Re-examining INSTI Effects on Weight Gain Among Treatment-Naïve People with HIV in North America

891

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BACKGROUND

A previous analysis in the North American AIDS Cohort Collaboration on Research & Design (NA-ACCORD) highlighted the association between starting **INSTI-based ART** and **weight gain** among treatment-naïve PWH. *(Bourgi, JIAS 2020)*

However, subsequent studies demonstrated a **weight-suppressive effect of TDF and EFV** in some individuals, which may have **affected** some of the observed **differences in weight gain by regimen and between INSTI core drugs.**

Here, we reassessed weight gain among ART-naïve PWH in NA-ACCORD, accounting for potentially weight-suppressive agents and incorporating data among PWH taking **TAF** and **newer INSTI-containing regimens**

METHODS

Inclusion Criteria:

- ✓ **Treatment-naïve** adults enrolled in 21 cohorts in NA-ACCORD
- ✓ Starting NNRTI, PI, or INSTI-based regimens between 01/01/2007 – 12/31/2020
- ✓ Remained on the same regimen for **≥12 months**
- ✓ ***Excluded:*** participants with *no follow-up weight*, those with *baseline HIV-1 RNA <400 copies/mL*, participants starting a *combination of NNRTI, PI, and/or INSTI*

Statistical Analysis:

- ✓ Weight changes were modeled using **multivariable linear mixed** effects models treating subjects as a random effect
- ✓ Participants were **censored** if they experienced *virological failure*, at the *time of ART switch*, *end of study period*, *discontinuation of ART*, or *lost to follow-up.*
- ✓ Models were **adjusted** for *birth sex*, *race*, *cohort*, *ART initiation year*, *NRTI backbone*, baseline measurements of *age*, *weight*, *viral load* ($\log_{10}$), and *CD4 count* (square-root-transformed)
- ✓ Baseline age, weight, viral load, CD4 count, ART initiation year, and years between the weight measurement and ART initiation date were modeled using **restricted cubic splines with 4 knots**
- ✓ Missing baseline data were multiply imputed using **10 replicates**

Outcomes Assessed:

- ✓ **Primary:** Compare weight gain over **five years** between treatment-naïve adults initiating **NNRTI-, PI-, or INSTI-based regimens**, and over **two years** by specific **INSTI core** drug, adjusting for baseline NRTI use.
- ✓ **Secondary:** Compare weight gain over **five** and **two years** between treatment-naïve adults, stratifying by baseline NRTI use

RESULTS

32,514 participants included in our analysis

		TOTAL	REGIMEN		
			INSTI	NNRTI	PI
N (%)		32,514	10,294 *(32%)*	13,344 *(41%)*	8,876 *(27%)*
Baseline Age, *(years)*		41 *(31, 51)*	39 *(29, 50)*	42 *(31, 51)*	42 *(32, 50)*
Birth sex, *N (%)*	Female	5,271 *(16%)*	1,523 *(15%)*	1,791 *(13%)*	1,957 *(22%)*
	Male	27,243 *(84%)*	8,771 *(85%)*	11,553 *(87%)*	6,919 *(78%)*
Race, *N (%)*	Black	14,497 *(45%)*	4,513 *(44%)*	5,985 *(45%)*	3,999 *(45%)*
	Non-Black	18,017 *(55%)*	5,781 *(56%)*	7,359 *(55%)*	4,877 *(55%)*
HIV Risk Category, *N (%)*	MSM	13,213 *(41%)*	4,502 *(44%)*	5,609 *(42%)*	3,102 *(35%)*
	Other	19,301 *(59%)*	5,792 *(56%)*	7,735 *(58%)*	5,774 *(65%)*
ART Initiation Year		2014 *(2009, 2014)*	2016 *(2014, 2018)*	2011 *(2009, 2012)*	2010 *(2009, 2012)*
Baseline BMI, *(kg/m²)*		25.4 *(22.5, 29.1)*	25.6 *(22.6, 29.6)*	25.4 *(22.5, 28.8)*	25.1 *(22.2, 28.7)*
Baseline CD4 cell count, *(cells/μL)*		329 *(182, 495)*	382 *(219, 569)*	329 *(202, 480)*	273 *(118, 422)*
Baseline log HIV-1 RNA, *(cps/mL)*		4.6 *(3.8, 5.1)*	4.6 *(3.8, 5.1)*	4.5 *(3.8, 5.0)*	4.6 *(3.9, 5.2)*
NRTI Backbone, *N (%)*	ABC/3TC	3,782 *(12%)*	2,262 *(22%)*	447 *(3%)*	1,073 *(12%)*
	TAF/FTC	3,721 *(11%)*	3,354 *(33%)*	265 *(2%)*	102 *(1%)*
	TDF/FTC	23,287 *(72%)*	4,457 *(43%)*	12,107 *(91%)*	6,723 *(76%)*
	Other	1,724 *(5%)*	221 *(2%)*	525 *(4%)*	978 *(11%)*

