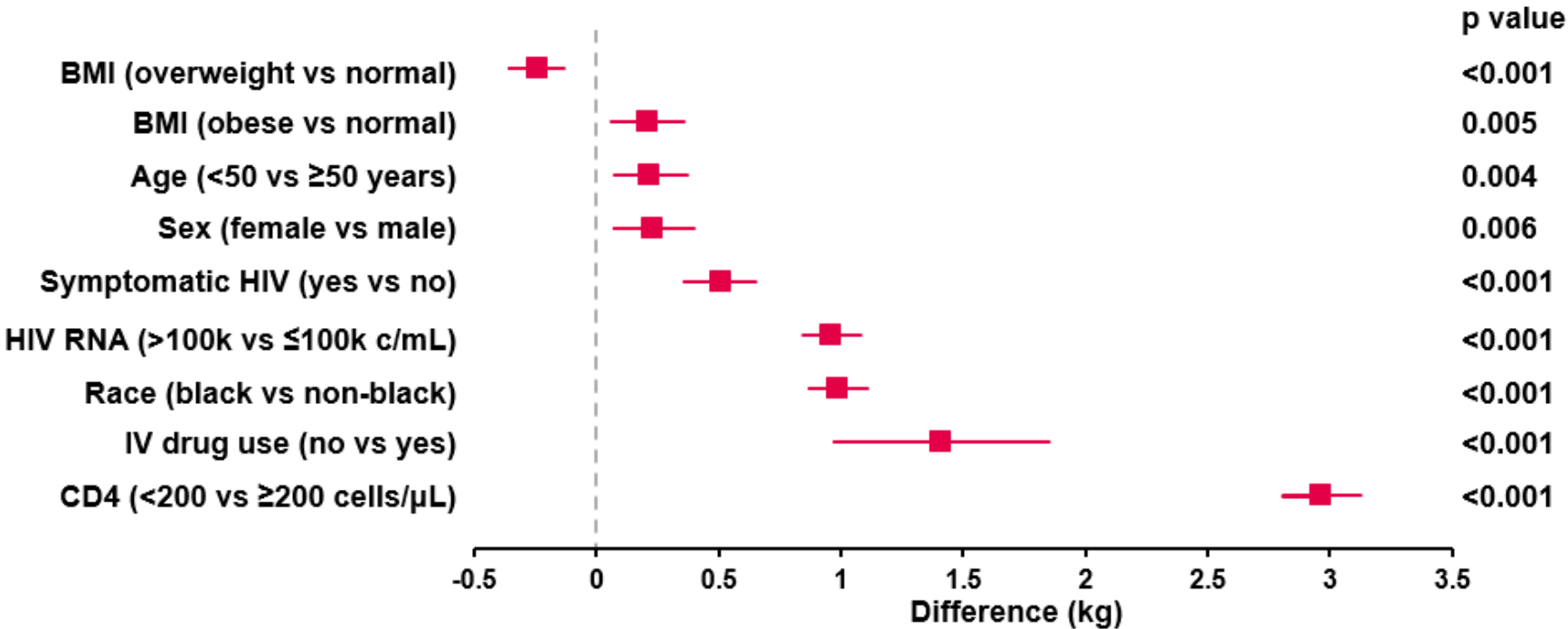
## Weight Change in Participants Initiating ARV therapy, Stratified by 3<sup>rd</sup> agent, INSTI, and NRTI



\*Color-coded to match respective comparators, denoting  $P \leq .05$  vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

- Participants taking INSTIs experienced the most weight gain (mean: 3.24 kg)
  - Participants taking BIC or DTG demonstrated similar weight gain, both greater than participants taking EVG/c
- Among NRTIs, TAF was associated with an increased risk of  $\geq 10\%$  weight gain vs. ABC and TDF
  - Mean weight gain: TAF = 4.25 kg; ABC = 3.08 kg; TDF = 2.07 kg

# Baseline Risk Factors for Weight Increase



## HIV, demographic & ART risk factors for Weight increase

- ↓ CD4 count
- ↑ HIV-1 RNA
- Non-overweight/obese
- Symptomatic
- No IV drug user

- Female
- Black

- BIC/DTG > EFV
- EVG/c > EFV
- RPV > EFV
- TAF > ABC, TDF or EFV

- Weight gain was common following ART initiation: ~50% of participants gained at least 3% body weight with a median weight gain of 2kg over 2 years of follow-up:
  - This degree of weight gain mirrors the obesity trend observed in the general US population.



# TAF vs TDF in 5 clinical trials in virologically suppressed patients

## Virologically Suppressed (5 studies; 4092 participants)

380-1878	N=488	OL 48 wk	B/F/TAF vs F/TDF + boosted PI
366-1160	N=875	DB 96 wk	FTC/RPV/TAF vs EFV/FTC/TDF
366-1216	N=630	DB 96 wk	FTC/RPV/TAF vs FTC/RPV/TDF
311-1089	N=663	DB 96 wk	F/TAF + 3rd agent vs F/TDF + 3rd agent
292-0109	N=1436	OL 96 wk	E/C/F/TAF vs TDF-containing regimens

OL = open label  
DB = double  
blind

Baseline Characteristic	TAF			TDF		
	All n=2291	Hispanic/ Latinx n=472	Black n=485	All n=1801	Hispanic/ Latinx n=332	Black n=403
Median age, y (range)	45 (20–78)	42 (21–74)	44 (20–74)	46 (19–79)	44 (19–71)	45 (22–76)
Female, n (%)	296 (13)	73 (15)	143 (29)	223 (12)	54 (16)	118 (29)
Median BMI, kg/m <sup>2</sup> (Q1, Q3)	26 (23, 29)	26 (24, 29)	27 (24, 31)	26 (23, 29)	27 (24, 30)	27 (24, 32)
Medical history, n (%)*						
Diabetes mellitus	70 (5)	15 (7)	32 (10)	65 (5)	10 (4)	31 (10)
Hypertension	357 (27)	40 (18)	127 (40)	352 (27)	58 (23)	104 (35)
Cardiovascular disease	46 (3)	4 (2)	8 (3)	33 (2)	4 (2)	8 (3)
Hyperlipidemia	494 (37)	77 (34)	113 (36)	451 (34)	84 (34)	94 (31)

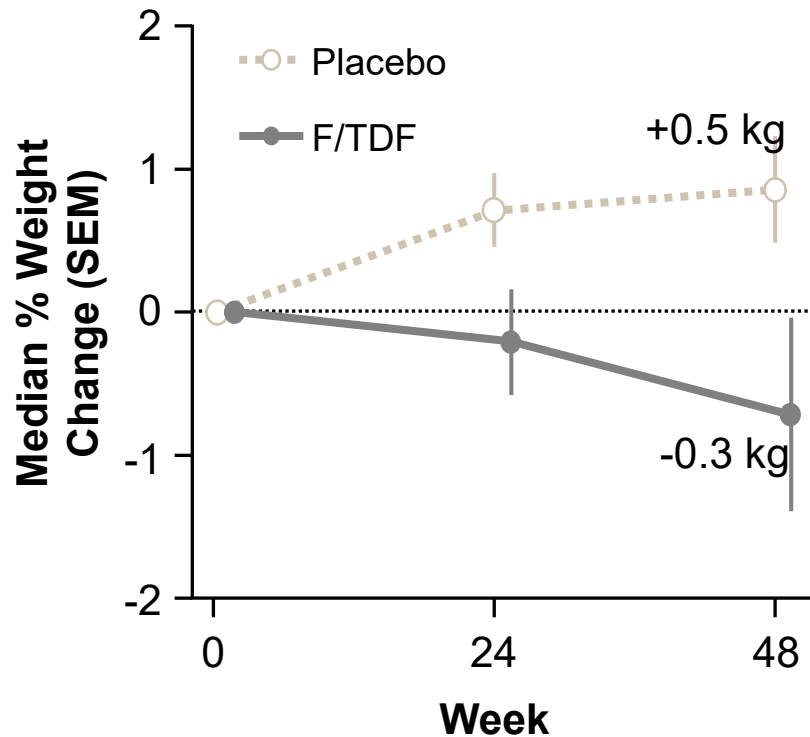
Weight change at week 96		
Median Change	TAF	TDF
All	+2.5	+0.5
	$\Delta$ 2.0; p <0.001	
Hispanic/Latinx	+2.3	+0.5
	$\Delta$ 1.8; p <0.001	
Black	+2.7	+0.4
	$\Delta$ 2.3; p <0.001	

¿Aumento de peso con INI o  
TAF en personas sin VIH?

