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SHORT COMMUNICATION

Should we expect weight changes in people with HIV and a reported weight gain only by switching antiretroviral therapy?

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SUMMARY

Weight gain following the initiation or the switch of antiretroviral therapy (ART) is well documented and mainly associated with some of the most recent drugs, such as integrase strand transfer inhibitors and tenofovir alafenamide. However, limited data have been published on weight trends in ART-experienced people living with HIV (PLWH) with a long exposure to HIV infection and antiretroviral drugs. In our study, we assessed changes in weight after switching ART among PLWH who reported weight gain under a previous regimen.

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Antiretroviral therapy (ART) can contribute to weight gain in people living with HIV (PLWH). In particular, this trend has recently been observed with the use of more modern ART regimens, both in naïve and ART-experienced PLWH (Sax *et al*., 2020; Erlandson *et al*., 2021). Weight gains in PLWH are associated with negative health outcomes, such as diabetes mellitus, cardiovascular disease and mortality (Kumar *et al*., 2018); for this reason, weight gain should be routinely monitored. Moreover, recently updated guidelines suggest that weight gain is described when widely used drugs are introduced, such as integrase strand transfer inhibitors (INSTIs) or tenofovir alafenamide (TAF) (European AIDS Clinical Society, 2021; Department of Health and Human Services, 2021). The aim of our study is to evaluate if switching ART for any reason may lead to weight changes in PLWH with a reported weight gain.

This is a monocentric, retrospective study conducted on adult PLWH on virological suppression followed at IRCCS San Raffaele Institute (Milan, Italy) who switched ART between 2008 and 2021 with at least two determinations showing a weight gain before switching ART and two determinations of weight after the switch.

Key words:
HIV, Antiretroviral Therapy, Drug Switching, Weight Gain, Body Mass Index.

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We considered as baseline the last switch satisfying the inclusion criteria for each PLWH; weight changes after ART switch were estimated according to both the antiretroviral class of the anchor drug and the most frequently used ART regimens before switching. Patients' characteristics were reported as median (interquartile range) or frequency (%) and compared using Chi-square test.

Two weight determinations before switch were averaged and used as baseline-weight; weight change after switch since baseline was then calculated using univariate linear regression. Univariate linear regression models were fitted for each individual to estimate weight slopes (mean change per year) after switch.

All participants provided written informed consent at first visit for being included in scientific publications.

We evaluated 1165 PLWH: at the time of ART switch, median age was 50 (43-55) years, 946 (81.2%) were male, 1100 (94.4%) Caucasian, median exposure to HIV infection was 15 (8-22) years and to ART 11 (5-18) years. Median CD4 count was 669 (482-876) cells/μL and median CD4/CD8 0.8 (0.5-1.1). Median Body Mass Index (BMI) was 24.6 (22.4-27.3) kg/m^2, median total cholesterol 188 (160-214) mg/dL, and median low-density lipoprotein cholesterol (LDL-c) 119 (96-140) mg/dL. Other patient characteristics are reported in the *Table 1*.

Pre-switch ART regimens were based on protease inhibitor (PI) in 513 (44.0%) PLWH, non-nucleoside reverse transcriptase inhibitor (NNRTI) in 268 (23.0%), INSTI in 196 (16.8%), and other regimens

in 188 (16.1%); a median increase of 2.0 kg (1.0-4.0) was observed under these regimens during a pre-switch median time of 178 days (116-329).
The median individual slope of weight post-switch was 0.47 (-0.61, 1.63) kg/year and the median calendar year of switch was 2015 (2013-2017); the median duration of the pre-switch ART regimen was 2.9 (1.5-5.1) years and the median follow-up post-switch was 2.2 (1.2-3.3) years.
The median individual slope of weight post-switch was 0.47 (-0.37, 1.52) kg/year in PLWH with BMI ≤25 kg/m², 0.48 (IQR: -0.87, 1.87) kg/year in BMI >25 to ≤30 kg/m², and 0.29 (-1.38, 2.17) kg/year in BMI >30 kg/m².
After ART switching, median total cholesterol was 184 (161-210) mg/dL and median low-density lipoprotein cholesterol (LDL-c) was 119 (97-140) mg/dL.
There was no antiretroviral class associated with a significant weight loss after switching ART in PLWH included in our analysis (*panel A, Figure 1*); however, a switch to an NNRTI was more frequently followed by weight gain compared to PI and INSTI (68.5% vs 60.5% vs 58.8%, respectively, p=0.03). Among the most-used pre-switch ART regimens, we documented a rising weight trend after the switch from rilpivirine (RPV) + emtricitabine (FTC) + tenofovir disoproxil fumarate (TDF) and efavirenz + FTC + TDF to RPV + FTC + TAF (57/75, 76.0% and 14/18, 77.8%, respectively) (panel B, Figure); as regards anchor drugs, switching from TDF- to TAF-based ART led to a weight gain (71/93, 76.3%).
Weight gain was less frequently described after switching from a triple therapy to dolutegravir + lamivudine (4/11, 36.4%), although this finding was reported in a small number of participants receiving a dual regimen.
Among PLWH included, 409 (35.1%) were overweight (BMI >25 to ≤30 kg/m²) and 110 (9.4%) were obese (BMI >30 kg/m²) before switching ART: after the switch, 391 (33.6%) had a BMI >25 to ≤30 kg/m² and 121 (10.5%) a BMI >30 kg/m².

