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BRIEF REPORT

Weight Gain: A Possible Side Effect of All Antiretrovirals

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Weight gain and body mass index (BMI) increase are central issues in patients living with HIV who need to minimize the risk of metabolic disease. Information collected through the SCOLTA cohort revealed significant 1-year BMI increase in patients treated with dolutegravir (P = .004), raltegravir (P = .0004), elvitegravir (P = .004), darunavir (P = .0006), and rilpivirine (P = .029). BMI gain correlated with low baseline BMI (P = .002) and older age (P = .0007) in Centers for Disease Control and Prevention stages A/B, with lower BMI (P = .005) and CD4+ T-cell count (P = .007) at enrollment in stage C.

Keywords. ART; BMI; cardiovascular risk; darunavir; INSTI; rilpivirine; weight.

People living with HIV (PLWHIV) are at higher risk of cardiovascular disease (CVD) when compared with the HIV-uninfected population [1], and for this reason, the control and correction of modifiable risk factors for CVD and metabolic disease, including body mass index (BMI) and weight, are crucial [2]. Previous studies did not find a direct correlation between higher BMI and risk of myocardial infarction (MI) in PLWHIV [3, 4], but on the other hand, higher BMI is a recognized risk factor for diabetes mellitus [5, 6], which in turn is a risk factor for MI in the general population and also in PLWHIV [7].

Combined antiretroviral therapy (cART) can be associated with weight changes, and on-cART weight gain has also been demonstrated as a risk factor for incident diabetes in PLWHIV [8]. Recent reports have highlighted a possible role of dolutegravir (DTG) in weight gain [9, 10] and body fat composition changes during raltegravir (RAL) treatment [11], which made us ask if integrase inhibitors (INSTIs) could potentially have a class effect in fat gain. However, these previous works did not adjust the final weight gain for initial BMI and advanced disease, introducing possible confounders in the interpretation of the results.

We reviewed all the data of patients enrolled in the observational SCOLTA project [12] and who started a regimen containing RAL, DTG, elvitegravir (EVG), darunavir (DRV), or rilpivirine (RPV). Patients enrolled in SCOLTA were prospectively followed up with the aim of identifying possible drug-related adverse events, and every 6 months, laboratory and clinical data, including body weight, are collected. The study protocol of the SCOLTA cohort was approved by local ethical committees, and written consent was obtained from all participants.

In order to minimize possible confounders, we decided to exclude naïve patients and experienced subjects with no therapy before enrollment. Globally, 755 cART-experienced patients with at least 1 year of follow-up while on the same therapy were included in the analysis (225 in DTG, 382 in RAL, and 148 in EVG). As control groups, we also analyzed 145 patients on a treatment including DRV without INSTI and 218 patients on RPV.

Overall, the median age of 1118 patients was 46.0 years (range, 19–81 years). Patients were 71.2% male, 19.2% had baseline CD4+ T-cell count <200 cells/μL, 38.1% were in Centers for Disease Control and Prevention (CDC) stage A, 30.5% were in CDC stage B, and 31.4% were in CDC stage C, and 39.9% had detectable HIV-RNA (>50 copies/dl) at the start of the new regimen. Of them, 71.5% were on a previous failing PI-based cART. The median time of previous cART was 10.8 years (range, 1 month–30.6 years). As regards BMI, 5.9% were underweight (BMI < 18.50), 60.5% were normal weight (BMI, 18.50–24.99), 27.0% were overweight (BMI, 25.00–29.99), and 6.6% were obese (BMI ≥ 30.00). The median BMI was 23.7 (range, 12.5–39.1); 31.0% had lipodystrophy or lipoatrophy at study entry.

In the whole population (any cART), there was a BMI change of +0.19 (±standard error, 0.03) at 6 months and +0.25 (±0.04) at 12 months (both P < .0001). At univariate analysis, all the considered treatments but RPV were associated with slight but statistically significant BMI rise at 1-year follow-up (Table 1). However, no direct comparison between the 2 control drugs and any INSTI was significant.

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To account for potential confounders, we used a general linear model multivariate analysis to evaluate whether BMI changes at 6-month and 12-month visits were significantly different from 0 in all cohorts. Comparisons were planned among single INSTIs and control cohorts. We also planned to simultaneously control for several factors potentially associated with weight gain, and we recorded the following at enrollment: sex (M/F), age (as a continuous variable), CD4+ T-cell count (<200 vs ≥200), CDC stage (A+B vs C), HIV-RNA (3 categories: <50, 50–1000, >1000 copies/mL), lipodystrophy/lipoatrophy (Y/N), cART duration (<3 or ≥3 years), and initial BMI class. After adjustment, the 1-year BMI modification was confirmed significantly different from 0 in all the study drugs. Again, no INSTI was significantly different from DRV or RPV in the adjusted analysis, whereas age at study entry ($P = .016$), BMI at enrollment ($P = .011$), and CD4 <200 cells/mL ($P = .006$) were significantly associated to BMI changes. Adjusted means are shown in Table 1.

