Weight Gain in Persons Living with HIV Treated with Bictegravir vs. Other Integrase Strand Transfer Inhibitor-Based Antiretroviral Therapy

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BACKGROUND

- Integrase strand transfer inhibitors (INSTIs) are currently exclusively recommended by the U.S. Department of Health and Human Services as part of the initial treatment regimen for "Most People with HIV" due to their efficacy, high barrier to resistance, and relatively tolerable side effect profile compared to previously developed classes of antiretroviral therapy (ART).
- Recent studies have given rise to the concern that some INSTI-based ART regimens may lead to significant weight gain in both treatment-naïve HIV patients and patients switched from non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based therapy[1,2].
- Most studies to date examining weight gain with INSTIs have not included bictegravir (BIC), co-formulated with emtricitabine (FTC) and tenofovir alafenamide (TAF) as Biktarvy®, which received FDA approval in February 2018 for treatment of HIV-1 infection.
- Data regarding the relationship between INSTI-associated weight gain with metabolic markers or other clinical outcomes is still emerging and has important implications in a patient population that may be at higher risk of cardiovascular events from the inflammatory sequelae of chronic immune activation by HIV infection[3].

OBJECTIVES

- To compare the incidence of weight gain between persons living with HIV (PLWH) receiving BIC-based ART vs. other INSTIs used with FTC/TAF
- To assess whether any differences in weight after INSTI + FTC/TAF initiation are associated with changes in metabolic parameters

METHODS

STUDY DESIGN

- Single-center, retrospective cohort study (11/2015 – 11/2019)
- Key inclusion criteria: INSTI + FTC/TAF ART regimens only, initiated at VA San Diego and continued for at least 6 months
- Key exclusion criteria: INSTI-based ART regimen including non-FTC/TAF agents, non-VA initiation of ART regimen of interest, use of prespecified weight-loss agents or enrollment in weight-loss program, lack of follow up after ART initiation
- Primary outcome: Weight gain within 18 months after initiation of studied INSTI
- Secondary outcome: Changes in parameters for metabolic syndrome
- Groups:

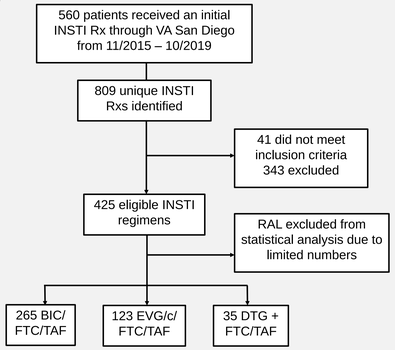
INSTI	+	NRTIs	=	Regimen
bictegravir (BIC)		emtricitabine (FTC) + tenofovir alafenamide (TAF)		Biktarvy®
dolutegravir (DTG)				Tivicay® + Descovy®
elvitegravir (EVG) + cobicistat				Genvoya®

STATISTICAL ANALYSIS

- Categorical variables: Chi square test
- Continuous variables: Mann-Whitney U test
- Correlation (continuous variables): Spearman's rho test

RESULTS

Figure 1



WEIGHT GAIN

Figure 2 – Weight Gain Over 18 Months

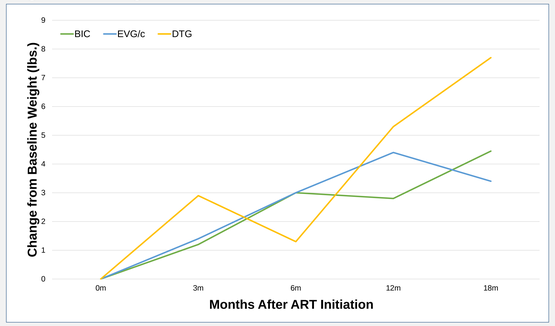


Table 1 – Weight Gain Compared to Baseline

Outcome – median lbs.	BIC			EVG/c			DTG		
	Baseline Weight	Current Weight	P-value	Baseline Weight	Current Weight	P-value	Baseline Weight	Current Weight	P-value
3 months	185.3	187.2	**0.001**	180.9	177.8	0.103	188.3	189.4	0.194
6 months		189.0	**<0.001**		182.0	**0.005**		189.4	0.269
12 months		192.0	**<0.001**		189.2	**<0.001**		191.5	**0.005**
18 months		189.4	**0.003**		189.3	**0.006**		195.0	**0.040**

