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RISK FACTORS FOR EXCESS WEIGHT GAIN FOLLOWING SWITCH TO INTEGRASE INHIBITOR-BASED ART

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ACTG AIDS CLINICAL TRIALS GROUP

The A5322 (HAILO) Study

Background

- Weight gain following antiretroviral therapy (ART) initiation occurs with all modern regimens.[1]
- Recent real-world reports from small studies suggest that integrase strand transfer inhibitor (INSTI)-based ART may be associated with excess weight gain.[2-4]
- We assessed weight gain following switch to INSTI-based ART among AIDS Clinical Trials Group (ACTG) participants in protocols A5001 and A5322, which provide(d) long-term observational follow-up of PLWH previously enrolled in randomized interventional trials.

Methods

Study Design: Prospective, observational cohort

Inclusion Criteria
- HIV+
- Enrolled in A5001 or A5332 from 2007-2017
- Switched to INSTI-based ART during follow-up
- Further restricted to period ≤2 years before and after switch to INSTI and HIV-1 RNA <200 copies/mL at time of switch

Statistical Analyses
- Within-person predicted weight trajectories were generated.
- Participants served as their own controls for estimation of background/age-related weight gain.
- Piecewise linear mixed effects models examined weight change before and after first switch to INSTI.
- Models were adjusted for age at switch, sex, race/ethnicity, baseline BMI and their interactions, nadir CD4⁺ T cell count, smoking history, diabetes and percent time with suppressed (<200 copies/mL) HIV-1 RNA.
- Linear spline models with a single knot accounted for non-linear trends.

Results

Table 1. Participant characteristics at switch (N=691)

Age	51 (46, 57)
Male sex	82%
Black race	26%
Hispanic ethnicity	19%
CD4⁺ T lymphocyte count (cells/μL)	610 (439, 816)
Nadir CD4⁺ T lymphocyte count (cells/μL)	185 (67, 294)
Nadir CD4+ T lymphocyte count <200 cells/μL	54%
BMI (kg/m²)	26.9 (23.7, 30.3)
ART prior to switch	
PI	63%
NNRTI	35%
NRTI backbone at switch/with INSTI	
ABC	25%
TDF	49%
TAF	14%
Smoking history	57%
Diabetes mellitus	12%

BMI=body mass index, ART=antiretroviral therapy, PI=protease inhibitor, NRTI=non-nucleoside reverse transcriptase inhibitor, NNRTI=non-NRTI, ABC=abacavir, TDF=tenofovir disoproxil fumarate, TAF=tenofovir alafenamide

References and Acknowledgements

[1]Lake et al. *CID.* 2017 May 15;64(10):1422-1429. [2]Bakal et al. *JAC.* 2018 Aug 1;73(8):2177-2185. [3]Norwood et al. *JAIDS.* 2017 Dec 15;76(5):527-531. [4]Menard et al. *AIDS.* 2017 Jun 19;31(10):1499-1500.

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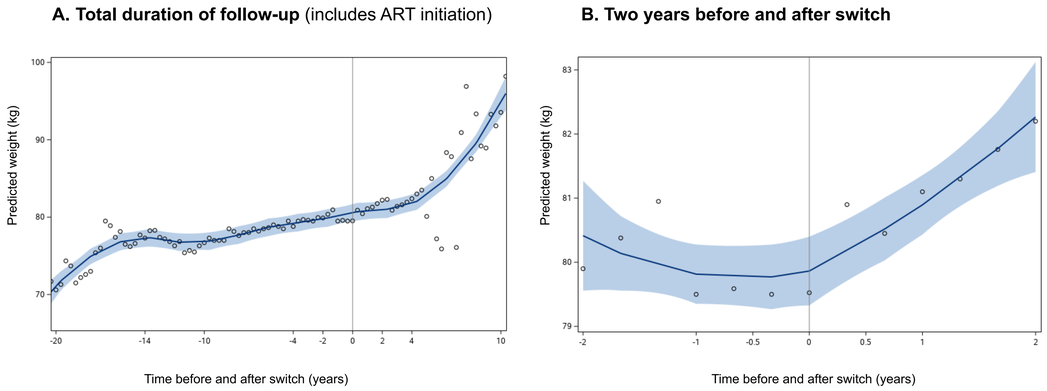
Results

Figure 1: Change in weight before and after switch to INSTI*



*For participants with HIV-1 RNA <200 copies/mL at time of switch to INSTI (n=691).

