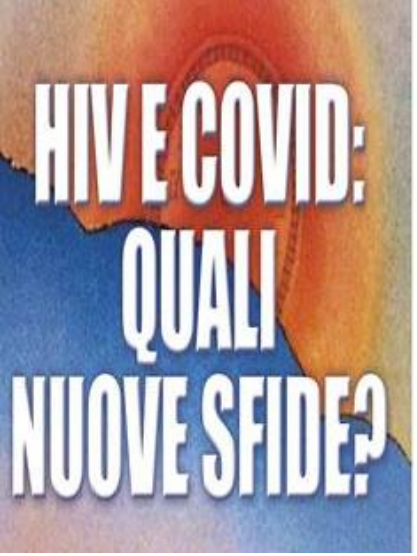

CONVEGNO
VIRTUAL EDITION
7-8 Giugno 2021

Weight gain: farmaci a confronto

Stefania Cicalini
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Disclosures

Dr. Cicalini has served as a paid consultant to Gilead Sciences, Janssen-Cilag, Merck and ViiV Healthcare and received research funding through National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS from Gilead Sciences.

Weight gain and ARVs

- Weigh gain (WG) after ART initiation is a well known phenomenon among PLWHIV and can occur with all antiretroviral classes.
- There is growing evidence that the use of integrase inhibitors (INSTIs) is associated with more WG than other classes of ARVs.
- In particular, dolutegravir has been associated with the greater risk in both observational and randomized studies, among naïve and experienced patients.
- Results from studies also suggest that there may be an additional effect of TAF on WG.

Outline

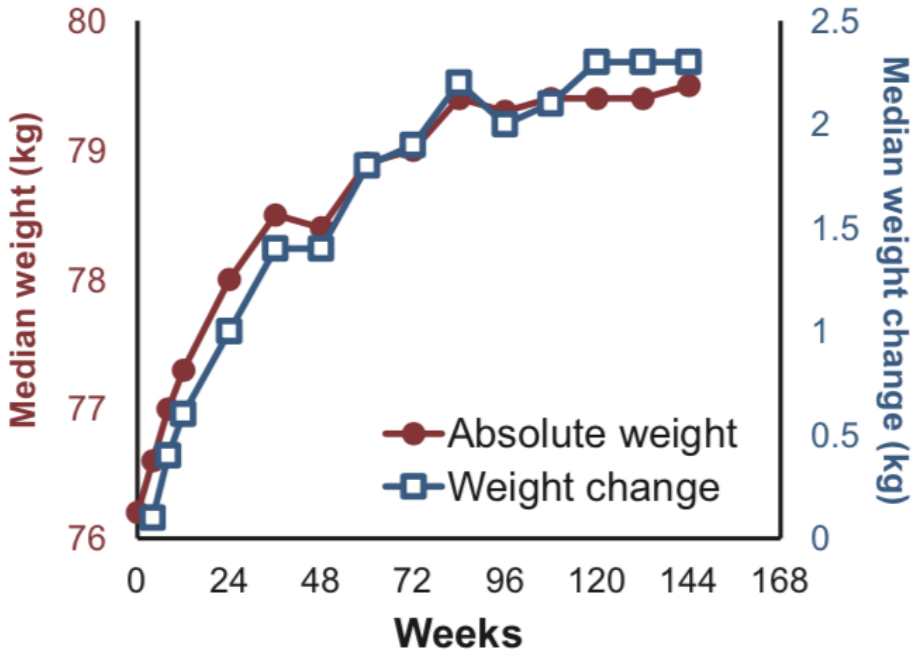
- Weight gain and INSTIs
    - Naive patients
        -data from RCTs
        -data from observational studies

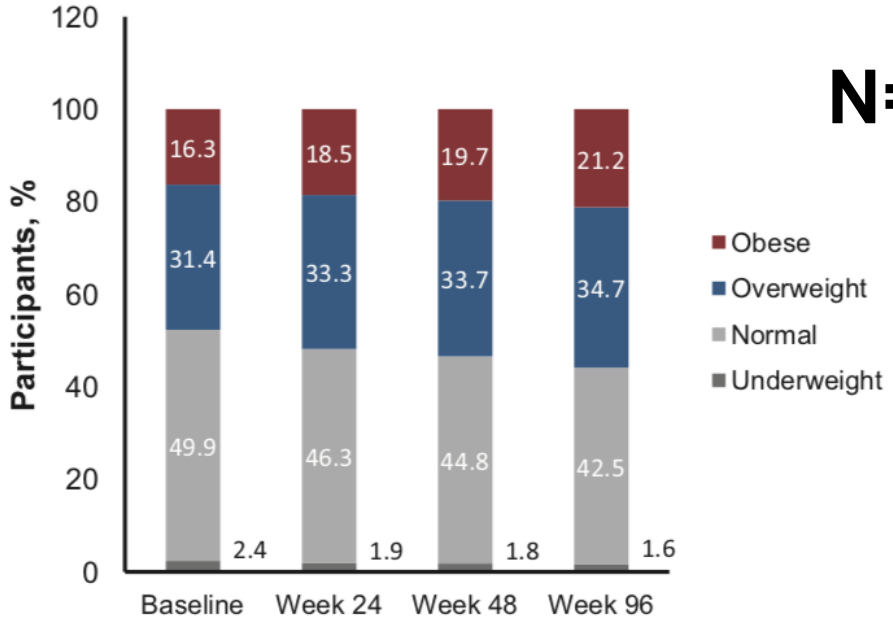
    - Experienced patients
        -data from RCTs
        -data from observational studies

- Weight gain and newest ARVs
- Role of backbone
- Weight gain and 2DR

Pooled analysis of 8 phase-3 RCTs of HIV-naïve patients initiating ART between 2003 and 2015

96-week Median (IQR) weight gain: 2.0 kg (-0.9 to 5.9)





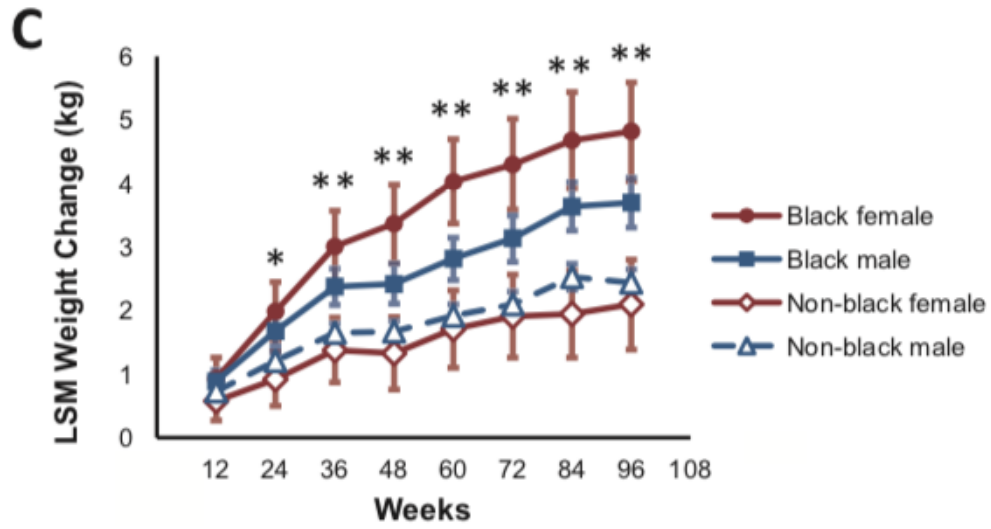
N=5680

Through 96 wks, 48.6%, 36.6%, and 17.3% of pts had at least 3%, 5%, and 10% weight increase from BL, respectively

