Understanding Who Does and Does Not Gain Weight with Integrase Inhibitors (INSTI)

Trio Health

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1. BACKGROUND

- Randomized clinical trials and retrospective cohort studies have demonstrated greater weight gain with INSTI regimens vs other classes of antiretrovirals. Recent pooled analysis of 8 randomized clinical trials of treatment-naïve people with HIV by Sax[1] et al reported > 5% gain in body weight in 37% of participants and weight loss in 30% of the participants from baseline to 96 weeks. Although patients receiving all drug classes gained weight, those on protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) had similar gains (NNRTI: 1.9 kg [95% CI, 1.6–2.3], PI: 1.7 kg [95% CI, 1.0–2.4]), while those on INSTIs gained the most (3.2 kg [95% CI, 3.0–3.5]).
- Why do some patients gain weight on INSTI and others do not? Are there synergies with other ARV agents and INSTI? We examined HIV patients in US clinical care switching to INSTIs and compared those with gain ≥5% body weight vs loss or gain <5% after 12 months on INSTIs.

2. METHODS

- Analysis was conducted in 387 subjects: patients ≥18 years, switched to INSTI regimens in January 2015-June 2018 for ≥12 months, with ≥12 months prior history, no INSTI 12 months prior, viral suppression and weights at regimen initiation (baseline) and 12 months (±2 months) [Figure 1].
- Univariate analyses were conducted via chi-square and t-test. Multivariable analysis with a binary outcome of gain ≥5% at 12 months was conducted using negative binomial model with log link function; variables significant in univariate analysis and other important demographic and clinical variables were considered [Figures 3a-b]. Final model included continuous variables age, baseline weight and categorical baseline AST <30 vs ≥30, prior use of PI and prior use of NNRTI.

FIGURE 1. PATIENT SELECTION

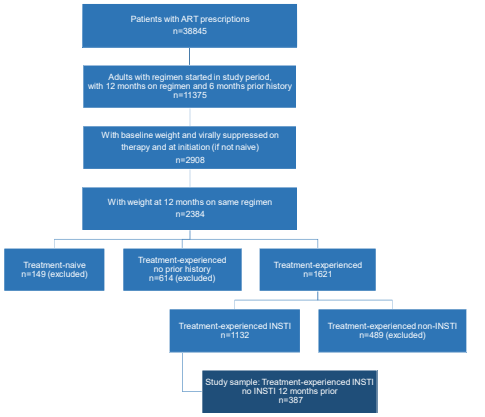


TABLE 1: PATIENT DEMOGRAPHICS, BASELINE VITALS, AND LABS

mean (SD) unless specified, N is provided if values are not available for all patients	Gain ≥ 5% (N=103)	Loss or gain <5% (N=284)	P-value
Age	47 (10.9)	49 (10.7)	0.109
Age >50, n (%)	44 (43)	140 (49)	0.252
Male gender, n (%)	76 (84)	237 (89)	0.317
White race, n (%)	55 (57)	149 (56)	
Black race, n (%)	27 (28)	78 (30)	0.916
Other race, n (%)	15 (15)	37 (14)	
eGFR <60 mL/min/1.73m², n (%)	7 (7)	26 (10)	0.058
Charlson Comorbidity Index	6.1 (2.3)	5.9 (2.7)	0.448
ALT (U/L)	28 (20.3) N=102	32.3 / 20.2 N=272	0.068
ALT <30 U/L, n (%)	70 (68)	149 (52)	**0.015**
AST (U/L)	23.5 (10.3) N=102	28.5 (16.2) N=272	**0.004**
AST <30 U/L, n(%)	87 (84)	190 (70)	**0.002**
AST/ALT ratio	1.0 (0.4) N=102	1.0 (0.3) N=272	0.522
AST/ALT ≥2, n (%)	2 (2)	3 (1)	0.520
Patient Weight (lb.)	176.8 (30.9)	187.1 (36.9)	**0.006**
Body Mass Index - BMI (kg/m²)	26.1 (4.5) N=97	27.5 (5.5) N=276	**0.024**
BMI Underweight, n (%)	3 (3)	4 (1)	
BMI Normal	40 (41)	92 (33)	0.223
BMI Overweight	37 (38)	109 (39)	
BMI Obese	17 (18)	71 (26)	
Cholesterol HDL (mg/dL)	54.1 (18.9) N=90	49.9 (18.0) N=238	0.073
Cholesterol LDL (mg/dL)	104.3 (35.5) N=86	105.4 (31.8) N=225	0.794
Cholesterol Total (mg/dL)	188.7 (43.4) N=90	187.4 (36.9) N=238	0.798
Triglycerides (mg/dL)	152.3 (93.7) N=88	166.9 (135.8) N=236	0.274
Current regimen duration (months)	26.9 (10.7)	27.1 (10.8)	0.840
Prior regimen duration (months)	35.3 (29.4)	34.5 (30.3)	0.821