Table 2: Annual rate of weight change pre-/post-switch to INSTI

Weight change in kg/year (p value) for 2 years before and after switch to INSTI (n=691).

	All	Women	Men	White race*	Black race	Age <40**	Age ≥60	BMI <18.5 kg/m²**	BMI >30 kg/m²
Pre-INSTI	0.4 (<0.0001)	0.3 (0.05)	0.5 (<0.0001)	0.4 (<0.0001)	0.3 (0.04)	1.1 (<0.0001)	-0.03 (0.85)	0.8 (0.7)	0.02 (0.89)
Post-INSTI	0.6 (<0.0001)	1.6 (<0.0001)	0.4 (0.0009)	0.4 (0.002)	1.2 (<0.0001)	-0.3 (0.42)	1.2 (<0.0001)	1.3 (0.03)	0.5 (0.05)
Pre-post Difference	0.2 (0.22)	1.3 (0.0003)	-0.1 (0.57)	0.01 (0.97)	0.9 (0.002)	-1.4 (0.01)	1.2 (0.001)	0.5 (0.58)	0.5 (0.20)

*Results for Hispanic ethnicity similar to white race
**No significant change in slope of weight gain among persons 40-60 years of age or for BMI 18.5-30 kg/m²

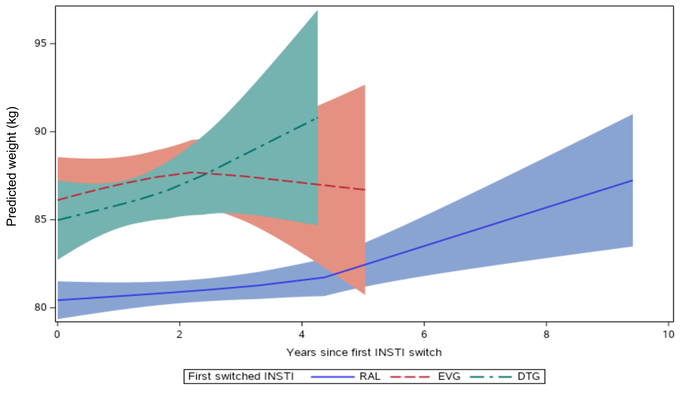
Table 3: Adjusted* annual rate of weight change by sex, race**, age⌘ and BMI⌘⌘ at switch

Weight change in kg/year (p value) for 2 years before and after switch to INSTI (n=691).

	Black Women	White Women	Black Men	White Men	Women age ≤40	Women Age ≥60	Men age ≤40	Men Age ≥60	Women ≥30 kg/m²
Pre-INSTI	0.4 (0.08)	0.6 (0.03)	0.4 (0.02)	0.4 (<0.0001)	1.5 (0.01)	-0.2 (0.61)	0.8 (0.009)	0.1 (0.46)	0.2 (0.54)
Post-INSTI	1.3 (<0.0001)	2.0 (<0.0001)	1.0 (0.002)	0.2 (0.09)	-1.0 (0.17)	1.8 (0.0005)	-0.1 (0.88)	0.9 (0.0008)	1.9 (<0.0001)
Pre-post Difference	0.9 (0.04)	1.4 (0.02)	0.6 (0.11)	-0.2 (0.38)	-2.5 (0.02)	2.0 (0.008)	-0.9 (0.20)	0.8 (0.04)	1.7 (0.002)

*Adjusted for factors listed in Methods
**No significant change for Hispanic men or women
⌘Women 40-49 not significant, 50-59 similar to ≥60; Men 40-49 similar to ≤40 and 50-59 not significant
⌘⌘Non-obese women and men of any BMI category not significant