Sax PE, CID 2020

Risk factors for WG following initiation of ART in the pooled analysis by Sax

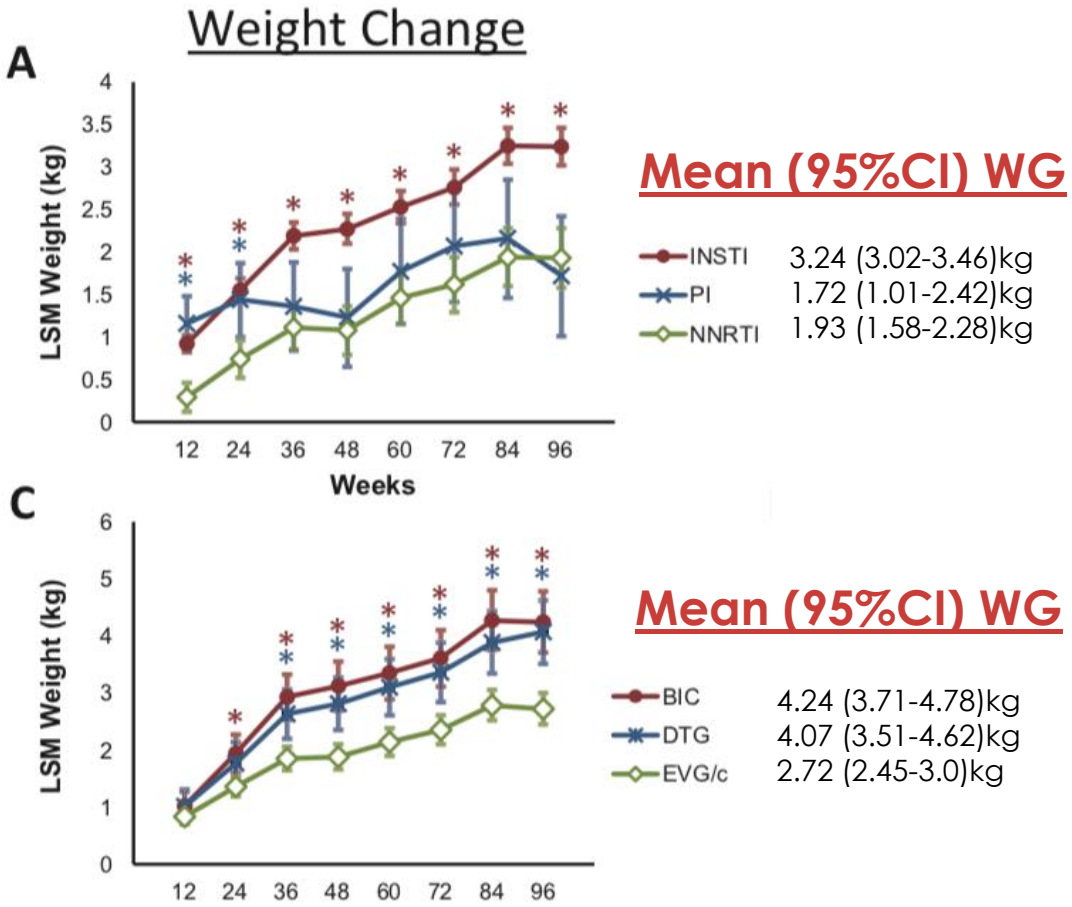
Variable	Difference, kg	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/μL)	2.97	(2.81–3.13)	<.001
IV drug use (no vs yes)	1.41	(.97–1.85)	<.001
Race (black vs non-black)	0.99	(.87–1.11)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	0.96	(.84–1.08)	<.001
Symptomatic HIV (yes vs no)	0.51	(.36–.65)	<.001
Sex (female vs male)	0.23	(.07–.4)	.006
Age (<50 vs ≥50 y)	0.22	(.07–.37)	.004
BMI			
Obese vs normal	0.21	(.06–.36)	.005
Overweight vs normal	0.24	(−.36 to −.13)	<.001



Sax PE, CID 2020

Pooled analysis of 8 phase-3 RCTs of HIV-naïve patients initiating ART between 2003 and 2015

N=5680

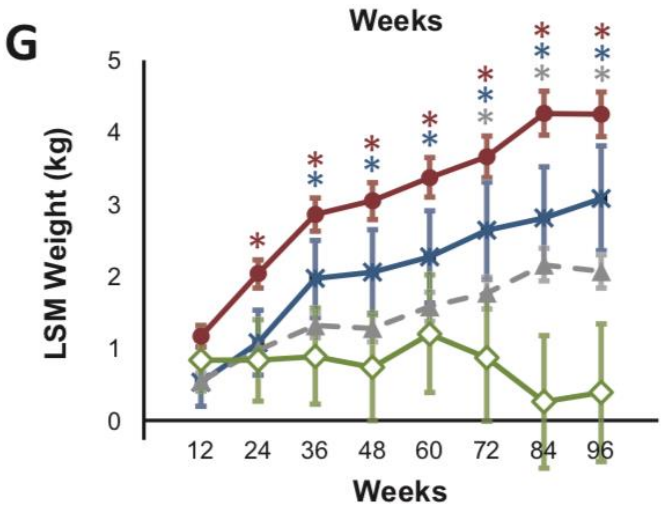


Mean (95%CI) WG

INSTI	3.24 (3.02-3.46)kg
PI	1.72 (1.01-2.42)kg
NNRTI	1.93 (1.58-2.28)kg

Mean (95%CI) WG

BIC	4.24 (3.71-4.78)kg
DTG	4.07 (3.51-4.62)kg
EVG/c	2.72 (2.45-3.0)kg



Mean (95%CI) WG

TAF	4.25 (3.94-4.56)kg
ABC	3.08 (2.36-3.81)kg
TDF	2.07 (1.84-2.30)kg
ZDV	0.39 (-0.57-1.34)kg

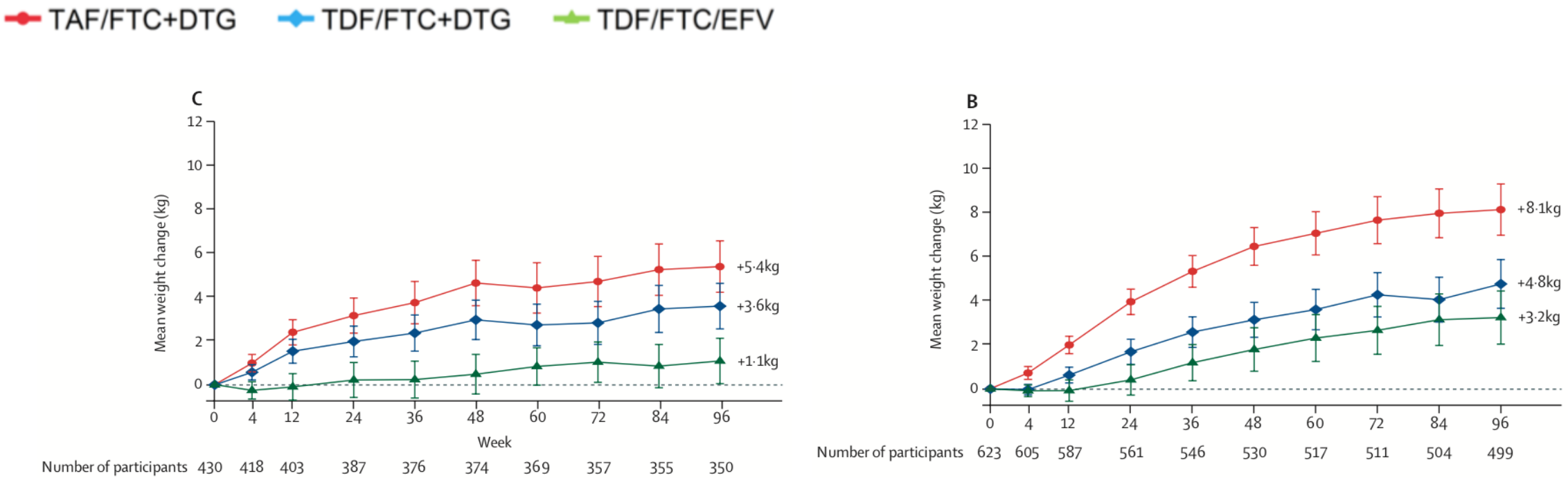
Sax PE, CID 2020

Risk factors for significant (≥10%) WG following initiation of ART in the pooled analysis by Sax

Variable	OR	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/all)	4.36	(3.6–5.27)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	1.98	(1.65–2.37)	<.001
BMI			
Normal vs overweight	1.54	(1.27–1.87)	<.001
Normal vs obese	1.66	(1.29–2.15)	<.001
Sex (female vs male)	1.54	(1.21–1.96)	<.001
Race (black vs non-black)	1.32	(1.10–1.59)	.003
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	.002
EVG/c vs EFV	1.36	(1.04–1.78)	.026
RPV vs EFV	1.51	(1.03–2.20)	.035
ATV/r vs EFV	0.92	(.59–1.45)	.73
NRTI			
TAF vs ZDV	1.75	(1.04–2.95)	.034
TDF vs ZDV	1.19	(.76–1.87)	.44
ABC vs ZDV	0.93	(.47–1.8)	.82
TAF vs ABC	1.9	(1.25–2.88)	.003
TDF vs ABC	1.29	(.79–2.11)	.31
TAF vs TDF	1.47	(1.14–1.90)	.003

Sax PE, Clin Infect Dis 2020

The ADVANCE study: a phase-3 RCT of naïve patients in South Africa. Mean change in weight (kg) to week 96



MEN **WOMEN**

- **Significantly greater WG with DTG vs EFV, with TAF vs TDF**
- **Significantly greater WG in female patients** than in male patients across all three groups with plateau in the increase after wk 48 in men but not in women

Venter, Lancet 2020

Outline

- **Weight gain and INSTIs**
    - **Naive patients**
        - -data from RCTs
        - -**data from observational studies**
    - Experienced patients
        - -data from RCTs
        - -data from observational studies
- Weight gain and newest ARVs
- Role of backbone
- Weight gain and 2DR