TABLE 2: WEIGHT GAIN BY DRUG CLASS AND DRUG

	n (%)	Gain ≥ 5% (N=103)	Loss or gain <5% (N=284)	P-value
Current Therapy	**Boosted** *(with ritonavir or cobicistat)*	57 (55)	158 (56)	0.959
	PI *(protease inhibitor)*	7 (7)	31 (11)	0.229
	NRTI *(nucleoside reverse transcriptase)*	100 (97)	274 (96)	0.769
	NNRTI *(non-nucleoside reverse transcriptase)*	6 (6)	15 (5)	0.835
	ABC *(abacavir)*	24 (23)	83 (29)	0.249
	TAF *(tenofovir alafenamide)*	70 (68)	164 (58)	0.069
	TDF *(tenofovir disoproxil fumarate)*	6 (6)	30 (11)	0.156
	DTG *(dolutegravir)*	40 (39)	127 (45)	0.302
	EVG *(elvitegravir)*	50 (49)	125 (44)	0.429
	BIC *(bictegravir)*	13 (13)	28 (10)	0.435
	RAL *(raltegravir)*	0 (0)	4 (1)	0.226
Prior Therapy	**Boosted**	39 (38)	137 (48)	0.070
	PI	27 (26)	111 (39)	**0.019**
	NRTI	98 (95)	279 (98)	0.090
	NNRTI	78 (76)	183 (64)	**0.036**
	ABC	15 (15)	56 (20)	0.247
	TAF	5 (5)	25 (9)	0.199
	TDF	82 (80)	208 (73)	0.201

3. RESULTS

- Of 387 patients switched to INSTIs, 140 (36%) lost weight or had 0% change, 144 (37%) gained <5%, 103 (27%) gained ≥5% weight [Figure 2]. In comparison to other study patients, those who gained ≥5% had significantly lower baseline weight, BMI, AST, AST≥30, and ALT≥30 [Table 1].
- In univariate analysis prior use of PI was significantly lower in patients who gained ≥ 5%, while prior use of NNRTI was significantly higher. There were no statistically significant differences by NRTI backbone, prior NRTI backbone, and INSTI component between those who gained ≥ 5% vs. those who did not [Table 2, Figures 3a-b].
- Patients were assessed for presence of the following baseline comorbidities based on ICD9/10 codes: alcohol abuse, depression, diabetes, hepatitis B and C, hypertension, hypogonadism, hyperlipidemia, neuropsychiatric disorders, smoking, substance abuse, cancer, congestive heart failure, cardiovascular, cerebrovascular, chronic pulmonary, peripheral vascular, renal and rheumatic diseases.
- Proportion of patients with cerebrovascular disease was statistically higher in INSTI patients with gain ≥ 5% (6% vs. 1%, p=0.006), however, due to low incidence, this variable was not considered in multivariable analysis. There were no statistically significant differences in the remaining comorbidities evaluated in the analysis.
- Based on multivariable analysis patients were more likely to gain ≥5% if they had baseline AST<30 (relative risk [RR]= 1.73 [CI 1.01-2.98], p=0.047) and less likely to gain ≥5% if they had higher baseline weight (RR=0.99 [CI 0.99-0.99], p=0.039) [Figure 4]. BMI, significant in univariate analysis, was not included in the final model to achieve better model fit and include patients with missing BMI. Crude risk estimates are provided in Figures 3a-b.
- Race and gender, shown to be predictors of weight gain in other studies, were not significant predictors in this subgroup of treatment-experienced patients who switched to INSTI and remained on therapy for a year.

