



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



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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

- ✓ **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

- ✓ 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<sub>10</sub>), 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**

- ✓ **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

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.

## 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	2016	2011	2010	
	(2009, 2014)	(2014, 2018)	(2009, 2012)	(2009, 2012)	
Baseline BMI, (kg/m <sup>2</sup> )	25.4	25.6	25.4	25.1	
	(22.5, 29.1)	(22.6, 29.6)	(22.5, 28.8)	(22.2, 28.7)	
Baseline CD4 cell count, (cells/μL)	329 (182, 495)	382 (219, 569)	329 (202, 480)	273 (118, 422)	
	4.6 (3.8, 5.1)	4.6 (3.8, 5.1)	4.5 (3.8, 5.0)	4.6 (3.9, 5.2)	
Baseline log HIV-1 RNA, (cps/mL)	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%)
NRTI Backbone, N (%)	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).

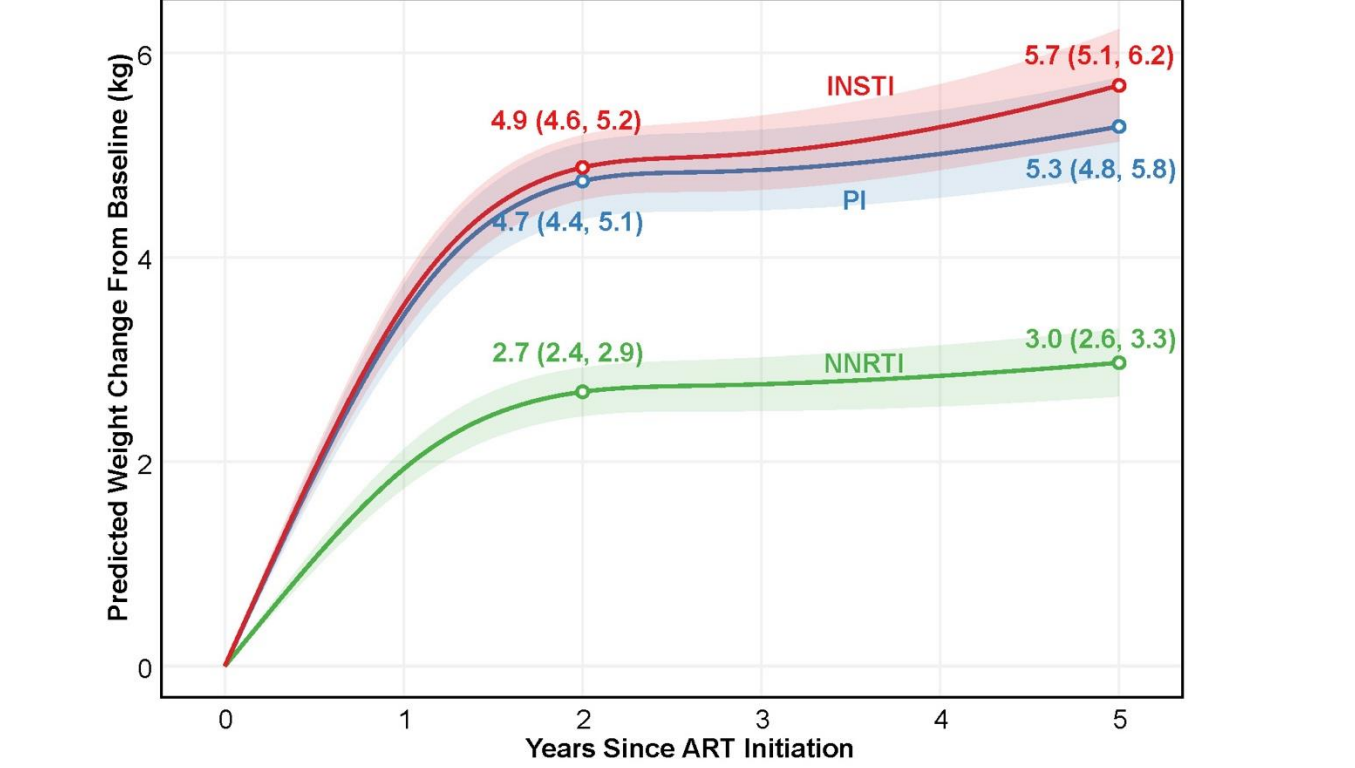


Figure 1. Changes in Predicted Weight Over 5 years by ART Regimen. (NNRTI: n=13,344 vs. PI: n=8,876 vs. INSTI: n=10,294)