Weight gain in observational studies of treatment-naive patients taking INSTIs

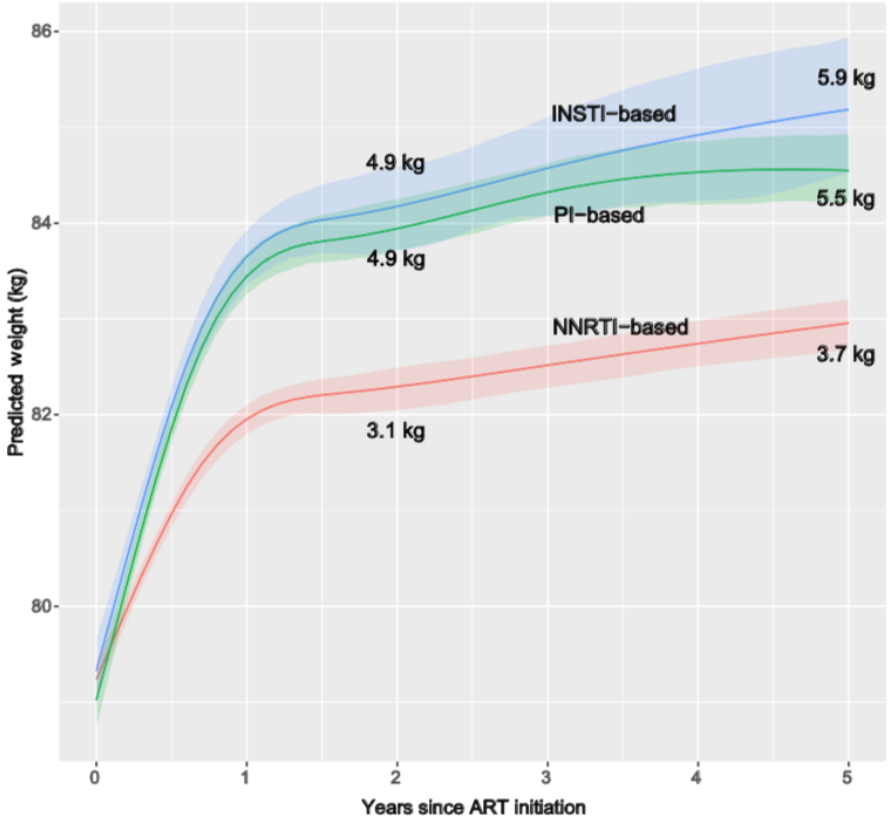
Study	Study arms	Weight changes observed (kg)
Calza et al. [31]		After 12 months[a]:
Italy	EVG/c ($n = 158$)	+ 2.14
	DRV ($n = 152$)	+ 1.85
	DTG ($n = 174$)	+ 2.38
	RAL ($n = 196$)	+ 1.93
Hsu et al. [28]		After 12 months[b]:
USA		
OPERA cohort	DTG ($n = 1562$)	+ 3.6
	EVG/c ($n = 2026$)	+ 3.5
	RAL ($n = 62$)	+ 2.9
	RPV ($n = 574$)	+ 2.1
	DRV ($n = 382$)	+ 4.7
Bourgi et al. [27, 32]		After 60 months[c]:
NA-ACCORD	INSTI ($n = 4638$)	+ 5.9
	PI ($n = 7038$)	+ 5.5
	NNRTI ($n = 11,296$)	+ 3.9
Rizzardo et al. [33]		After 12 months[d]:
	DTG monotherapy ($n = 20$)	+ 3.82
Bourgi et al. [29]		After 18 months[e]:
Vanderbilt Comprehensive Care Clinic Cohort	DTG ($n = 135$)	+ 6kg
	RAL ($n = 63$)	+ 3.4kg
	EVG ($n = 153$)	+ 0.5kg
	NNRTI ($n = 347$)	+ 2.6kg
	PI ($n = 454$)	+ 4.1kg
Ruderman et al. [30]		At 6 months[f]:
CNICS cohort		
USA	EFV ($n = 415$)	EFV + 0.22
	RPV ($n = 341$)	RPV + 0vs.13
	ATV/r ($n = 95$)	ATV + 2.66
	DRV/r ($n = 258$)	DRV + 4.11
	RAL ($n = 95$)	RAL + 2.52
	EVG/c/TDF ($n = 780$)	EVG/TDF + 2.29
	EVG/c/TAF ($n = 282$)	EVG/TAF + 2.46
	DTG/TDF ($n = 233$)	DTG/TDF + 3.11
	DTG/TAF ($n = 116$)	DTG/TAF + 4.88
	DTG/ABC ($n = 383$)	DTG/ABC + 2.83

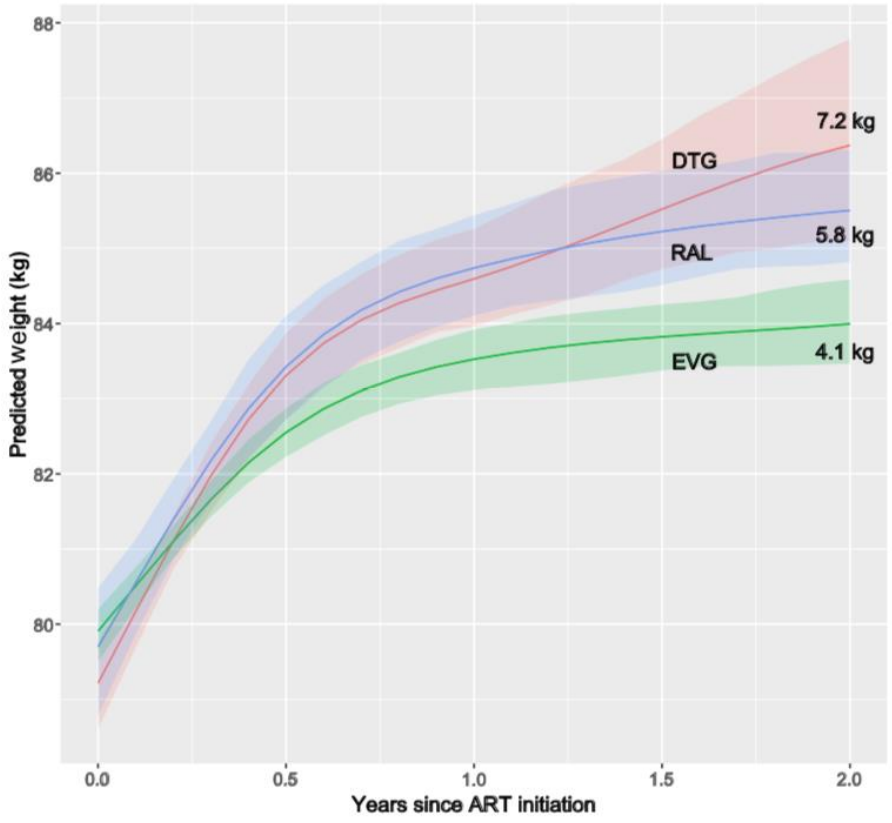
Shah, Drugs 2021

IeDEA & NA-ACCORD

Treatment-naïve PLWH starting INSTIs are at higher risk of WG compared to NNRTI-class regimens