To better understand the role of cohort drugs on BMI variation, we reran the multivariate analyses in strata of variables that could indicate the current clinical status of patients. CDC stage (A+B or C). At 12 months, patients in stage A+B (n = 767, of which 20.7% were in DTG, 30.2% were in RAL, 14.5% were in EVG, 11.1% were in DRV, and 23.5% were in RPV) experienced a mean BMI increase of 0.13 (±0.06), which was related to lower BMI at enrollment ($P = .002$) and older age ($P = .0007$). BMI increase was significantly different from 0 in EVG and DRV. As compared with DRV, RAL patients had a significantly lower BMI modification ($P = .038$), but no other significant difference was observed. Focusing instead on patients in CDC stage C (n = 351, 18.8% in DTG, 42.7% in RAL, 10.5% in EVG, 17.1% in DRV, and 10.8% in RPV), the mean BMI increase at 12 months was 0.46 (±0.08) and was correlated with BMI ($P = .005$) and CD4+ at enrollment ($P = .007$). In this group, DTG, RAL, DRV, and RPV use was correlated with BMI increase (Table 1). Indeed, it is possible that in the EVG cohort, the sample size was too small and the effect, less marked than that observed in more used drugs, too low to achieve significance.

To further investigate the effect of other clinical variables, we also repeated the analysis, stratifying patients on the basis of baseline CD4+ T-cell count and years of cART. Using CD4+ level at enrollment as an indicator of advanced disease, instead of CDC stage, BMI increases were consistently similar in subjects without and with advanced disease, through drug cohorts (Table 1). Moreover, patients with a history of cART ≥3 years experienced a significant BMI increase with all the drug regimens (Table 1). BMI increase was also observed in

Table 1. BMI Changes in 1118 Patients on Dolutegravir, Raltegravir, Elvitegravir, Darunavir, or Rilpivirine, Before and After Adjustment for Baseline Characteristics, and After Stratification for CDC Stage of Disease, CD4+ at Baseline, Previous ART Duration

	Dolutegravir	Raltegravir	Elvitegravir	Darunavir	Rilpivirine
BMI, mean ± SE, kg/m^2	N = 225	N = 382	N = 148	N = 145	N = 218
6-mo visit	0.18 ± 0.08	0.17 ± 0.07	0.21 ± 0.07	0.32 ± 0.09	0.06 ± 0.07
	$P = .016$	$P = .014$	$P = .004$	$P = .0009$	$P = .39$
12-mo visit	0.30 ± 0.10	0.24 ± 0.08	0.23 ± 0.10	0.41 ± 0.10	0.06 ± 0.08
	$P = .005$	$P = .003$	$P = .017$	$P = .0001$	$P = .51$
6-mo visit[a]	0.28 ± 0.10	0.26 ± 0.08	0.42 ± 0.11	0.35 ± 0.11	0.30 ± 0.11
	$P = .006$	$P = .001$	$P = .0003$	$P = .001$	$P = .005$
12-mo visit[a]	0.37 ± 0.13	0.36 ± 0.10	0.42 ± 0.15	0.48 ± 0.14	0.30 ± 0.14
	$P = .004$	$P = .0004$	$P = .004$	$P = .0006$	$P = .029$
12-mo visit, in strata of:					
CDC stage A+B[b]	0.22 ± 0.15	0.02 ± 0.12	0.38 ± 0.156	0.36 ± 0.16	0.10 ± 0.15
n = 767	$P = .16$	$P = .90$	$P = .019$	$P = .029$	$P = .51$
CDC stage C[b]	0.66 ± 0.24	0.86 ± 0.19	0.29 ± 0.30	0.64 ± 0.25	0.63 ± 0.31
n = 351	$P = .007$	$P < .0001$	$P = .35$	$P = .012$	$P = .04$
CD4+ ≥200 cells/mL[c]	0.15 ± 0.14	0.16 ± 0.11	0.33 ± 0.15	0.45 ± 0.16	0.10 ± 0.14
n = 903	$P = .28$	$P = .17$	$P = .031$	$P = .005$	$P = .46$
CD4+ <200 cells/mL[c]	1.24 ± 0.41	0.70 ± 0.25	0.08 ± 0.44	0.46 ± 0.31	1.34 ± 0.66
n = 215	$P = .003$	$P = .006$	$P = .85$	$P = .14$	$P = .044$
Previous ART <3 y[d]	0.68 ± 0.42	0.78 ± 0.35	0.32 ± 0.42	1.42 ± 0.51	0.08 ± 0.40
n = 195	$P = .11$	$P = .029$	$P = .45$	$P = .006$	$P = .85$
Previous ART ≥3 y[d]	0.34 ± 0.13	0.32 ± 0.09	0.50 ± 0.16	0.38 ± 0.13	0.36 ± 0.14
n = 921	$P = .009$	$P = .0007$	$P = .001$	$P = .004$	$P = .011$

P refers to change from baseline: if $P < .05$, means are significantly different from 0.