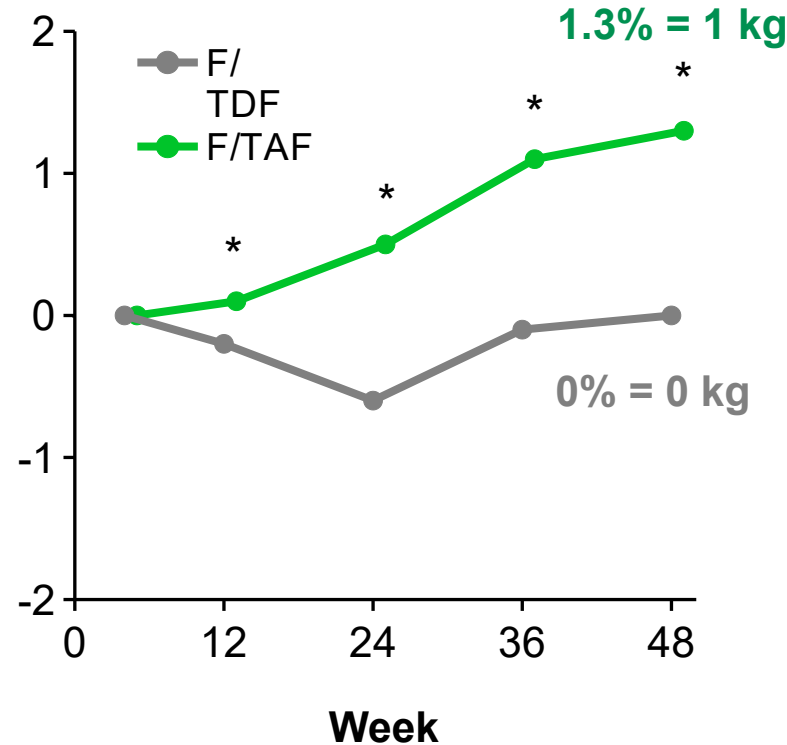
No hay retorno a la normalidad

# Weight Gain in PrEP Trials

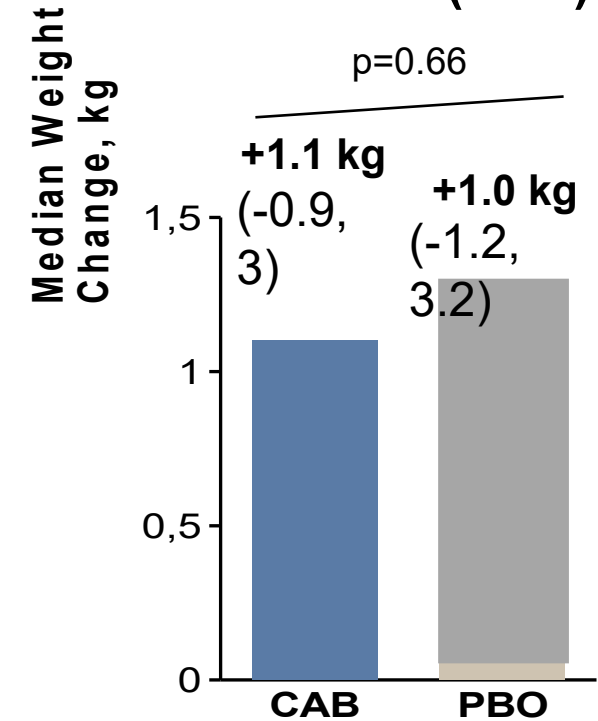
## iPrEx



## DISCOVER



## HPTN 077(W41)



- Differences driven by fat mass (limb and trunk)
- Apparently suppressive effect of TDF/FTC on fat accumulation.
- No evidence of altered fat distribution.
- Lean body mass was stable.

- $\geq 5\%$ : 22% vs 18% ( $p=.62$ )
- No differences by BMI category, sex, race, dosing or smoking
- Changes in fasting glucose or lipids did not differ by treatment arm

CAB, cabotegravir; PBO, placebo; SEM, standard error of mean

# Weight Gain in HBV Monoinfection Studies (TDF and TAF)

- Data from HBV clinical trials

- There is evidence to suggest that TDF may have a small suppressive effect on weight.
- In Studies 108 and 110 (pivotal trials of TAF for HBV treatment), minimal weight changes in weight were observed at Week 48, with a small decrease in the TDF arms and a small increase in the TAF arms.

Study	TAF	TDF	Difference (kg)
GS-US-320-0108	0.8	-0.7	1.5
GS-US-320-0110			

- A low proportion of subjects across both TDF and TAF treatment groups (1.2%) experienced a weight increase of  $\geq 10$  kg at Week 48
- A tenofovir (TFV) pharmacokinetic/pharmacodynamic analysis revealed that a decrease in weight in HBV-infected subjects was associated with the highest quartile of plasma TFV concentrations, which occurred with TDF.

Factores implicados en el aumento de peso

¿A qué se deben las diferencias en aumento de peso en África y en Occidente?

# Ensayos clínicos con datos de ↑ peso: Características basales

<b>Naive</b>	<b>GS-1489</b>	<b>GS-1490</b>	<b>AMBER</b>	<b>GEMINIs</b>	<b>ADVANCE</b>	<b>NAMSAL</b>
Países	USA, EU	USA, EU, Aus	USA, EU	5 continents	Sudáfrica	Camerún
Edad media	31	33	34	33	32	<b>37</b>
Mujeres	9%	12%	12%	15	<b>60%</b>	<b>66%</b>
Raza negra	36%	30%	11%	12%	<b>99%</b>	<b>99%</b>
CD4	446	440	453	461	<b>340</b>	<b>281</b>
CV>100K	17%	20%	18%	20%	22%	<b>66%</b>
IMC, kg/m <sup>2</sup>	25	25			21 H/26M	<b>23</b>

<b>Switch</b>	<b>TANGO</b>	<b>EMERALD</b>	<b>NEAT 022</b>	<b>GS-4030</b>
Países	USA, EU, Aus, Jap	USA, Europa	Europa	
Edad media	40	46	53	51
Mujeres	8%	18%	11%	15%
Raza negra	15%	21%	15%	23%
CD4	700	628	617	650
TAR nuevo	DTG+3TC vs Continuar	DRV/c/F/TAF vs Continuar	DTG+2NRTI vs Continuar	BIC/F/TAF vs DTG+TAF/F

# Factores implicados en el aumento de peso en VIH

## Independientemente del TAR:

- Sexo femenino
- Raza negra
- ↓ CD4
- ↑ Carga viral
- Peso bajo o normal
- Entorno obesogénico
- Fc. genéticos

En países africanos el sobrepeso/obesidad están “bien vistos”



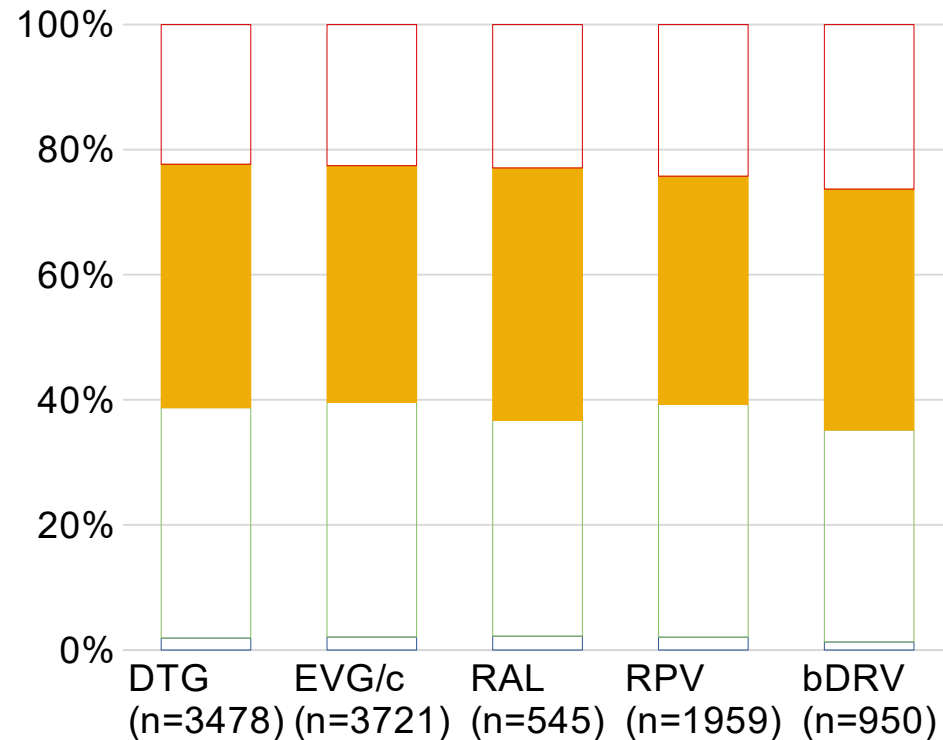
# ¿Factores genéticos implicados en el aumento de peso?