METABOLIC CHANGES

Figure 3 – Metabolic Changes at 12 Months

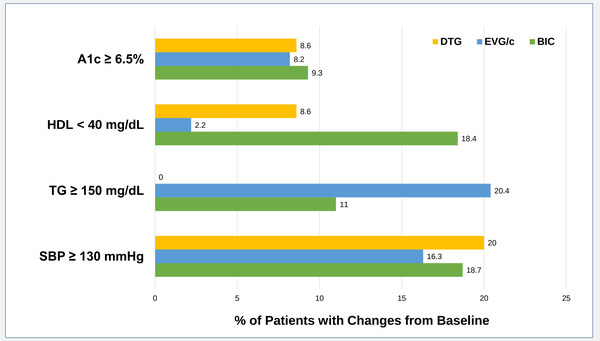


Table 2 – Correlations Between Weight Gain and Metabolic Changes

Outcome – Correlation (r^2) with change in weight from baseline to 12 months	All Groups	BIC	EVG/c	DTG
Change in SBP at 12 months	0.081	0.066	0.025	0.237
Change in TG at 12 months	0.249	0.107	**0.412**	**0.479**
Change in HDL at 12 months	0.020	0.057	0.145	**-0.637**
Change in A1c at 12 months	0.224	0.198	**0.389**	-0.109

Table 3 – Baseline Characteristics

Variable – n (%), median (IQR)	BIC (n=265)	EVG/c (n=123)	P-value (BIC/EVG)	DTG (n=35)	P-value (BIC/DTG)
Age (years)	56 (47-64)	48 (39-58)	<0.05	57 (49-67)	0.381
Male	257 (97.0)	121 (98.4)	0.514	34 (97.1)	0.958
Race					
White (vs. non-white)	165 (62.3)	65 (52.8)	0.079	24 (68.6)	0.528
Black or African-American	61 (23.0)	30 (24.4)	-	7 (20.0)	-
Other	39 (14.8)	28 (22.8)	-	4 (11.4)	-
BMI (kg/m²)	27.3 (24.4-30.9)	26.7 (23.6-29.8)	0.210	28.3 (23.6-31.9)	0.987
Diabetes mellitus	45 (17.0)	13 (10.6)	0.228	5 (14.3)	0.688
Hypertension	100 (37.7)	31 (25.2)	0.046	15 (42.9)	0.558
Dyslipidemia	126 (46.4)	46 (37.4)	0.061	12 (34.3)	0.139
Time since HIV dx (years)	17 (9-27)	11 (5-19.5)	**<0.001**	23 (11-27)	0.638
HIV viral load at baseline (copies/mL)					
<20 copies/mL or not detected	205 (77.4)	83 (67.5)	**0.030**	31 (88.6)	0.322
<200 copies/mL	34 (12.9)	17 (13.8)		2 (5.7)	
≥200 copies/mL	25 (9.5)	23 (18.7)		2 (5.7)	
Baseline CD4 count (cells/mm³)	667 (494-865)	630 (433-798)	0.154	660 (469-879)	0.775
ART experience					
Previous ART	253 (95.5)	111 (90.2)	**0.047**	35 (100)	0.199
Previous INSTI	149 (56.2)	13 (10.6)	**<0.001**	17 (48.6)	0.168
Previous TAF/FTC	161 (60.8)	14 (11.4)	**<0.001**	13 (37.1)	**0.033**

DISCUSSION

- Changes in weight across 18 months were similar between BIC, EVG/c, and DTG groups, with no significant differences between any combination of groups at any of the time points collected.
- Weight gain compared to baseline at INSTI initiation was significant for all INSTI groups at 12 and 18 months, supporting the association between weight gain and INSTI use seen in previous studies. Additionally, weight gain appeared to increase steadily in the BIC and DTG groups over 18 months, with no apparent plateau in this study compared to data from previous studies, suggesting the possibility of significant INSTI-associated weight gain beyond 18 months.
- This study did not include a non-INSTI control group, so the impact of age-related weight changes is unclear. The role of TAF on observed weight gain in this study is not fully evaluated, although a subgroup analysis of BIC showed a lack of sustained differences in weight changes at 18 months between TAF-naïve patients vs. those switched from another regimen including TAF.
- No clear trends in correlations emerged between use of a particular INSTI and changes in metabolic parameters associated with the observed weight gain. Correlations between weight gain and metabolic changes were not consistent between groups, although utility of these analyses were limited due to lack of metabolic labs for many of the patients included.
- Strengths of this study include the analysis of bictegravir, which received FDA approval relatively recently and was not included in earlier studies examining weight gain with INSTI use, as well as the exclusive use of TAF/FTC as the NRTI backbone to minimize non-INSTI differences in weight change between groups.
- Some limitations of this study were inherent to the nature of a retrospective analysis, including the lack of data at prespecified time points – especially metabolic data, as well as inability to collect values more specific to metabolic syndrome, such as waist circumference or other means of monitoring changes in central adiposity. Other limitations include the inability to study longer-term data due to the relatively recent availability of Biktarvy® for use in clinical practice.

CONCLUSION

- Weight gain is likely associated with INSTI use, although the anticipated magnitude of weight gain and duration of effect with each INSTI is unclear.
- Implications of this study along with existing data include a potential role for more stringent metabolic monitoring of PLWH treated with INSTIs, further research into mechanisms of ART- and INSTI-associated weight gain, and longer-term outcomes of INSTI use, including weight gain beyond 18 months and impact on clinical outcomes.

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