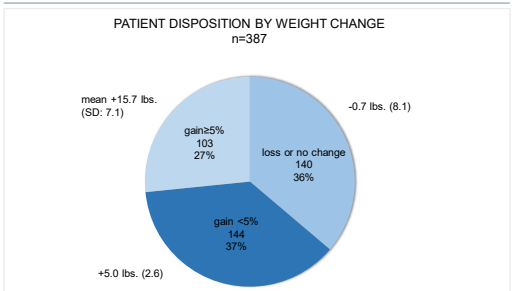
4. LIMITATIONS

- The study accounted only for treatment received at sites participating in the database and may not have fully accounted for prior treatment.
- The practices that contributed data may not reflect the national patient experience either in patient demographics or practice patterns.
- Exclusion of patients based on missing weights and documented viral suppression and the retrospective nature of the study may have confounded the analysis.
- The impact of changes in diet, exercise, and other lifestyle modifications that may influence weight were not accounted for.
- Patients were retrospectively observed for a year since switch; therefore, long term effects were also not accounted for.

5. CONCLUSION

- Of 387 patients switching to INSTIs, over 1/3 lost or maintained weight, over 1/3 experienced weight gain <5%, while remaining 27% experienced gain ≥5% after 12 months on therapy.
- Univariate analysis indicated ≥5% gain was associated with prior regimen components (NNRTI, PI) and baseline factors, of which only baseline weight and AST remained significant in multivariable analysis. The NRTI agents used with INSTIs in this population were not significantly associated with gain ≥5%.
- Future research questions include clinical significance of weight gain thresholds that have implications for morbidity, impact of abnormal liver function tests on weight changes as well as heterogeneity of responses to ARV agents.

FIGURE 2. PATIENT DISPOSITION BY WEIGHT CHANGE



FIGURES 3A & 3B. BASELINE CHARACTERISTICS AND REGIMENS ASSOCIATED WITH WEIGHT GAIN ≥5% AT 12 MONTHS

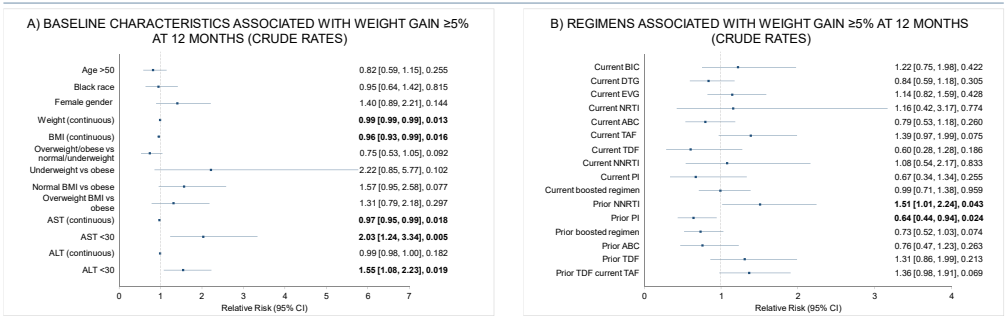
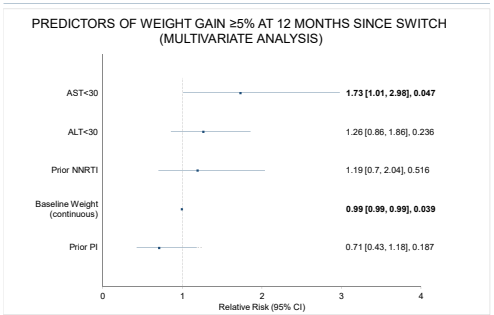


FIGURE 4. PREDICTORS OF WEIGHT GAIN ≥5% AT 12 MONTHS



[1]Sax PE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2019 Oct 14).

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