[a]Adjusted for sex, age, CD4+, detectable viral load, CDC stage, duration of ART, lipodystrophy, and BMI at study entry.

[b]Adjusted for sex, age, CD4+, detectable viral load, duration of ART, lipodystrophy, and BMI at study entry.

[c]Adjusted for sex, age, detectable viral load, CDC stage, duration of ART, lipodystrophy, and BMI at study entry.

[d]Adjusted for sex, age, CD4+, detectable viral load, CDC stage, lipodystrophy, and BMI at study entry.

the group with shorter cART duration, but due to lower sample size (n = 195), this change did not achieve statistical significance; however, in our cohorts, the direct adjusted comparison between these groups did not highlight a significant difference.

Finally, we performed an analysis in strata of HIV-RNA (<50, 50–1000, >1000 copies/mL). BMI change by HIV-RNA load was U-shaped, with a minimum in subjects with 50–999 copies/mL, but without significant differences among strata after adjustment for other variables.

While in previous studies performed on the general population, a BMI increase was found more likely in people with normal BMI or overweight [13], we found in PLWHIV a higher BMI gain in those who had lower baseline values. Moreover, in the European population, the proportion of overweight is higher in more advanced ages [14]. In our cohort, a link between age and BMI was confirmed in CDC stages A+B, while in patients with more advanced stage disease, only the lower baseline BMI and CD4+ T-cell count were linked to significant BMI increases, independent of chronological age. The correlation between BMI change and low CD4+ T-cell counts was already found in previous studies [15] and was confirmed by our data, which might suggest a role of nutritional rehabilitation following weight loss from advanced disease. Finally, previous studies demonstrated that the greatest increase in BMI occurred in the first year of therapy [15], while here a significant increase was demonstrated also in patients who had already been in treatment for more than 3 years.

The study has possible biases related to its observational design. Indeed, patients taking different drugs had different baseline characteristics and were enrolled in different years. Moreover, data on personal choices or sociopsychological conditions influencing weight loss or gain were not recorded, limiting the generalizability of these data. With these limitations, our study found that a BMI increase can be observed in PLWHIV taking cART, also after many years of treatment and especially in those with lower baseline BMI. An age-related BMI increase, independent of exposure to cART, can partially justify this finding in CDC stages A+B, while patients in stage C have significant increases independent from their age. Patients in stage C who were in treatment with DTG, RAL, DRV, and RPV also had significant increases, independent from baseline BMI. In our study, there was not a significant difference among patients in different antiretroviral drugs, including integrase inhibitors. To assess the role of single drugs, studies with fewer confounders and adequate sample size in different drug classes are still needed.

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References

1. Armah KA, Chang CC, Baker JV, et al; Veterans Aging Cohort Study (VACS) Project Team. Prehypertension, hypertension, and the risk of acute myocardial infarction in HIV-infected and -uninfected veterans. Clin Infect Dis **2014**; 58:121–9.
2. European AIDS Clinical Society (EACS). EACS Guidelines. **2017**. Available at: http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Accessed 10 August 2017.
3. Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc **2014**; 3:e001035.
4. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med **2013**; 173:614–22.
5. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al; Veterans Aging Cohort Study. HIV infection and the risk of diabetes mellitus. AIDS **2009**; 23:1227–34.
6. Capeau J, Bouteloup V, Katlama C, et al; ANRS CO8 APROCO-COPILOTE Cohort Study Group. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. AIDS **2012**; 26:303–14.
7. Friis-Møller N, Sabin CA, Weber R, et al; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med **2003**; 349:1993–2003.
8. Herrin M, Tate JP, Akgün KM, et al. Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. J Acquir Immune Defic Syndr **2016**; 73:228–36.
9. Norwood J, Koethe JR, Turner M, et al. Weight gain in persons with HIV switched from Efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr **2017**; doi: 10.1097/QAI.0000000000001525.
10. Menard A, Meddeb L, Tissot-Dupont H, et al. Dolutegravir and weight gain: an unexpected bothering side effect? AIDS **2017**; 31:1499–500.
11. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis **2016**; 62:853–62.
12. Bonfanti P, Martinelli C, Ricci E, et al; CISAI Group (Italian Coordinators for the Study of Allergies HIV Infection). An Italian approach to postmarketing monitoring: preliminary results from the SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) project on the safety of lopinavir/ritonavir. J Acquir Immune Defic Syndr **2005**; 39:317–20.
13. Stenholm S, Vahtera J, Kawachi I, et al. Patterns of weight gain in middle-aged and older US adults, 1992–2010. Epidemiology **2015**; 26:165–8.
14. European Commission. Eurostat Statistic Explained. **2014**. Available at: http://ec.europa.eu/eurostat/statistics-explained/index.php/Overweight_and_obesity_-_BMI_statistics. Accessed 23 October 2017.
15. Koethe JR, Jenkins CA, Lau B, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res Hum Retroviruses **2016**; 32:50–8.