- OPERA cohort (USA). N=10.653

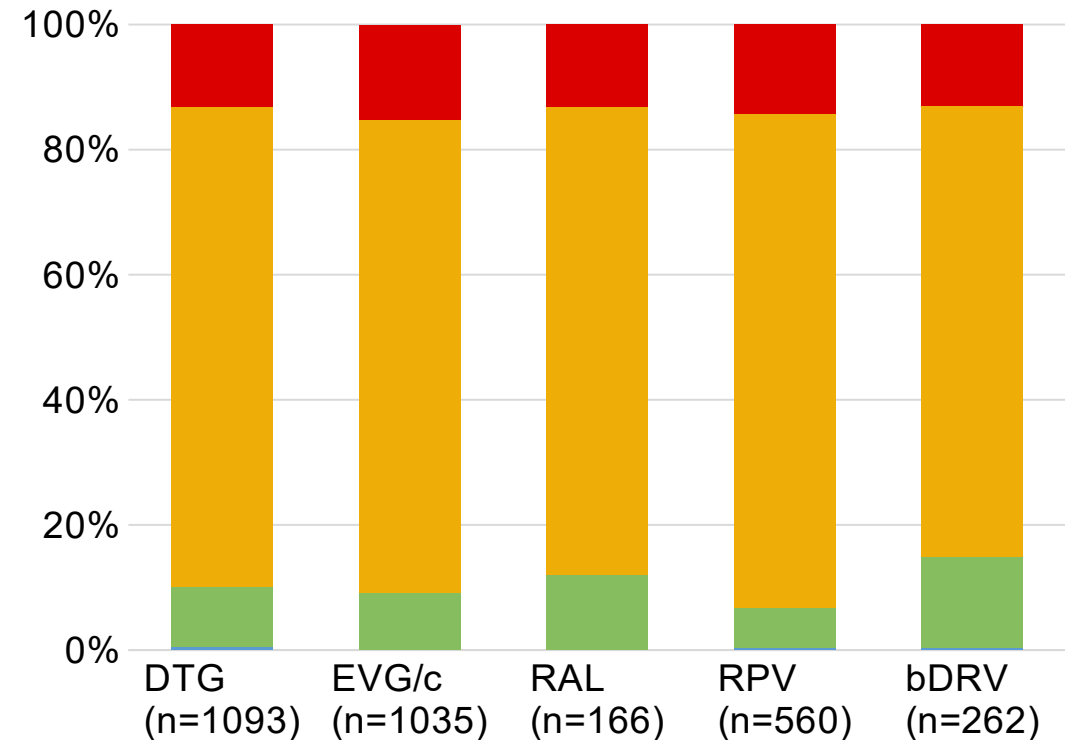
12-Month BMI Among Overweight PLWH at Baseline

■ Underweight (BMI <18.5) ■ Normal (BMI ≥18.5 to <25) ■ Overweight (BMI ≥25 to <30) ■ Obese (BMI ≥30)

## Baseline



## 12-month



- En todos los estudios (cohortes y EC), aunque la tendencia clara sea a aumentar peso, hay un porcentaje de patients que pierden peso con diferentes características basales y diferentes TARs: ¿Fc GENÉTICOS?



# ¿Factores genéticos implicados en el aumento de peso?

## Outliers: Casos clínicos con aumento de peso muy importante con INSTI

Case	Previous ART	Switch to	Weight gain	Switch to	Weigh change
1) Caucasian female, 58 yrs. Rheumatoid arthritis	EFV/FTC/TDF	<b>EVG/c/FTC/TDF</b> Then to: <b>DTG + TDF/FTC</b>	↑ 9 kg in 12 months ↑ 9 kg in 6 months	ATV/c + TDF/FTC	↓ 7 kg in 2 months
2) Black African male, 42 yrs.	EFV/FTC/TDF (renal function)	<b>DTG/ABC/3TC</b>	↑ 16 kg in 9 months	No ART change	
3) Caucasian male, 53 yrs.	DRV/r + TDF/FTC	<b>DTG + TDF/FTC</b>	↑ 13 kg in 12 months	NVP + TDF/FTC	Complete reversal of weight gain
4) Caucasian male 56 yrs. CD4 35/ mm <sup>3</sup>	<b>RAL + TDF/FTC</b>	<b>DTG + DRV/r (RAMs)</b>	↑ 5 kg in 2 months	No ART change	
5) Caucasian male, 37 yrs. CD4 34/mm <sup>3</sup> VL 1.500.000 c/mL	DRV/r + TDF/FTC	<b>DTG/ABC/3TC</b>	↑ 13 kg in 2 months (↑CD4 279/mm <sup>3</sup> , ↓ VL to <50 c/mL)	No ART change	

¿Alguna explicación  
además de retorno a la  
normalidad para un  
aumento de peso extra?



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

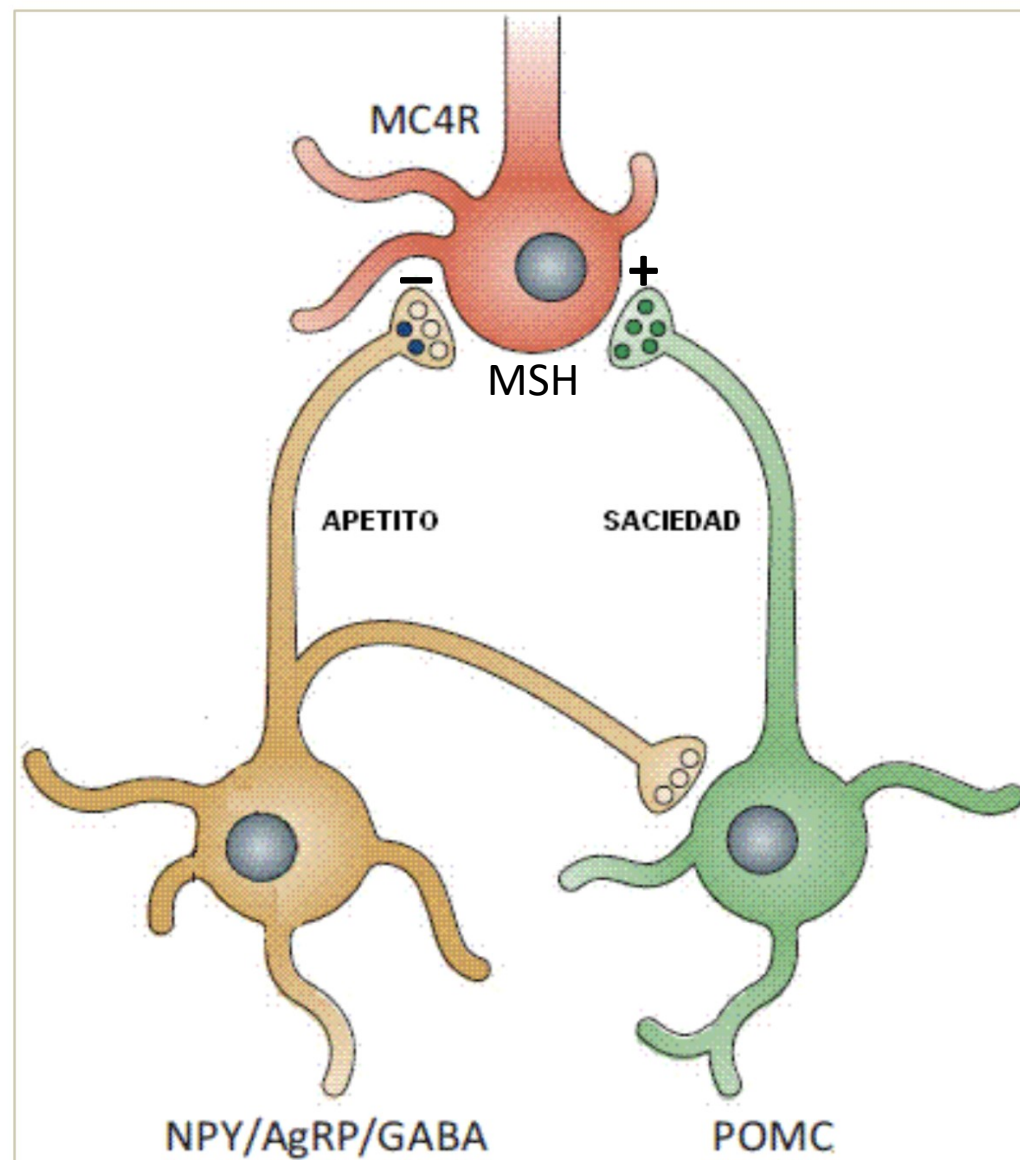
21 November 2013

Procedure No. EMEA/H/C/002753/0000

In vitro, dolutegravir inhibited the binding of radiolabeled  $\alpha$ -melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) receptor by 64% at a concentration equal to the clinical  $C_{max}$ .

The MC4R is involved notably in the regulation of energy homeostasis and food intake, and deficiency in the MC4R is associated with monogenic obesity.