N= 22972





- No difference by race (white vs non-white) or sex

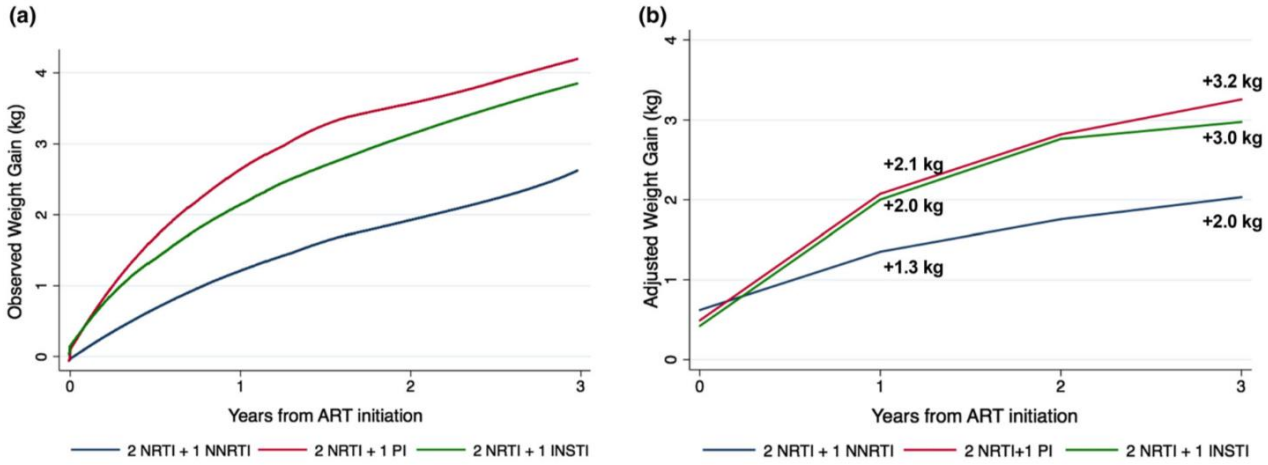
Bourgi K, JIAS 2020

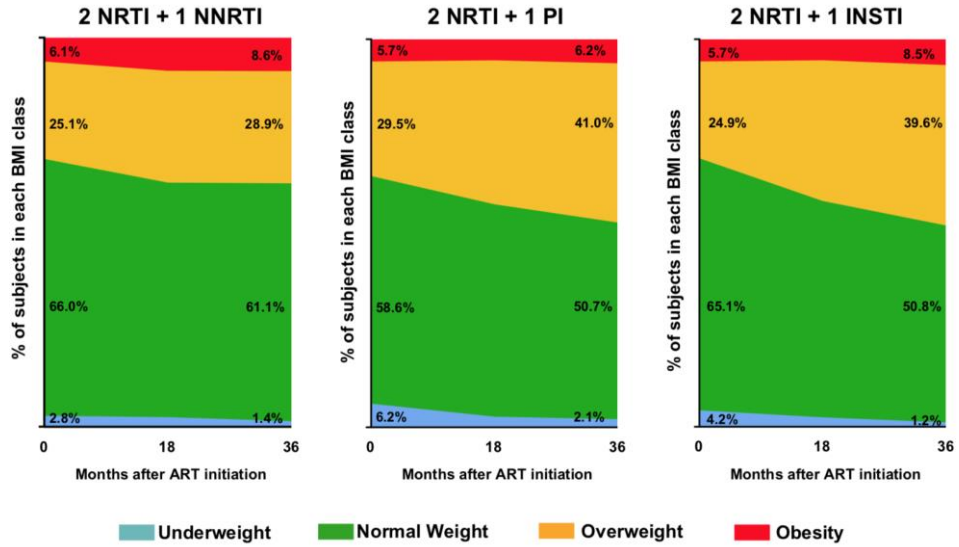
CoRIS Cohort

Prospective multicentre study in Spain

1631 patients, median age 36 (IQR 30-44), men 87%

Median follow-up 47 months (IQR 28-75)





- INSTI and PI- based first line ARTs are associated with greater WG compared to NNRTI-based ART
- No significant differences between PI- and INSTI- based ART with similar WG with respect to NNRTI-based ART
- No significant differences among INSTI drugs (no BIC patients included)

Martinez-Sanz, JAIDS 2021

Outline

- **Weight gain and INSTIs**
    - Naive patients
        -data from RCTs
        -data from observational studies

    - **Experienced patients**
        -data from RCTs
        -data from observational studies

- Weight gain and newest ARVs
- Role of backbone
- Weight gain and 2DR

Weight gain in RCTs of treatment-experienced patients switching to INSTIs

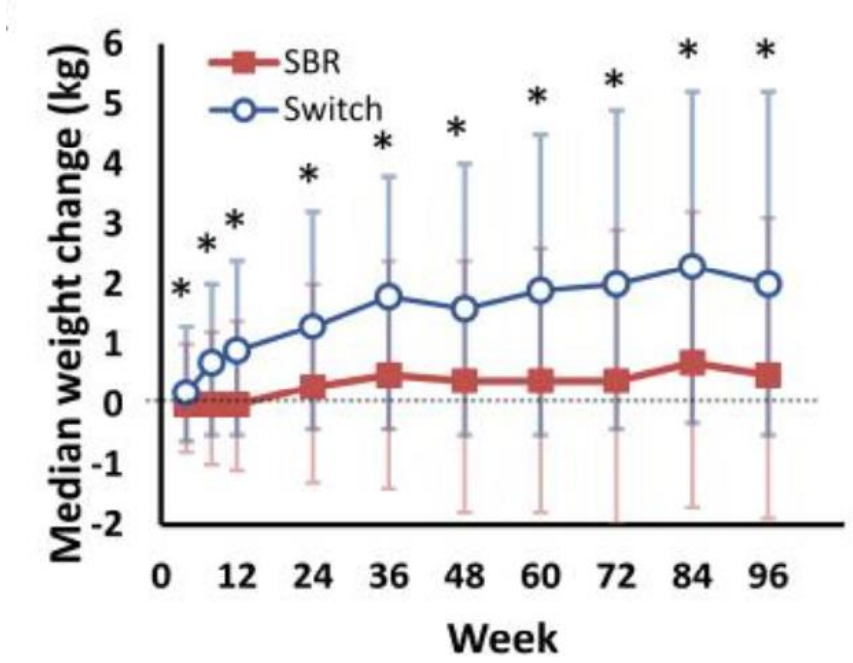
Study	Study arms	Observed weight changes (kg)
Hill et al. [56] Visend Arm A Zambia		At week 24[a]:
	TAF/FTC + DTG ($n = 210$)	+ 1.8
	TDF/3TC + DTG ($n = 209$)	+ 0.4
Hill et al. [56] Visend Arm B Zambia		At week 24[a]:
	TAF/FTC + DTG ($n = 209$)	+ 2.7
	TDF/FTC + DTG ($n = 209$)	+ 1.9
	AZT + 3TC + LPVr/ATVr ($n = 289$)	+ 1.3
Waters et al. [57] NEAT-022 Europe		At week 48[b]:
	DTG-I ($n = 205$)	+ 0.82
	DTG-D (n=210)	+ 0.2
		At week 96:
		+ 0.03
		+ 0.98

[a]VISEND switch is from TDF/XTC/EFV. VISEND Arm A: HIV-1 RNA <1000 copies/mL; VISEND Arm B: HIV-1 RNA ≥1000 copies/mL

[b]Participants with potential high CVD risk (age over 50 y or Framingham >10%), stable and suppressed for ≥6/12 on a PI/r-based triple regimen were randomised to immediate switch for 96 weeks (DTG-I) or to remain on PI/r for 48 weeks followed by deferred switch to DTG (DTG-D) for 48 weeks

Shah, Drugs 2021

Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from 12 Randomized Clinical Trials



- At wk 48

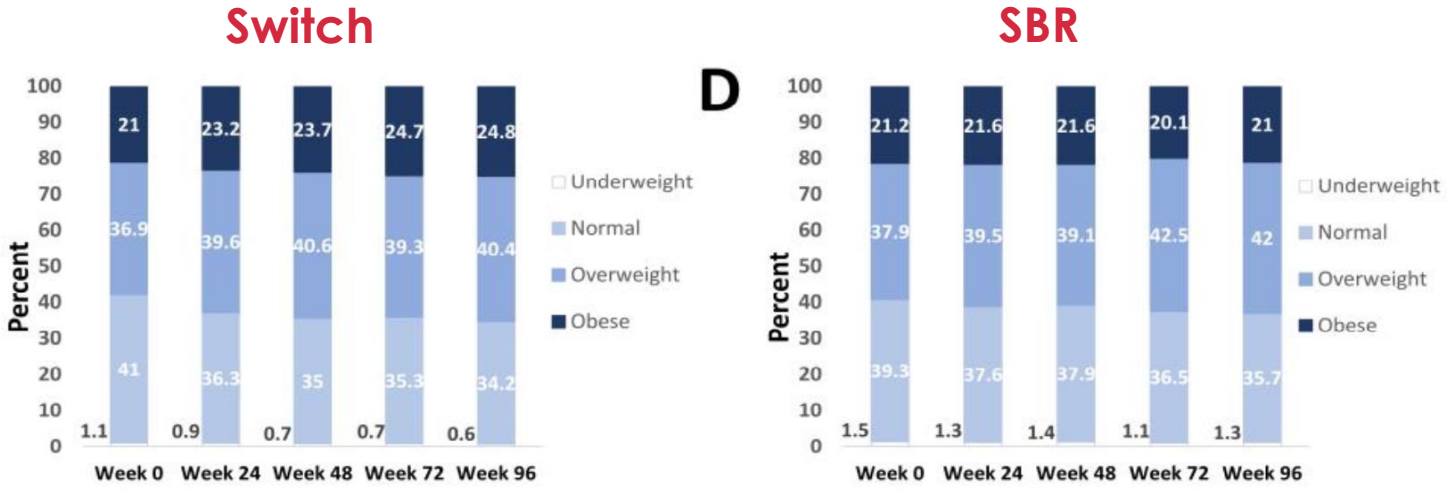
Median WG in switch pts (n=3930) versus SBR pts (n=2943)

1.6 kg (IQR -0.5, 4.0) and 0.4 (IQR -1.8, 2.4), respectively (p<0.0001)

- At wk 96

Median WG in switch pts (n=2598) versus SBR pts (n=1838)

2.0 kg (IQR -0.5, 5.2) and 0.5 (IQR -1.9, 3.1), respectively (p<0.0001)



- The proportion of participants with an obese BMI increased from 21% to 25% over 96 weeks among switch participants but remained stable (21%) among SBR participants
- The proportion of pts who were overweight increased similarly between groups.