Table 1. Baseline clinical and demographic characteristics of the study population. Continuous variables are reported as median (IQR).

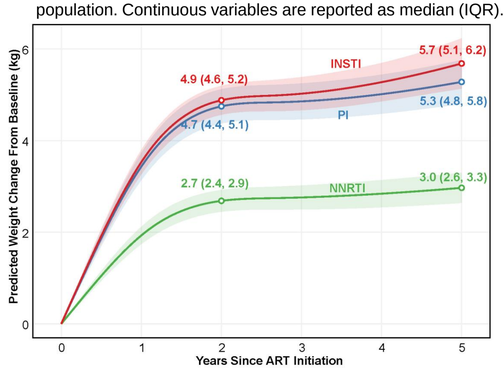


Figure 1. Changes in Predicted Weight Over 5 years by **ART Regimen.** *(NNRTI: n=13,344 vs. PI: n=8,876 vs. INSTI: n=10,294)*

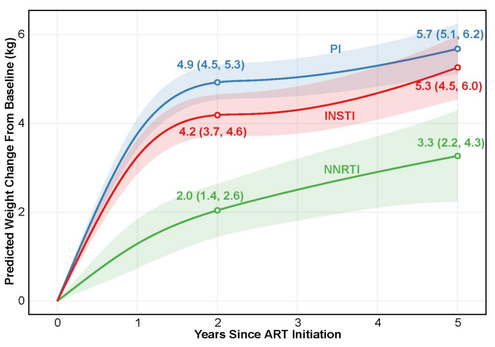


Figure 2. Change in Predicted Weight Over 5 Years By **ART Regimen** Among Participants Starting **TDF/FTC**-Containing Regimens, Excluding EFV. *(non-EFV NNRTI: n=1,792 vs. PI: n=6,723 vs. INSTI: n=4,457)*