## REGULACIÓN ENDOCRINA DE LA OBESIDAD

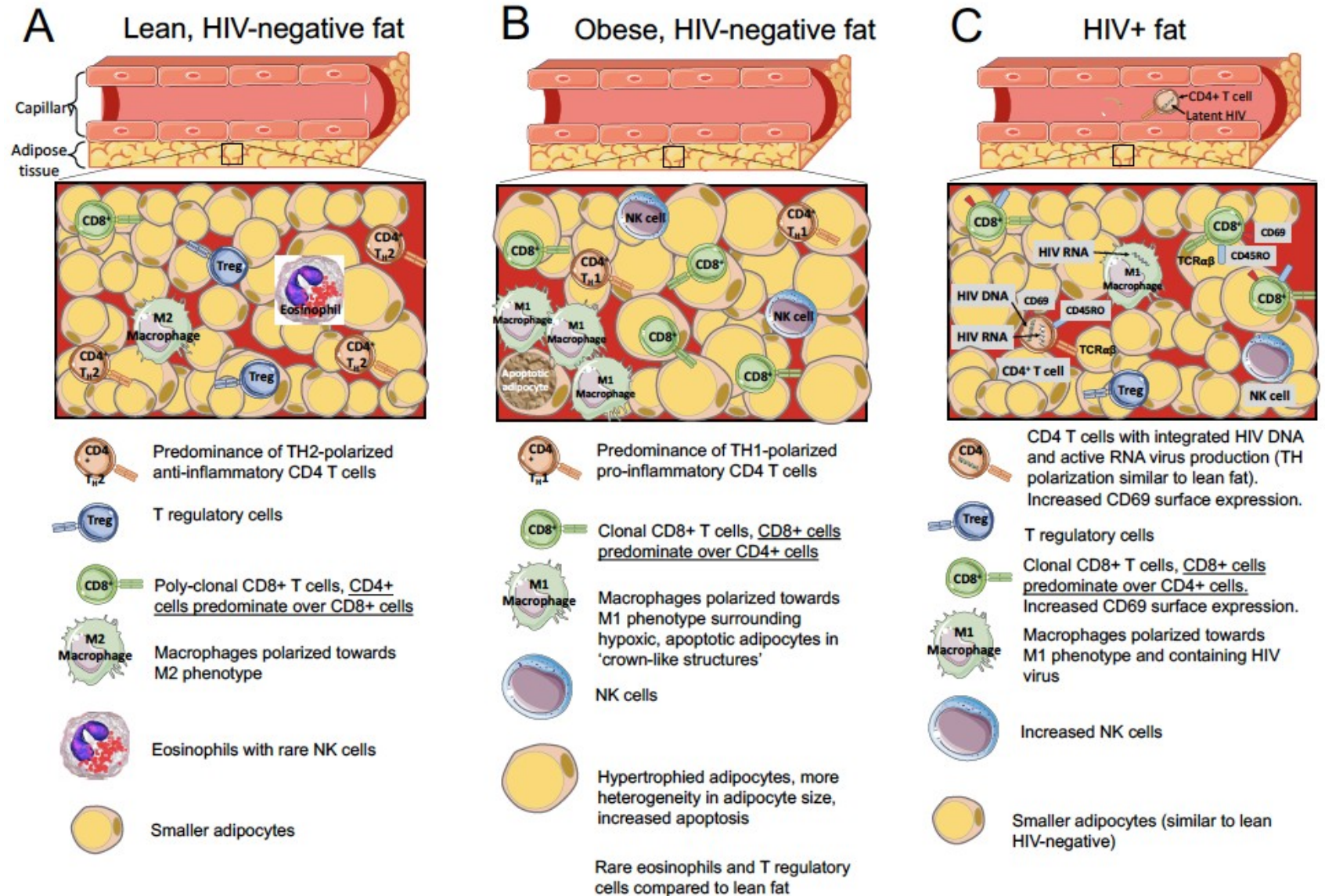


# ¿Factores genéticos implicados en el aumento de peso?

- In HIV, adipocytes are similar in size to lean HIV-negative persons, but with can greater heterogeneity and impaired adipogenesis and lipid metabolism.
- Marked enrichment in CD8+ T cell and few infiltrating macrophages.
- CD4+ T cells predominantly CD69+.
- In HIV a notable exception is the presence of latently HIV/SIV-infected CD4+ T cells capable of producing viral proteins and RNA virus.

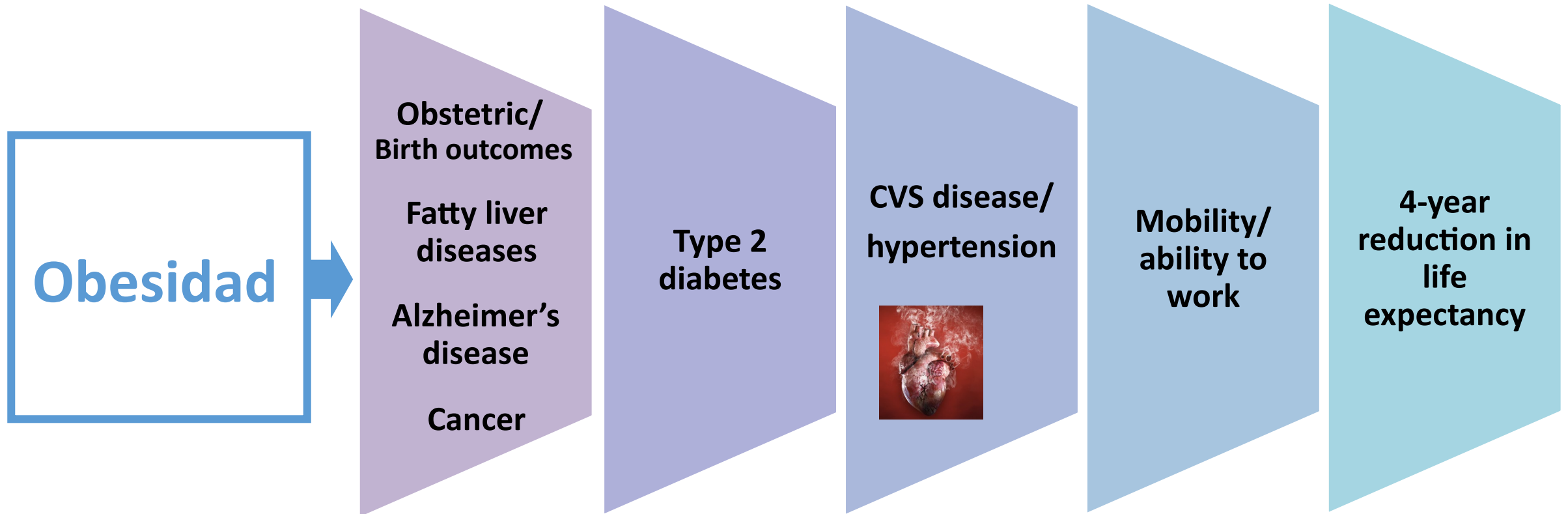
INSTI penetran mejor en tejido adiposo  
¿Mayor eliminación de VIH con ↑grasa?

Otros mecanismos:  
¿Metabolismo Triptófano-Kynurenina?  
EACS ¿Efecto proadipogénico e insulín R?



# Impacto clínico del aumento de peso

# Clinical implications of obesity in HIV-negative (BMI $\geq 30$ kg/m<sup>2</sup>)



# OMS ¿Cómo puede reducirse el sobrepeso y la obesidad?



8



## Advertising regulation

Compulsory front-of-pack (FOP) warning labels



El sobrepeso y la obesidad, así como las enfermedades no transmisibles vinculadas, pueden prevenirse en su mayoría. Son fundamentales unos entornos y comunidades favorables que permitan influir en las elecciones de las personas, de modo que la opción más sencilla (la más accesible, disponible y asequible) sea la más saludable en materia de alimentos y actividad física periódica, y en consecuencia prevenir el sobrepeso y la obesidad.

En el plano individual, las personas pueden optar por:

- limitar la ingesta energética procedente de la cantidad de grasa total y de azúcares;
- aumentar el consumo de frutas y verduras, así como de legumbres, cereales integrales y frutos secos; y
- realizar una actividad física periódica (60 minutos diarios para los jóvenes y 150 minutos semanales para los adultos).

# Impacto clínico del aumento de peso en las personas con HIV

## Riesgo de diabetes

### Cohorte VACS<sup>1</sup>

- Menor incidencia basal de DM en VIH que en No-VIH.
- ↑ de peso de 2.3 kg (5 lb) incrementa el riesgo de DM:
  - 14% en HIV

### Cohorte D:A:D<sup>2</sup>

- 12% ↑ riesgo de DM por unidad de IMC (1 kg/m<sup>2</sup>)
- ↑ 2,6 veces riesgo de diabetes en el cuartil más elevado de ↑ BMI.

## Riesgo Cardiovascular

### D:A:D cohort<sup>2</sup>

- Riesgo CV por cada unidad que aumenta el IMC según el peso basal:
  - Bajo peso: ↓ riesgo 10%
  - Peso Normal: ↑ riesgo 18%
  - Sobrepeso/obesidad ↔

## Mortalidad

### Cohorte VACS<sup>3</sup>

- ↑ de peso con TAR en pacientes sin sobrepeso basal se asocia a disminución de la mortalidad