Erlandson, CID 2021

SBR, standard baseline regimen

Weight Change Following Antiretroviral Therapy Switch in People with Viral Suppression: Pooled Data from Randomized Clinical Trials

Factors associated with ≥10% WG up to wk 48

Variable	Odds Ratio	P-value
Third agent switch		
EFV→RPV vs Stay on EFV	4.2 (2.36, 7.47)	<0.0001
EFV→EVG vs Stay on EFV	3.01 (1.72, 5.27)	0.0001
NVP→EVG vs Stay on NVP	1.65 (0.44, 6.19)	0.4548
DTG→BIC vs Stay on DTG	1.38 (0.78, 2.42)	0.2641
PI→BIC vs Stay on PI	1.26 (0.75, 2.10)	0.3871
EVG→BIC vs Stay on EVG	0.95 (0.48, 1.90)	0.8879
PI→EVG vs Stay on PI	0.93 (0.60, 1.45)	0.7563
Stay on DTG vs Stay on EFV	1.77 (0.92, 3.38)	0.0853
Stay on PI vs Stay on EFV	1.55 (0.90, 2.68)	0.1144
Stay on RAL vs Stay on EFV	1.5 (0.67, 3.36)	0.32
Stay on EVG vs Stay on EFV	1.35 (0.74, 2.45)	0.3284
Stay on RPV vs Stay on EFV	1.32 (0.73, 2.39)	0.3533
Stay on NVP vs Stay on EFV	1.16 (0.54, 2.49)	0.696
NRTI Switch		
TDF→TAF vs Stay on F/TDF	2.58 (1.94, 3.43)	<0.0001
ABC→TAF vs Stay on ABC/3TC	1.12 (0.59, 2.12)	0.7383
Stay on ABC/3TC vs Stay on F/TAF	1.23 (0.64, 2.34)	0.5382
Stay on FTC/TDF vs Stay on F/TAF	1.08 (0.62, 1.89)	0.7797
Baseline characteristics		
BMI category (underweight/normal vs obese)	2.42 (1.80, 3.26)	<0.0001
BMI category (underweight/normal vs overweight)	1.67 (1.34, 2.08)	<0.0001
Age category (≤35 vs > 35 years)	1.5 (1.20, 1.87)	0.0003
P values are derived from a logistic regression model including baseline BMI and age as risk factors and third agent switch and NRTI switch as fixed effects		

Erlandson, CID 2021

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        -data from observational studies

- Weight gain and newest ARVs
- Role of backbone
- Weight gain and 2DR

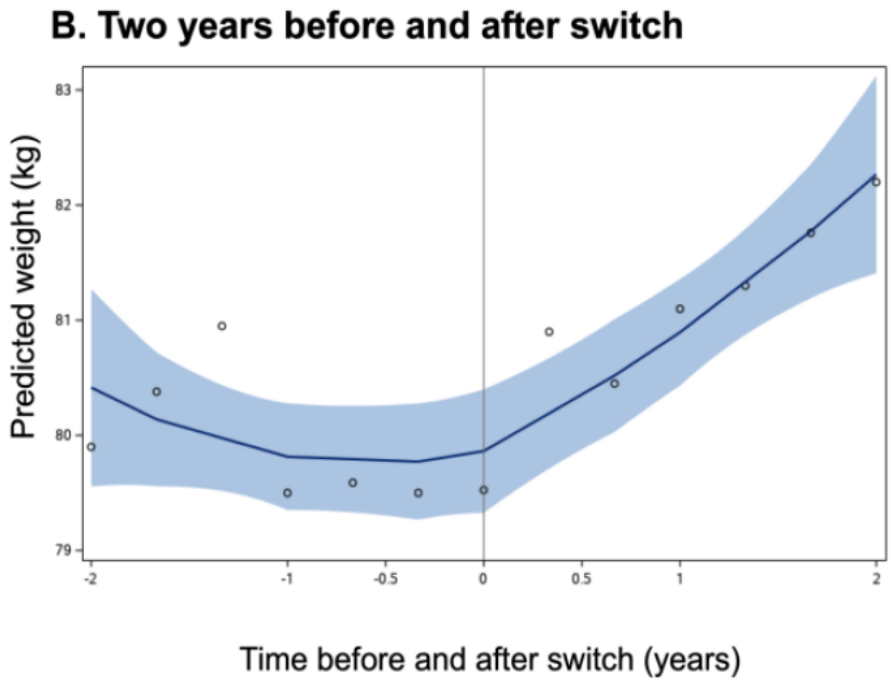
Weight gain in observational studies of treatment-experienced patients switching to INSTIs

Study	Study arms	Observed weight changes (kg)
Lake et al. [19]		Pre-switch vs post-switch[a]:
	DTG ($n = 211$)	+ 1.0 kg/year
	EVG ($n = 222$)	+ 0.5 kg/year
	RAL ($n = 539$)	−0.2 kg/year
Norwood et al. [34] Vanderbilt Comprehensive Care Clinic (VCCC) USA		At 18 months[b]:
	INSTI-based regimen (DTG, RAL, EVG) ($n = 136$)	+ 2.9 kg
	PI-based regimen ($n = 34$)	+ 0.7 kg
	TDF/FTC/EFV ($n = 325$)	+ 0.9 kg
Kerchberger et al. [35] Women's Interagency HIV Study (WIHS) USA		At 2 years[c]:
	INSTI-based ($n = 234$)	+ 2.1 kg (mean gain INSTI vs non-INSTI)
	Non-INSTI based ($n = 884$)	
Vizcarra et al. [36] DOLbi Spain		At 12 months[d]:
	DTG/RPV ($n = 37$)	+ 1.8 kg
	Boosted darunavir/3TC ($n = 17$)	+ 0.7 kg
Burns et al. [42] London, UK		At <2 years[e]:
	RAL ($n = 248$)	+ 0.05 kg/year
	DTG ($n = 130$)	+ 0.05 kg/year
Mugglin et al. [37] Swiss HIV cohort study Switzerland		At 18 months[f]:
	DTG ($n = 2186$)	+ 1 kg
Koethe et al. [38] Na-ACCORD North America		At 2 years[g]:
	NNRTI → INSTI ($n = 343$)	+ 1.13 kg/year
	PI → INSTI ($n = 527$)	+ 0.34 kg/year
Saber et al. [40] USA		At 17 months[h]:
	PI/NNRTI → INSTI ($n = 119$)	+ 2.73 kg
	Remain on NNRTI ($n = 56$)	+ 0.45 kg
Mounzer et al. [41] OPERA cohort USA	DTG ($n = 2658$)	Not reported[i]
	EVG ($n = 2670$)	
	RAL ($n = 383$)	
	RPV ($n = 1472$)	
	DRV/r ($n = 674$)	
Zimmerman et al. [82] USA		At 18 months[j]:
	INSTI ($n = 90$)	+ 2.2 kg
Menard et al. [44] France	DTG-based regimen ($n = 517$)	+ 4 kg (women)[k]
		+ 2 kg (men)

Shah, Drugs 2021

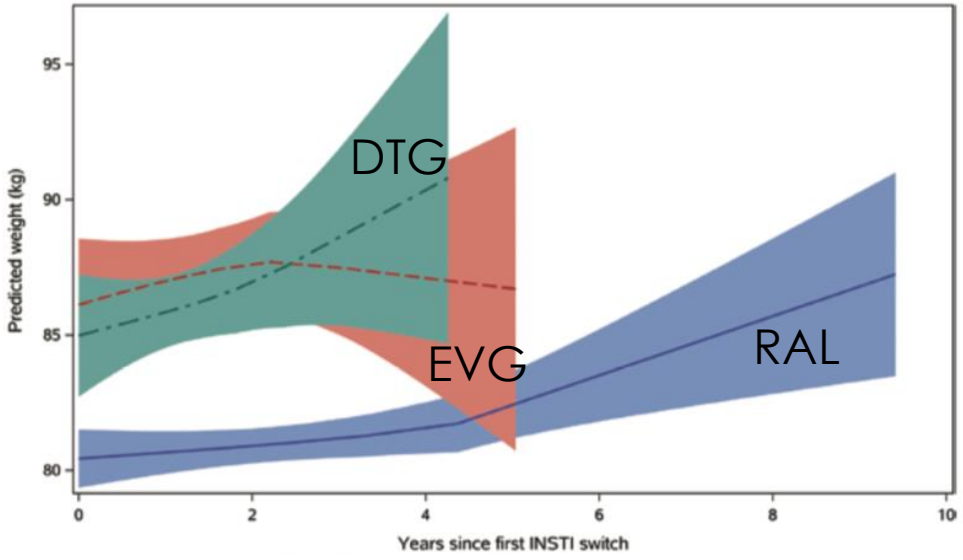
WG following switch to INSTIs

ACTG cohort A5001-A5322



Lake JE, CID 2020

691 virologically suppressed pts (HIV-RNA <200)