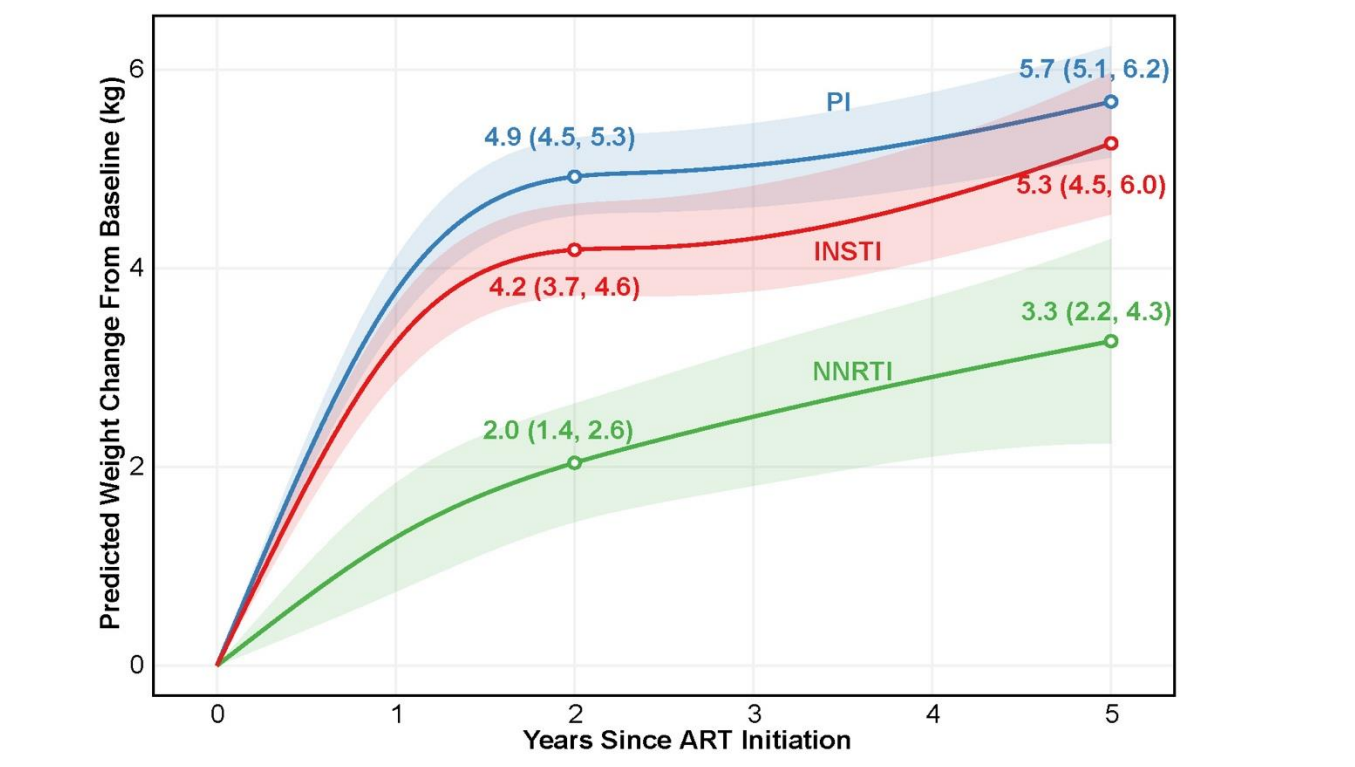


Figure 2. Change in Predicted Weight Over 5 Years By ART Regimen Among Participants Starting TDF/FTC-Containing Regimens, Excluding EFV. (non-EFV NNRTI: n=1,792 vs. PI: n=6,723 vs. INSTI: n=4,457)