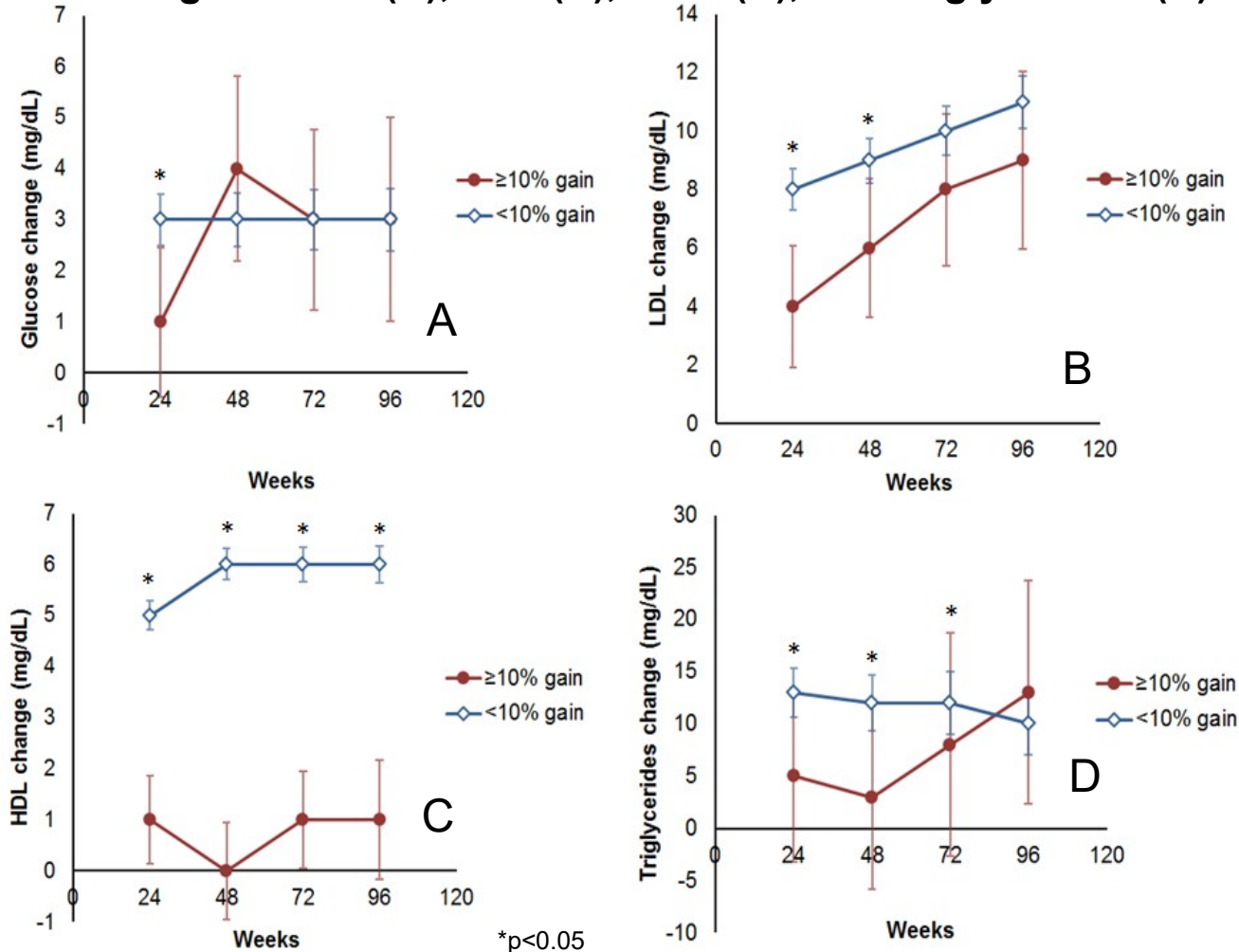
### Cohorte FRAM<sup>4</sup>

- La adiposidad central se asocia a elevada mortalidad



# Weight Trends in Participants Initiating ARV Therapy

**Mean Change from BL in Fasting Metabolic Parameters, including Glucose (A), LDL (B), HDL (C), and Triglycerides (D)**



**At Week 96 for <10% weight gain vs. ≥10%:**

- No significant difference in fasting glucose change (Fig. A)
  - Mean change was 3 mg/dL for both groups
- Similar small increases in LDL (Fig. B) and triglycerides (Fig. D). Small but significant increase in HDL (Fig. C) in those with <10% gain vs ≥10% gain
- Total cholesterol:HDL ratio was slightly higher in the ≥10% weight gain group (median 3.7 vs. 3.5)
- No significant differences between diabetes- or hyperglycemia-related AEs between groups
- Blood pressure: no clinically significant changes were observed (wk 96 weighted mean change from baseline in systolic and diastolic blood pressure are 2.2 and 1.5 mmHg respectively).

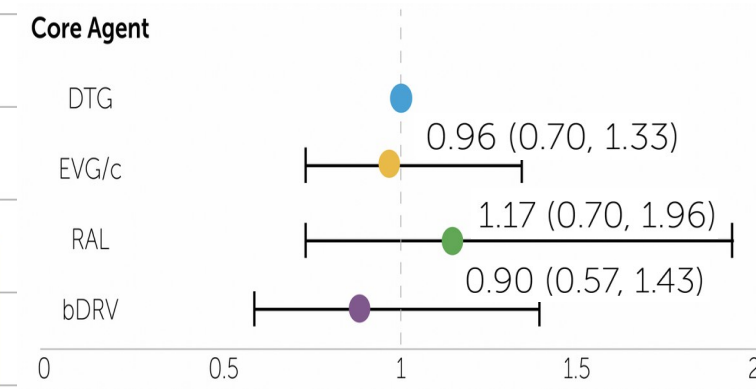
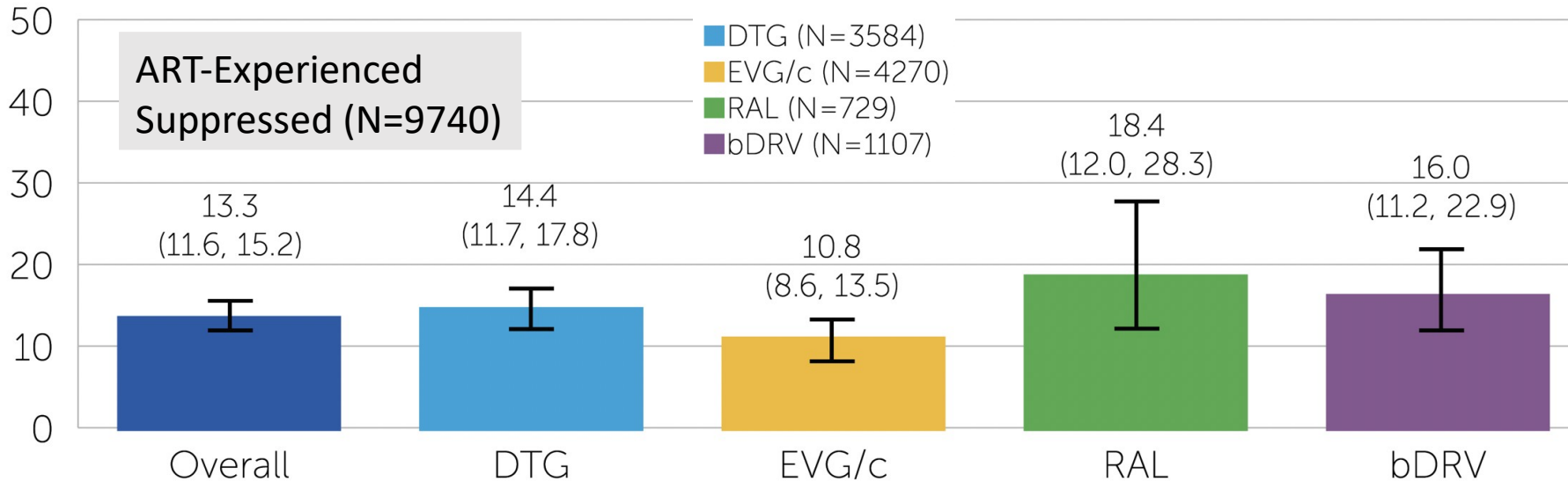
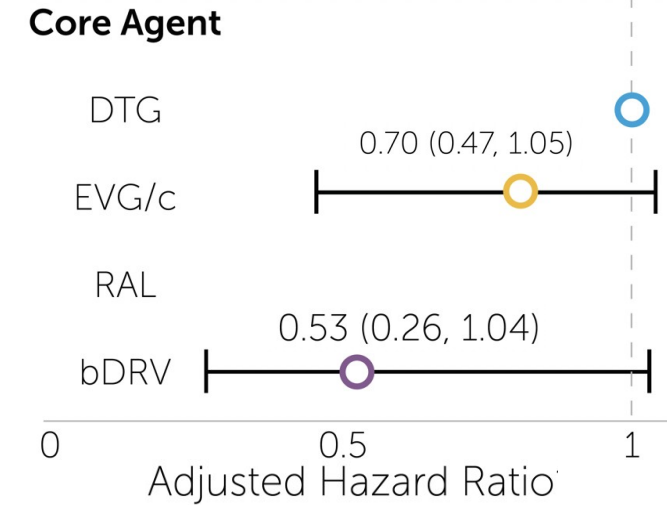
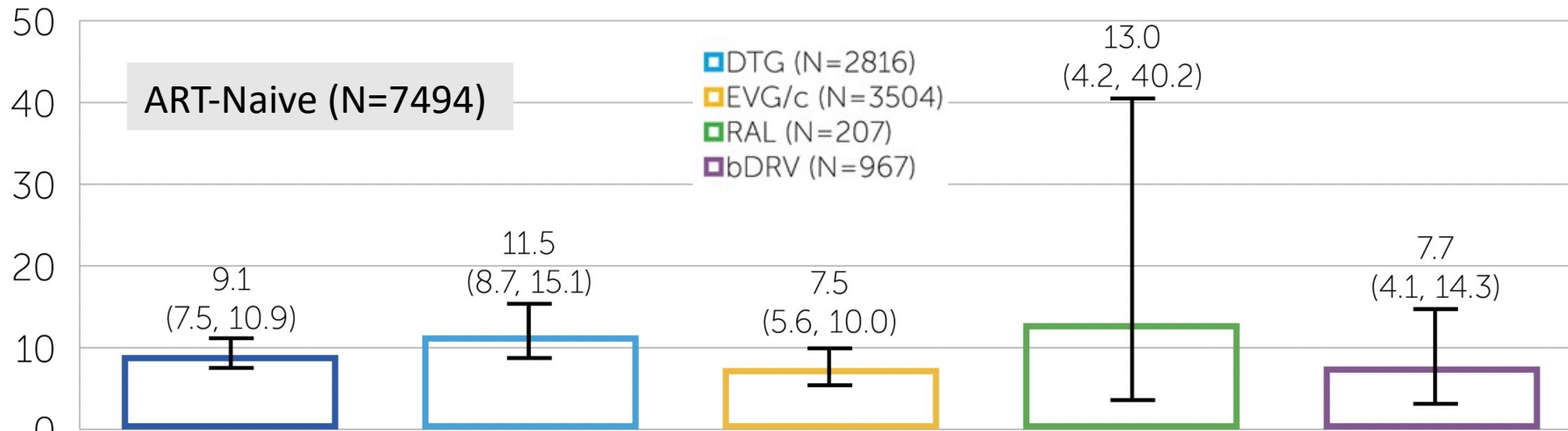
**There was no clinically significant metabolic impact of weight gain in these trials as measured by fasting glucose and investigator-reported AEs**