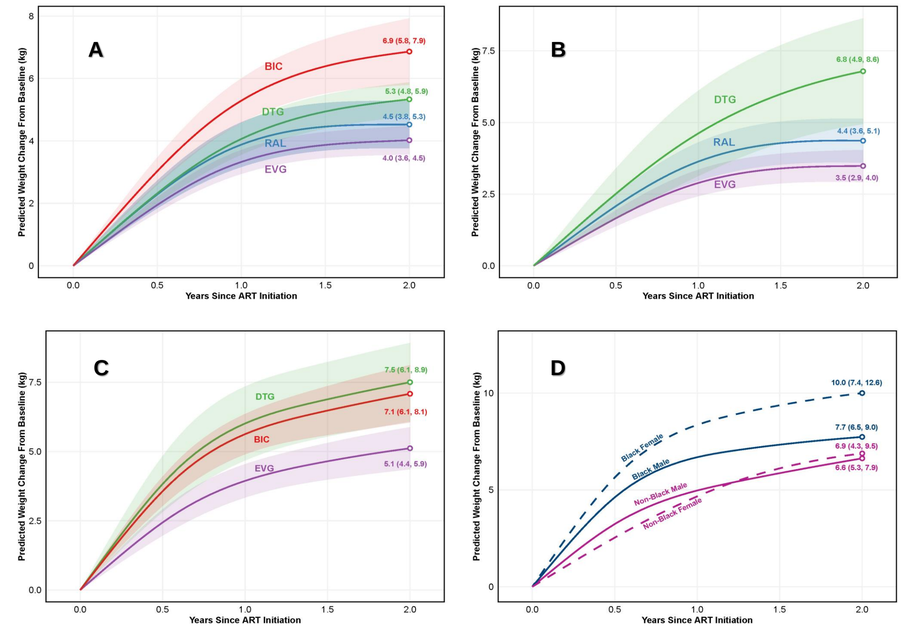


Figure 3A. Change in Weight by **INSTI Drug** in **ALL patients** *(BIC: n=1,581; DTG: n=3,150; RAL: n=2,003; EVG: n=3,560)*
Figure 3B. Change in Weight by **INSTI Drug** in **TDF/FTC**-containing regimens *(DTG: n=482; RAL: n=1,752; EVG: n=2,223)*
Figure 3C. Change in Weight by **INSTI Drug** in **TAF/FTC**-containing regimens *(BIC: n=1,577; DTG: n=431; EVG: n=1,327)*
Figure 3D. Change in Weight **Stratified by Sex and Race** for Participants on **(DTG or BIC) + TAF/FTC** *(Black Female: n=674 ; Black Male: n=4,057 ; Non-Black Female: n=76 ; Non-Black Male: n=2,146)*. Patients with unknown race were categorized as "Non-Black"

CONCLUSIONS

1. Study has **several limitations**: *retrospective chart review*, possibility *of unmeasured confounders* (dietary habits, concurrent medications), bias from *incomplete or missing data*, potential for *measurement errors*, lack of *lifestyle or behavioral data* …
2. Treatment-naïve PWH who initiated **INSTI- or PI-based regimens gained more weight than those starting NNRTI-based** regimens. Weight gain was similar among those initiating INSTI vs. PI-based regimens.
3. Previously reported differences in **weight gain between ART regimens may not be entirely explained by EFV's weight-suppressive effects or its frequent coformulation with TDF**. Findings suggest other NNRTIs may also have weight suppressive effects.
4. Among INSTI users, **those on EVG(c) gained less weight than those on DTG or BIC,** and the difference in weight gained was **not entirely attributable to differences in NRTI backbone.**
5. The results highlight notable differences in weight trajectories after ART initiation across **race and sex** among **participants starting DTG or BIC with TAF/FTC**, with **Black females** experiencing the **most pronounced weight gain**.

Abbreviations: 3TC: *Lamivudine*; **ABC:** *Abacavir*; **ART:** *Antiretroviral Therapy*; **BIC:** *Bictegravir*; **BMI:** *Body Mass Index*; **DTG:** *Dolutegravir*; **EFV:** *Efavirenz*; **EVG:** *Elvitegravir*; **FTC:** *Emtricitabine*; **IQR:** *Interquartile Range*; **INSTI:** *Integrase Strand Transfer Inhibitor*; **MSM:** *Men Who Have Sex With Men*; **NA-ACCORD:** *North American AIDS Cohort Collaboration on Research and Design*; **NIAID:** *National Institute of Allergy and Infectious Diseases*; **NIH:** *National Institutes of Health*; **NNRTI:** *Non-Nucleoside Reverse Transcriptase Inhibitor*; **PI:** *Protease Inhibitor*; **PWH:** *People with HIV*; **RAL:** *Raltegravir*; **RNA:** *Ribonucleic Acid*; **TAF:** *Tenofovir Alafenamide*; **TDF:** *Tenofovir Disoproxil Fumarate*.

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