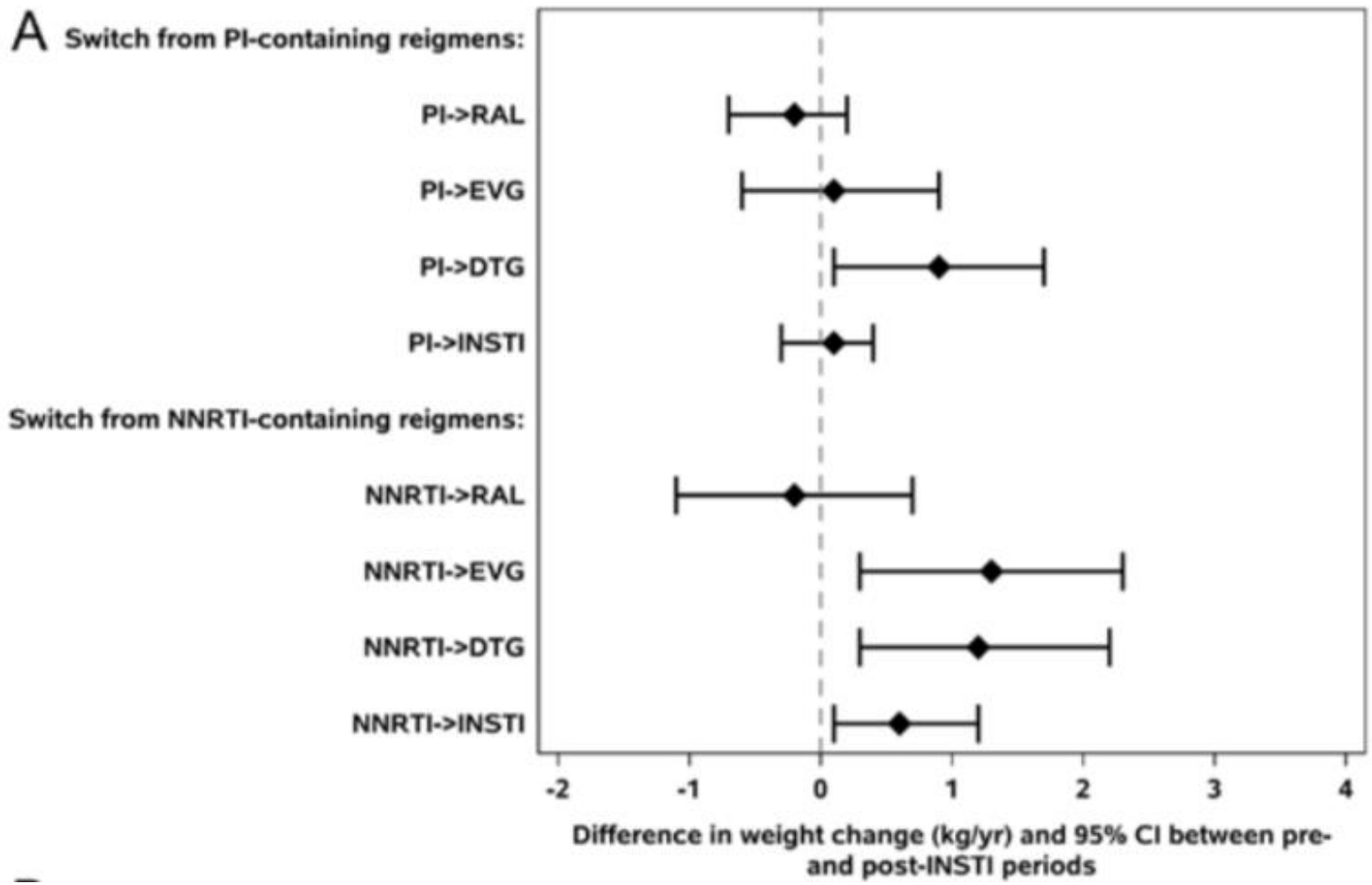


	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2 (0.1)	0.5 (0.008)	0.5 (<0.001)
Post-INSTI	1.3 (<0.001)	0.9 (<0.001)	0.3 (0.05)
Pre-post difference	1.0 (<0.001)	0.5 (0.1)	-0.2 (0.4)

kg/year (p value)

WG following switch to INSTIs

ACTG cohort A5001-A5322



Lake JE, CID 2020

WG following switch to INSTIs

Crude and adjusted hazard ratios (AHR) of experiencing WG after switching to a new ARV drug-class **in the ICONA Cohort**

OUTCOME 2 **WG = increase of weight ≥10% respect baseline or BMI ≥30, N=104/610 (17.5%)**								
Overall analysis	**HR**	**95%CI**		**p**	**AHR***	**95%CI**		**p**
INSTIs vs b/PIs	0.70	0.30	-1.65	0.415	0.77	0.38	-1.53	0.448
INSTIs vs NNRTIs	1.29	0.81	-2.03	0.280	1.31	0.83	-2.08	0.245
Sensitivity analysis^	**HR**	**95%CI**		**p**	**AHR***	**95%CI**		**p**
INSTIs vs b/PIs	0.76	0.30	-1.92	0.559	0.81	0.38	-1.74	0.594
INSTIs vs NNRTIs	1.87	1.12	-3.11	**0.017**	1.95	1.16	-3.27	**0.012**

adjusted for **gender, age at baseline, time-updated CD4, duration of virological suppression, previous drug-class regimen, weight at baseline**
^ excluding patients with BMI ≥30 or≤18.5 at baseline and patients receiving TAF

No different risk was observed after stratification by type of INSTI used (RAL, DTG, EVG)

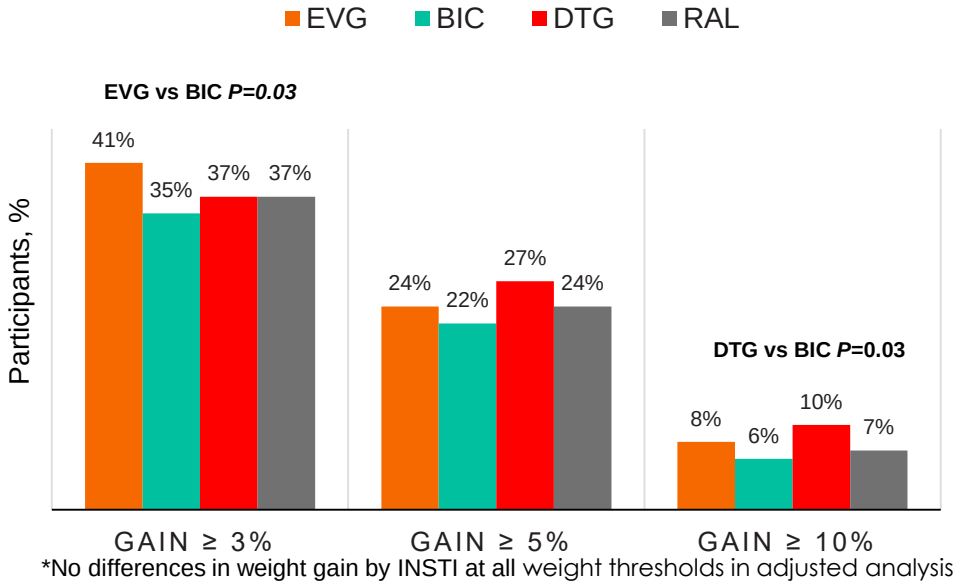
Cicalini, OC 45, ICAR 2020

TRIO Cohort (US)

Weight Gain After Switching to Different Integrase Strand Transfer Inhibitors

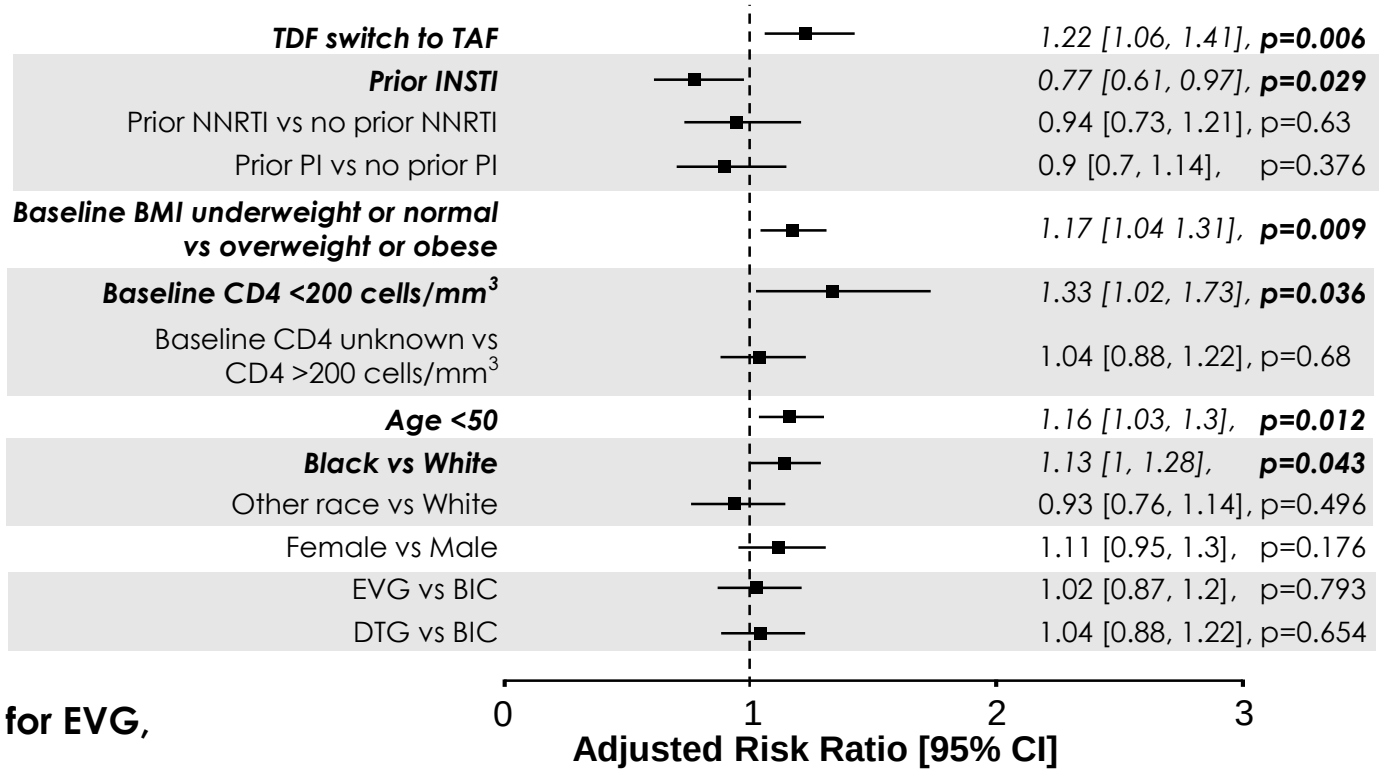
Retrospective observational assessment of INSTI association with weight gain in treatment-experienced, virologically suppressed adults switching to a new INSTI-based regimen, Jan 2015-Jun 2019 (N= 2,272)