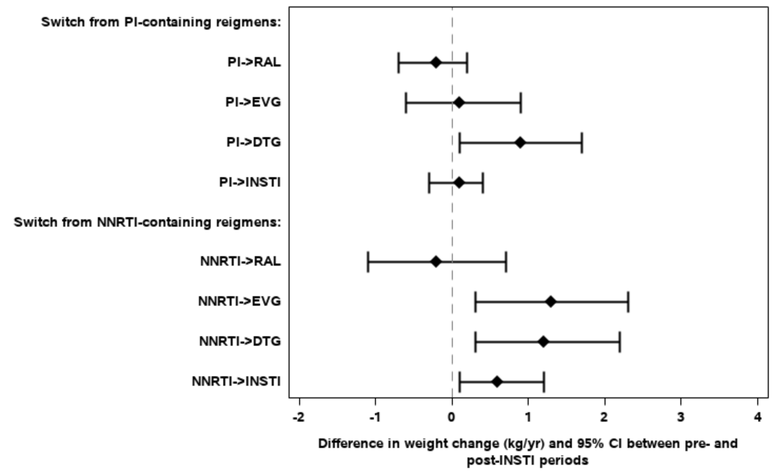
Figure 2: Weight gain pre-/post-switch to INSTI by agent



	DTG (n=198)	EVG (n=204)	RAL (n=289)
Pre-INSTI	0.2 (0.11)	0.5 (0.008)	0.5 (<0.0001)
Post-INSTI	1.3 (<0.0001)	0.9 (<0.0001)	0.3 (0.045)
Pre-post difference	1.0 (0.0009)	0.5 (0.11)	-0.2 (0.37)

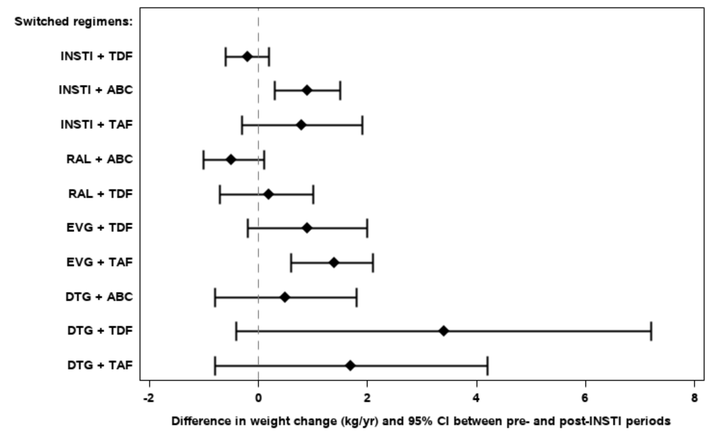
kg/year (p value)
DTG=dolutegravir, EVG=elvitegravir, RAL=raltegravir

Figure 3: Annual weight gain by pre-switch ART class



- Switch to DTG from PI or NNRTI, and switch to EVG from NNRTI statistically significant (p<0.05), though subset analyses limited by sample size.

Figure 4: Annual weight gain by NRTI backbone at switch



- Switch to any INSTI with ABC and switch to EVG with TAF statistically significant (p<0.05), though subset analyses limited by sample size.
- 61% of ABC, 87% TDF, 4% of TAF use at switch to INSTI had same NRTI backbone pre-switch

Summary & Conclusions

In this cohort of adults with HIV on suppressive ART and long-term observational follow-up after participation in ACTG interventional trials:

- **Annual within-person weight gain increased following switch to INSTI-based ART.**
- **Increases in weight gain following switch to INSTI were most prominent for women, blacks and persons age ≥60.**
- **Compared to pre-switch weight changes on stable suppressive ART, these data suggest post-switch increases in weight/fat mass greater than expected for age.**
- **Change in rate of weight gain following switch to INSTI appears greater with dolutegravir than elvitegravir or raltegravir.**
- **Although further studies are needed, choice of NRTI backbone may modify INSTI-associated weight gain.**
- **The cardiometabolic implications of increased weight gain following switch to INSTI-based ART need to be established.**