Impacto metabólico de los diferentes ARV

**¿Mayor impacto de los que se asocian a  
aumento de peso?**

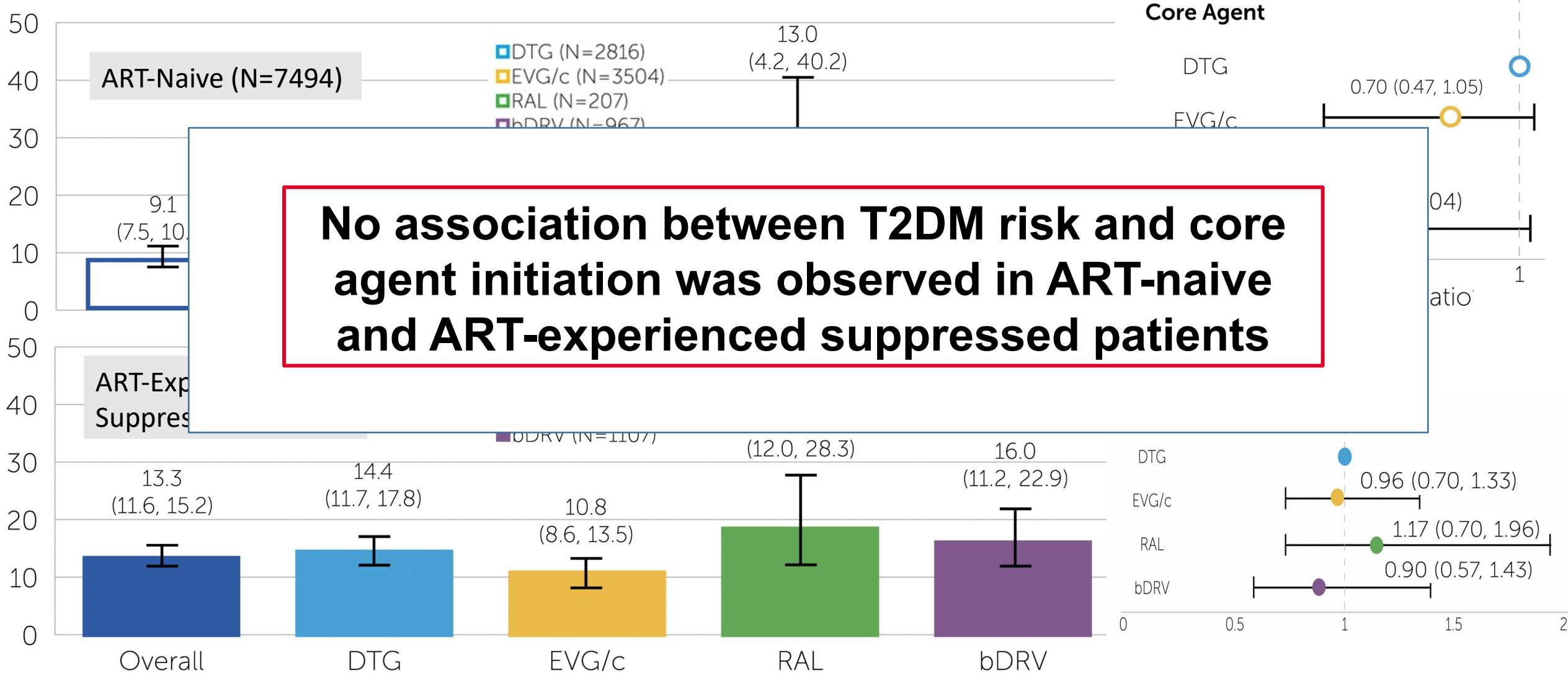
# OPERA: Risk of Type-2 Diabetes Mellitus After Initiating Integrase and Protease Inhibitors in Individuals Living With HIV in the United States