Observed Proportion of PLWH with Weight Gain 1 Year after INSTI switch*



*No differences in weight gain by INSTI at all weight thresholds in adjusted analysis

Variables Associated with Risk of Weight Gain ≥ 3% 12 Months after INSTI Switch



- **Mean increase in weight 1 year after switch was 1.5 kg for EVG, 0.9 kg for BIC, 1.2 kg for DTG and 1.9 kg for RAL**
- **There was no difference in weight gain by INSTI after accounting for age, gender, race, baseline BMI, CD4, pre-switch and post-switch drug class and TDF-to-TAF switch or pre-switch TDF at all gain thresholds (≥ 3%, 5% or 10%) at 12 months**

McComsey, CROI 2021. Abs 503

Outline

- Weight gain and INSTIs
    - Naive patients
        - -data from RCTs
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    - Experienced patients
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        - -data from observational studies
- **Weight gain and newest ARVs**
- Role of backbone
- Weight gain and 2DR

WG with the newest ARVs

Bictegravir

- WG similar to DTG in two RCTs of BIC versus DTG in ART-naïve-patients (GS-US-380-1489; GS-US-380-1490). **Confounding effect of TAF?**
- No difference in WG after switch to BIC/FTC/TAF from EFV/TDF/FTC in virologically suppressed patients (Lowman, HIV Glasgow 2020)

Cabotegravir

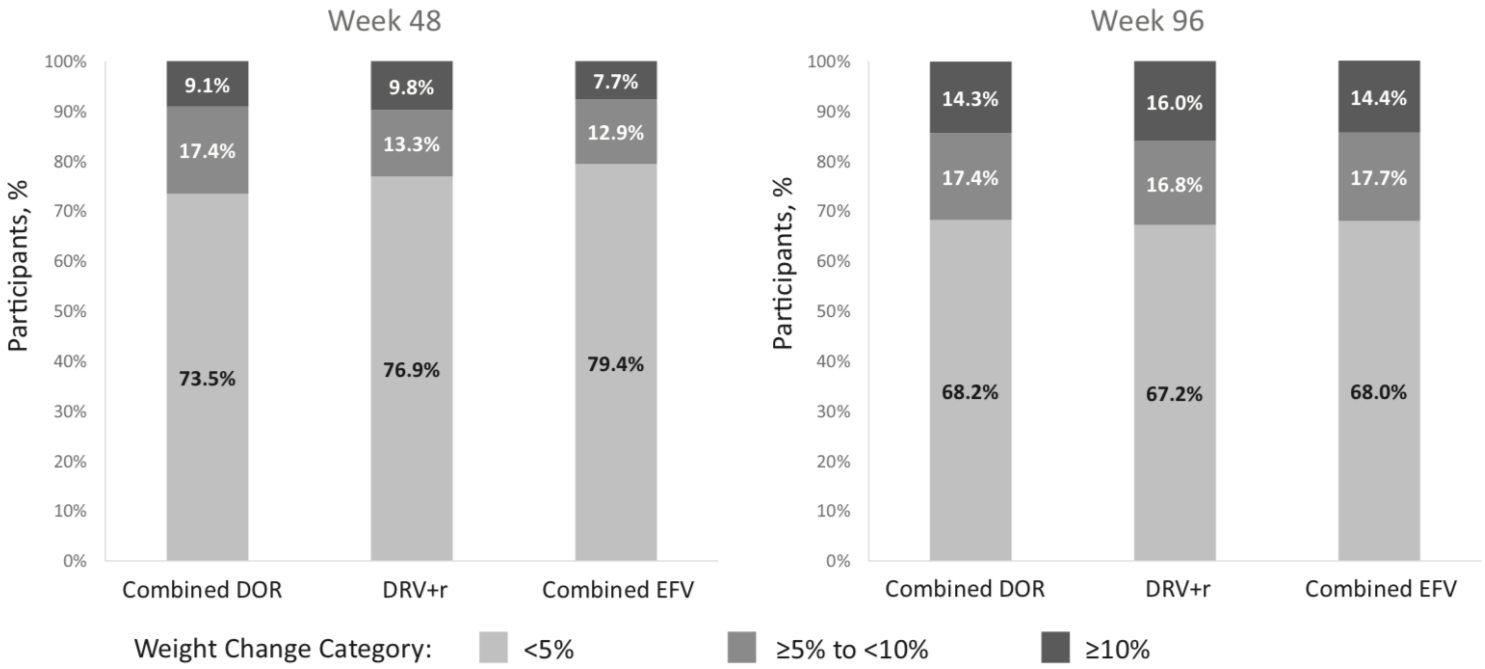
- No difference in WG in RCT of cabotegravir versus placebo in HIV-uninfected individuals (Landovitz, CID 2020).
- Modest and similar changes in weight and lipids over 48 wks in GIV-infected receiving CAB RPV long acting versus oral comparator ARV therapy in a pooled analysis from ATLAS, FLAIR, ATLAS-2M (Patel, CROI 2021, abs 505)

Doravirine

- No difference in WG and BMI over 96 weeks in phase 2/3 trials of DOR versus DRV/r or EFV (Orkin, AIDS 2021)
- Modest WG after switch to DOR/3TC/TDF in DRIVE SHIFT phase 3 trial (mean change <1kg at 6 and 12 months after switch) (Kumar, IAS 2020)

WG and BMI with first-line doravirine-based therapy

Post-hoc analysis of 3 RCTs in pts starting an ARV regimen including DOR or r/DRV or EFV



- **Mean (median) weight change accross groups at wk 96**

	DOR	r/DRV	EFV
Wk 48	1.7 (1.0) kg	1.4 (0.6) kg	0.6 (0.0) kg
Wk 96	2.4 (1.5) kg	1.8 (0.7) kg	1.6 (1.0) kg

- No significant differences between treatment groups on the proportion of patients **with at least 10% WG** or the proportion of patients with BMI class increase at either time point
- **Low CD4 T cell count and high HIV RNA at BL were significantly associated with at least10% WG and BMI class increase in both time points**

Orkin, AIDS 2021

Outline

- Weight gain and INSTIs
    - Naive patients
        -data from RCTs
        -data from observational studies

    - Experienced patients
        -data from RCTs
        -data from observational studies