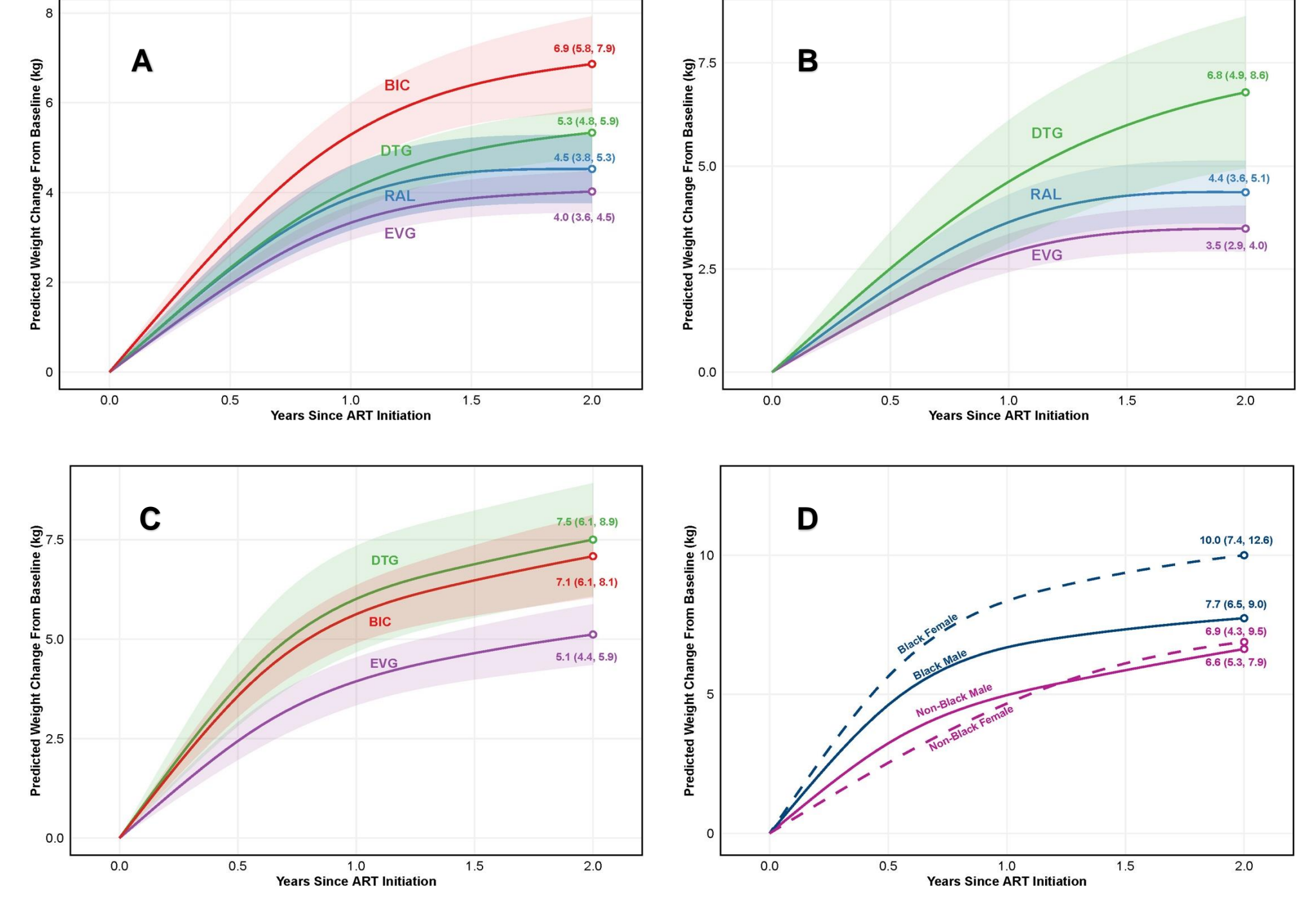


Figure 3A. Change in Weight by INSTI Drug in ALL patients (BIC: n=1,581; DTG: n=3,150; RAL: n=2,003; EVG: n=3,560)  
Figure 3B. Change in Weight by INSTI Drug in TDF/FTC-containing regimens (DTG: n=482; RAL: n=1,752; EVG: n=2,223)  
Figure 3C. Change in Weight by INSTI Drug in TAF/FTC-containing regimens (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**.

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