## Incidence Rates of T2DM per 1,000 Person-Years (95% CI)



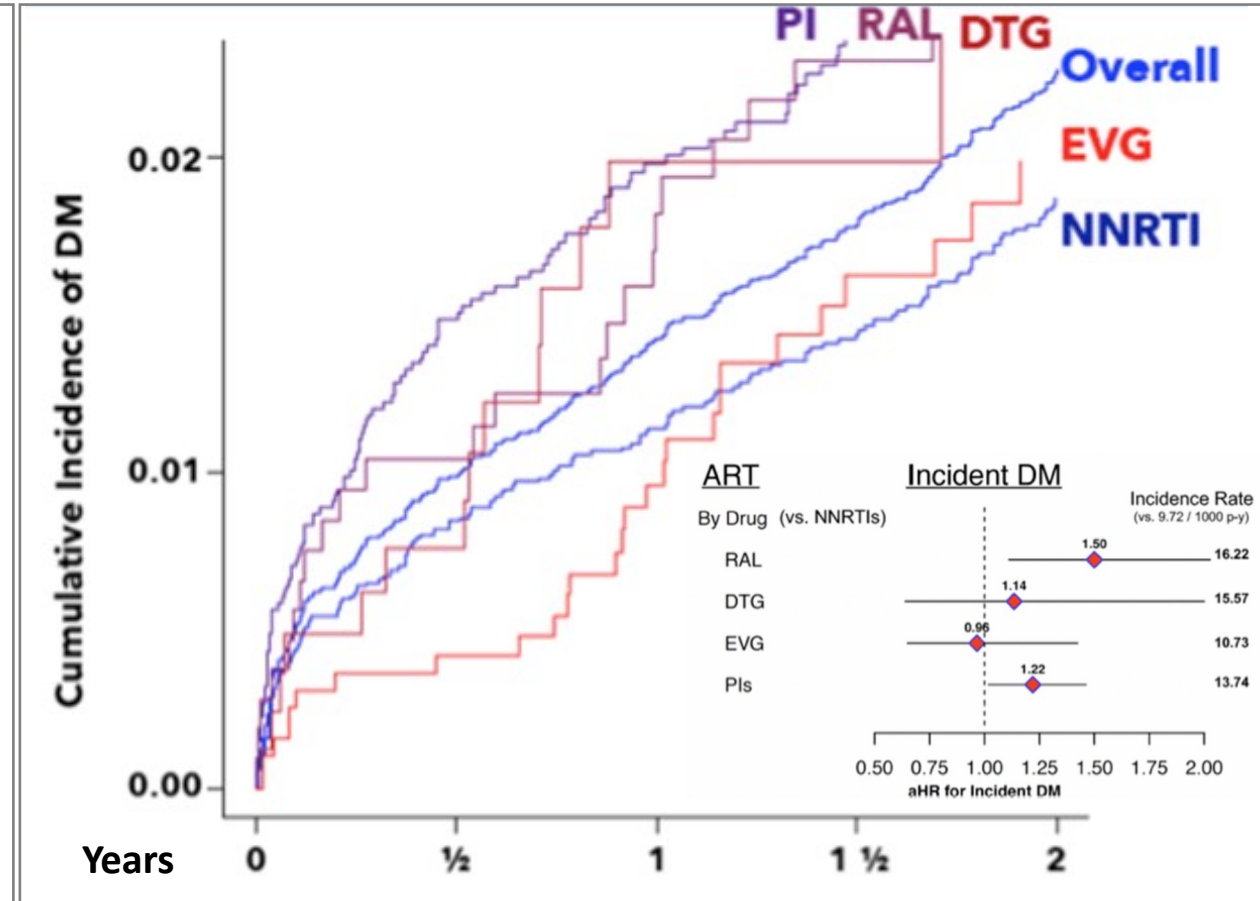
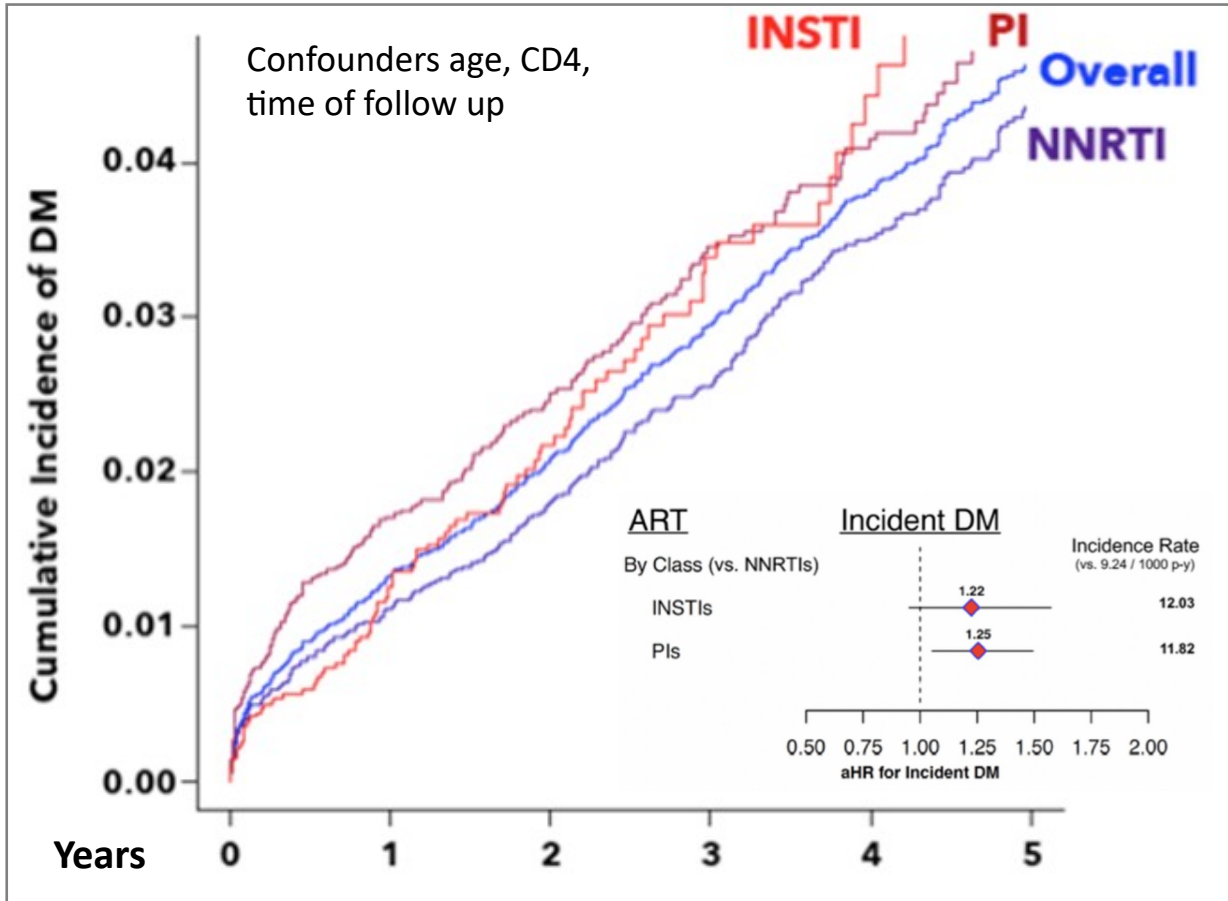
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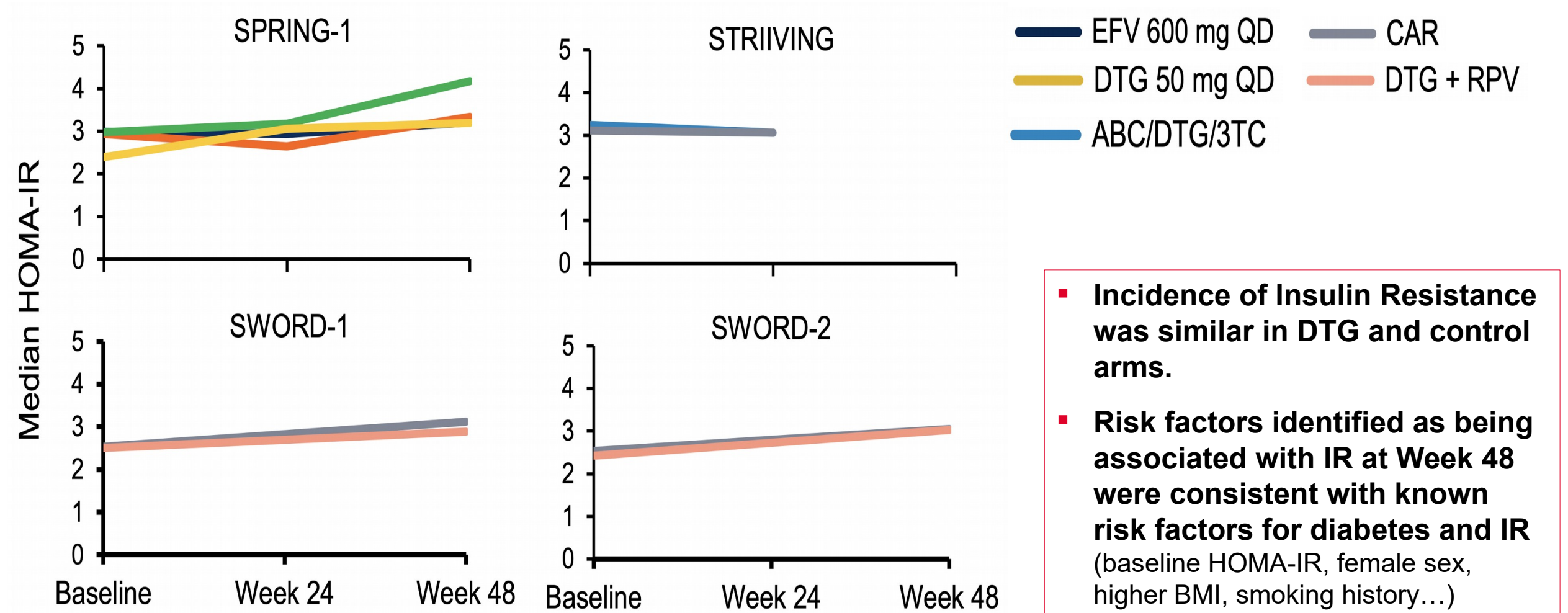
# NA-ACCORD: Effect of INSTI vs PI vs NNRTI ART on progression to Diabetes

- USA cohort Incident DM: INSTI 0.02 (106/4286), NNRTI 0.03 (336/10553), PI 0.03 (227/6677)



- Initiating INSTI- or PI- vs NNRTI-based regimens may confer increased risk of DM.
- Risk is heterogeneous among INSTIs.

# Dolutegravir and Insulin Resistance

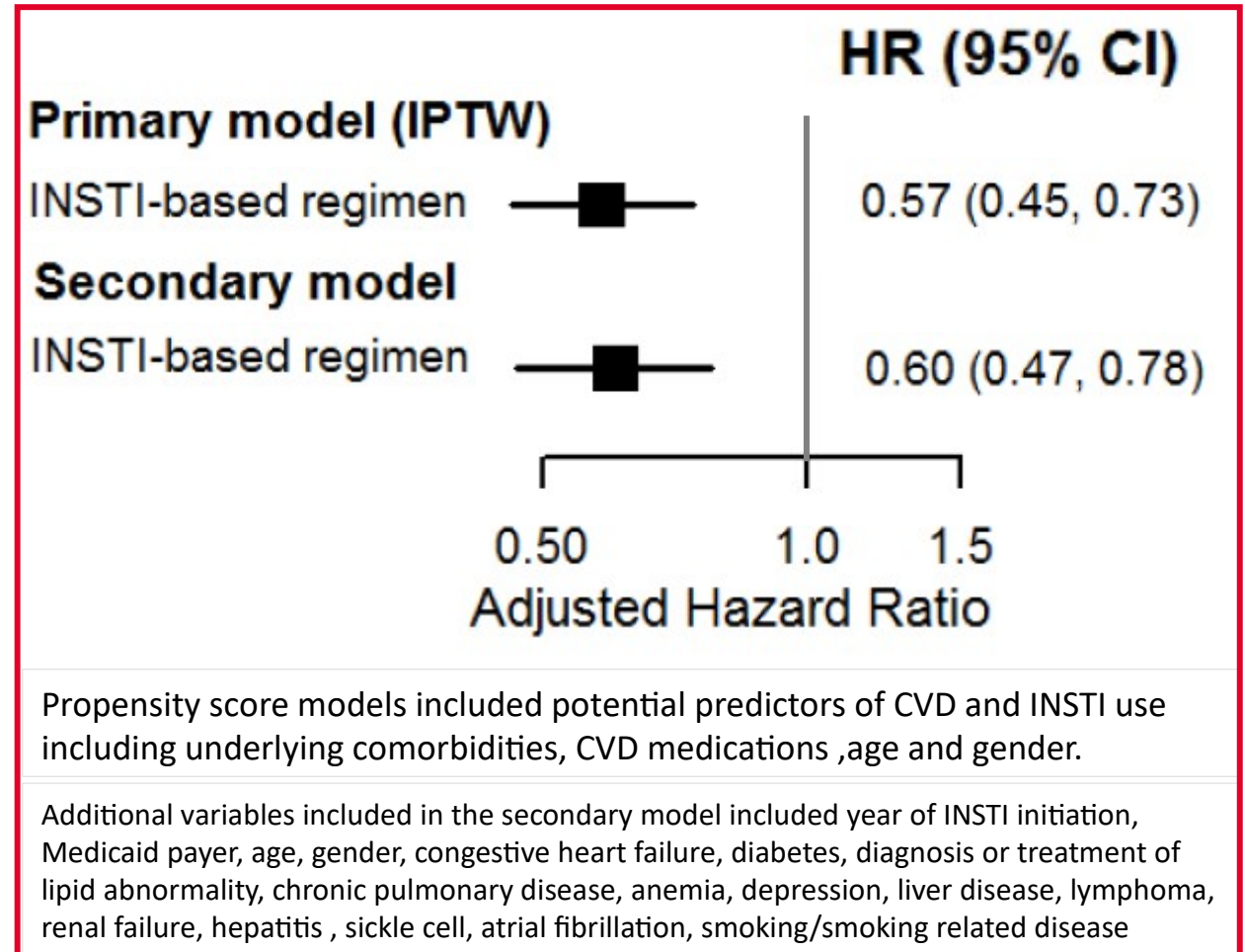


# Lower Cardiovascular Disease Risk Associated with INSTI

- USA cohort with 20459 new ART initiators (2008-15):
  - INSTI 5128 (25%) (RAL33%, EVG 49%, DTG 18%)
  - NNRTI 11191 (55%)
  - PI 4145 (20%)
- Median duration of follow up was 561
- Mean age was 40.6 years, 79 were male,