- Weight gain and newest ARVs
- **Role of the backbone**
- Weight gain and 2DR

Other potential predictors of WG. Role of the backbone

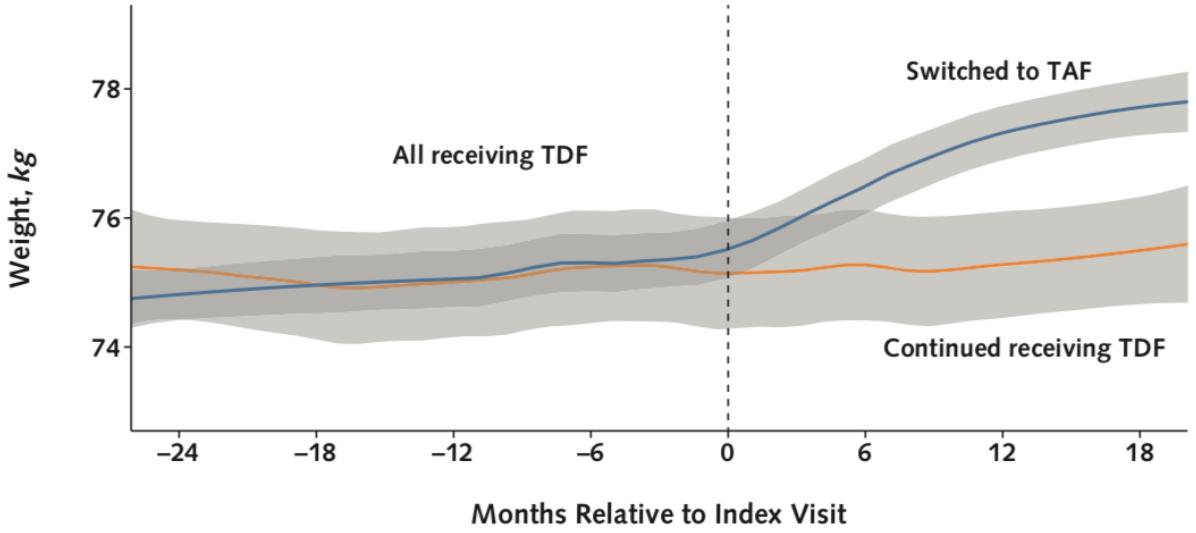
TAF

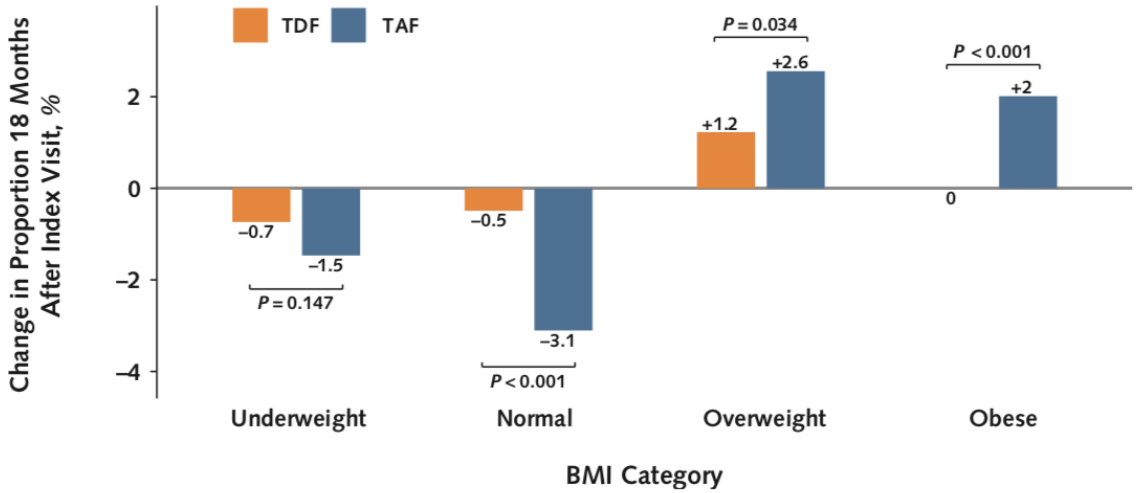
- Greater WG with TAF as compared to TDF in both randomized (ADVANCE Trial, NEJM 2019, Lancet 2020; Sax, CID 2020; AMBER study, Orkin AIDS 2020; Erlandson, CID 2021) and observational studies (CoRIS study, Martinez-Sanz JAIDS 2021; Gomez, Infection 2019; Taramasso, AIDS 2020; the OPERA Cohort, Mallon JAIDS 2021; the Swiss Cohort, Surial, Ann Inter Med 2021), among naïve and experienced patients and in HIV-uninfected individuals in PrEP studies (Mayer, Lancet 2020).
- **Loss of the protective effect of TDF in switch studies?**

Weight and Metabolic Changes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living With HIV

The Swiss Cohort

N= 4375



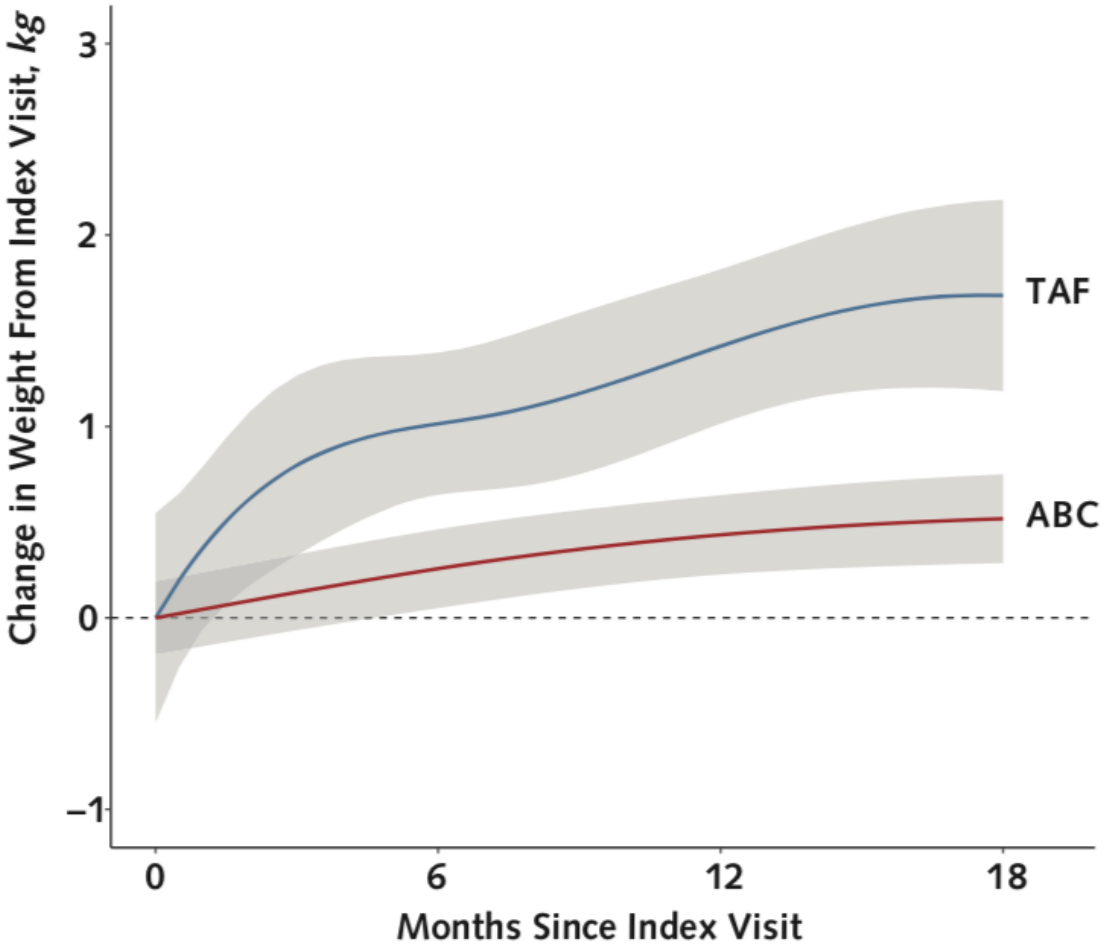


- At 18 months, switching to TAF was associated with an adjusted mean weight increase of 1.7 kg (95% CI, 1.5-2.0) compared with 0.7 kg (95%CI 0.4-1.0) with the continued use of TDF
- 13.8% of pts with normal BMI who switched to TAF became overweight/obese, compared to 8.4% of those continuing TDF

Surial, Ann Intern Med 2021

The Swiss Cohort

Analysis of pts who received ABC and continued ABC or switched to TAF



- Switching from ABC to TAF was associated to a WG of 1.7 kg (95%CI 1.0-2.4) after 18 months, compared to 0.5 kg (95%CI 0.3-0.7) with the continuous use of ABC

Surial, Ann Intern Med 2021

Outline

- Weight gain and INSTIs
    - Naive patients
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        - -data from observational studies
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- Role of backbone
- **Weight gain and 2DR**

WG and dual therapy

GEMINI 1 & 2: WG at wk 96

- <2% of pts in either group reported WG as an adverse event
- **Mean WG +3.1 kg in the 3TC+DTG** group and **+2.1 kg in the TDF/3TC+DTG** group, respectively.

Cahn, IAS 2019

TANGO: Weight Change at wk 48

- Overall weight gains minimal, comparable between treatment arms

Weight Parameter	DTG/3TC (n = 343)	TAF-Based ART (n = 343)
Adjusted mean weight change from BL, kg (SE)	0.81 (0.23)	0.76 (0.22)
▪ Prior TAF duration < 1 yr*	1.45 (0.46)	1.35 (0.47)
▪ Prior TAF duration ≥ 1 yr†	0.60 (0.26)	0.60 (0.25)
▪ Boosted baseline regimen	0.81 (0.27)	0.88 (0.25)
▪ Unboosted baseline regimen	0.81 (0.45)	0.40 (0.44)
Weight increase ≥ 10% from BL, n (%)	11 (3)	13 (4)

*DTG/3TC, n = 83; TAF-based ART, n = 76. †DTG/3TC, n = 260; TAF-based ART, n = 267.

vanWyk, IAS 2020

Conclusions

- Increasing data suggest that INSTIs cause more WG than other ARV regimens, particularly NNRTIs.
- Whether there is a difference between INSTIs is still unclear; DTG and BIC appear to have the greatest effect, with perhaps minimal effect of EVG.
- TAF may have greater adverse weight effect compared to other NRTS, particularly TDF.
- Whether WG associated with INSTIs (and TAF) also contribute to increase the risk of cardio-metabolic comorbidities are still to be defined.