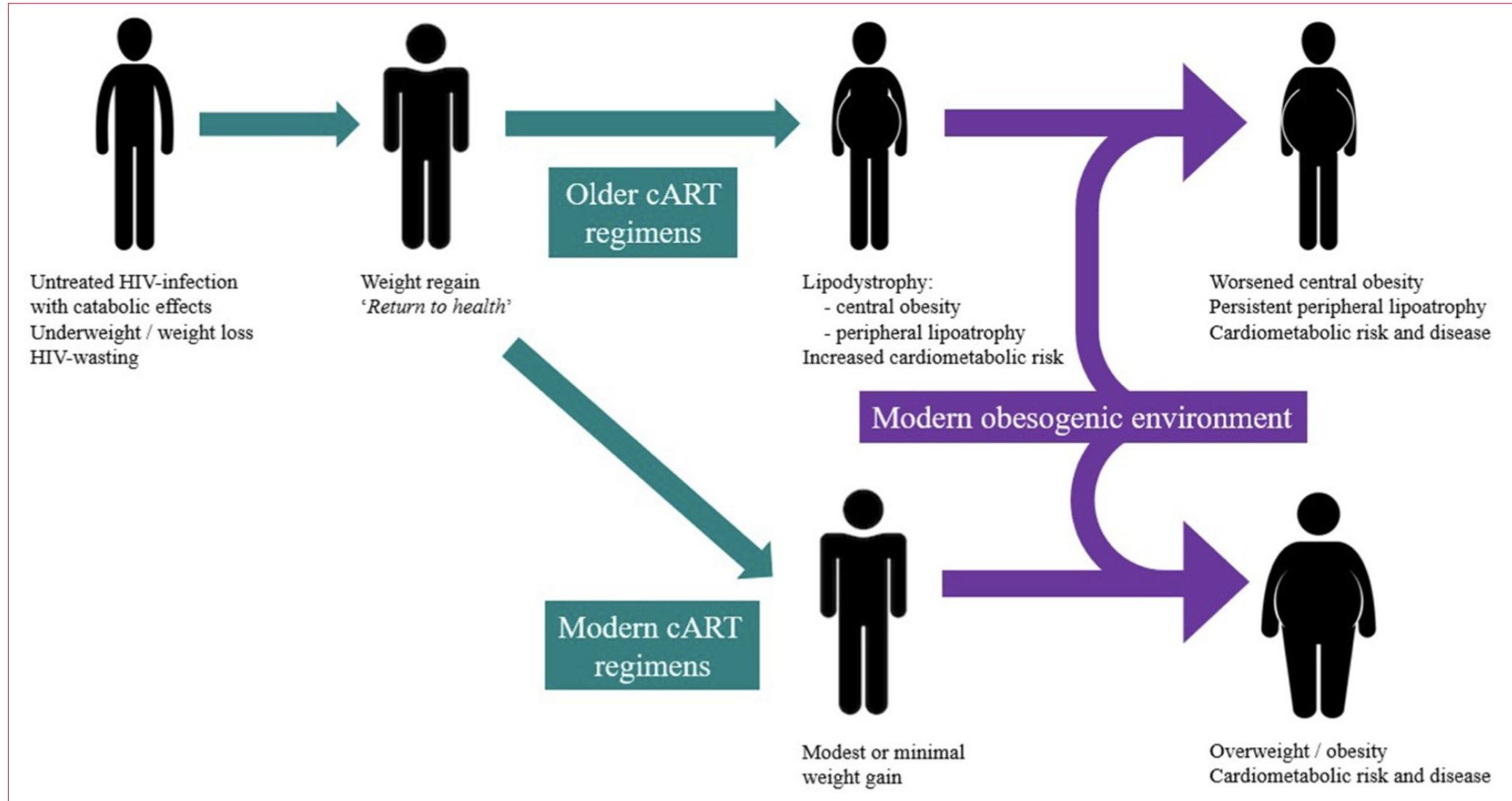
Major adverse cardiac event outcomes		
Outcomes	Non INSTI n=15,331	INSTI n=5,128
Overall MACE	130 (0.85)	31 (0.60)
Acute myocardial infarction	55 (0.36%)	11 (0.21%)
Stroke	48 (0.31)	14 (0.27%)
Coronary artery bypass	6 (0.04%)	1 (0.02%)
Percutaneous coronary intervention	21 (0.14%)	5 (0.10%)

MACE: major adverse cardiac event



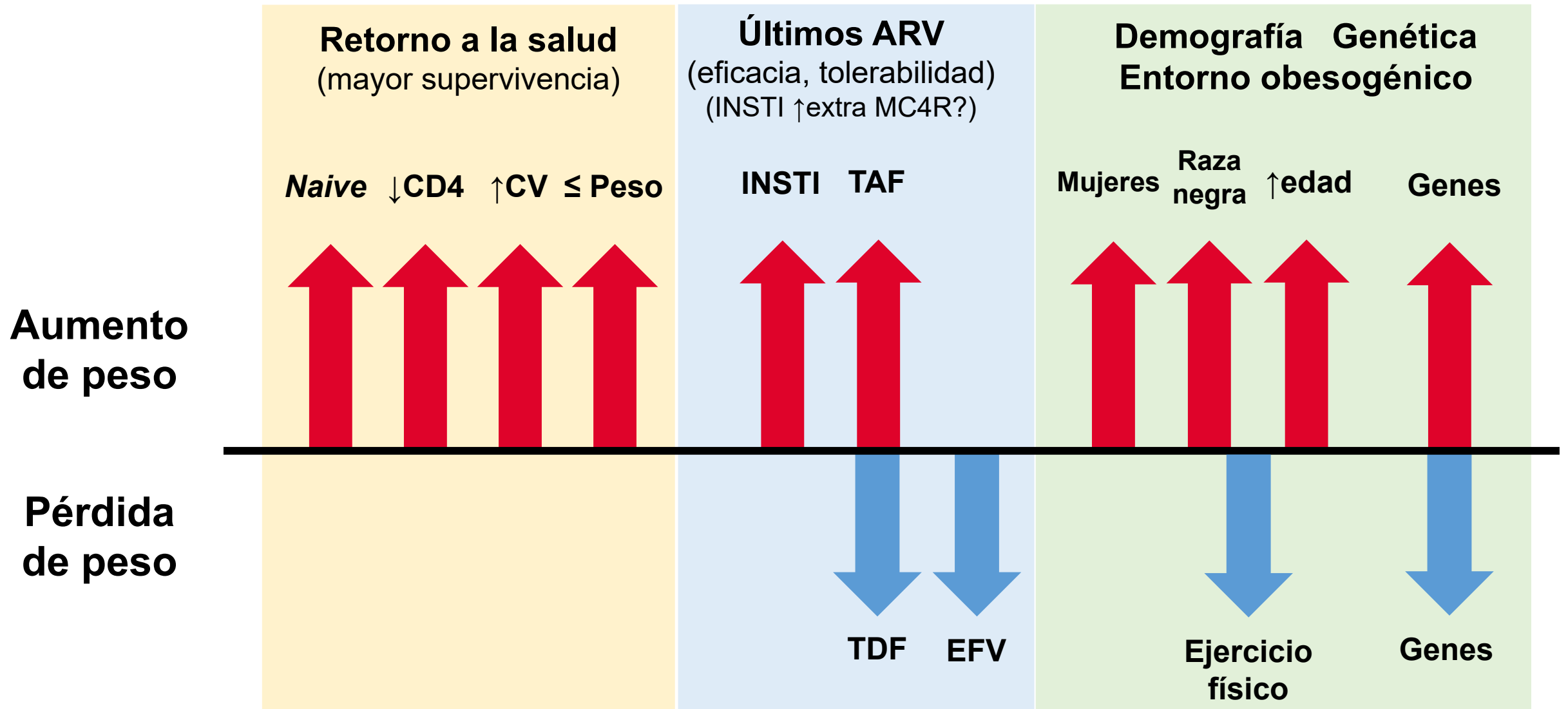
- Treatment with an INSTI-based regimen was associated with a 43% reduction in major adverse cardiovascular events.**

# Intersección entre la epidemia actual de obesidad y los cambios históricos en el TAR y su contribución en el aumento de peso





# Factores relacionados con la ganancia/pérdida de peso con el TAR



Administrar los **mejores ARV** (inicio, simplificación o rescate)

Insistir en **suspender tabaco** si es fumador

Recomendaciones de **dieta saludable**

Recomendaciones de **ejercicio físico**

Control/tratamiento **comorbilidades** (diabetes, HTA, RCV...)



GRACIES