Table 1 - *Patients' characteristics.*

Characteristics at baseline	*People living with HIV included (n=1165)*
Male, n (%)	946 (81.2%)
Age, median (interquartile range, IQR), years	50 (43-55)
Caucasian, n (%)	1100 (94.4%)
Exposure to HIV infection, median (IQR), years	15 (8-22)
Exposure to ART, median (IQR), years	11 (5-18)
Calendar year of switch, median (IQR)	2015 (2013-2017)
CD4 count, median (IQR), cells/µL	669 (482-876)
CD4/CD8 ratio, median (IQR)	0.8 (0.5-1.1)
Body Mass Index (BMI), median (IQR), kg/m²	24.6 (22.4-27.3)
BMI>25 to ≤30 kg/m², median (IQR)	409 (35.1%)
BMI >30 kg/m², median (IQR)	110 (9.4%)
Total cholesterol, median (IQR), mg/dL	188 (160-214)
LDL cholesterol, median (IQR), mg/dL	119 (96-140)

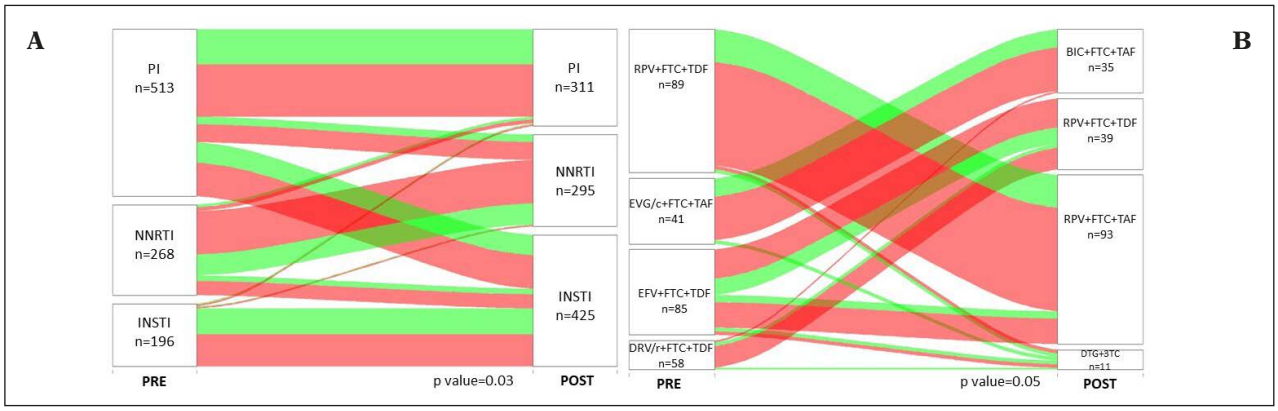

Figure 1 - *Weight changes after switching antiretroviral therapy.*
Panel A. Trend of weight after the switch of therapy stratified according to the antiretroviral class.
Panel B. Trend of weight after the switch of therapy stratified according to the most frequent (pre-switch) antiretroviral regimens.
Legend: red lines: increasing trend of weight after the switch of antiretroviral therapy (slope≥0); green lines: decreasing trend of weight after the switch of antiretroviral therapy (slope <0).
Abbreviations: PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; RPV, rilpivirine; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EVG/c, elvitegravir/cobicistat; TAF, tenofovir alafenamide; BIC, bictegravir; EFV, efavirenz; DRV/r, darunavir/ritonavir; DTG, dolutegravir; 3TG, lamivudine.

Based on our findings, ART switch regardless of the class used does not lead to weight changes in ART-experienced PLWH with a reported weight gain while receiving antiretroviral drugs. In fact, PLWH maintained a stable weight or had a physiological fluctuation, estimated at about 0.3-0.5 kg/year for European adults.

Consistent with data from the literature, switching from a TDF- to a TAF-containing regimen was generally associated with weight gain (Surial *et al*., 2021; Bansi-Matharu *et al*., 2021), even though mechanisms underlying weight changes related to TAF are still debatable.

Moreover, PLWH who experienced weight gain were more likely to have a suboptimal lipid profile: in our study, both the median pre- and post-switch LDL-c were higher than 116 mg/dL, which is the recommended cut-off value for people with a low 10-year risk of fatal cardiovascular disease (Mach *et al*., 2020). The number of people with BMI >25 in our analysis remained unaltered during the study period, needing a careful evaluation to prevent long-term comorbidities. Therefore, accurate management of weight gain and metabolic complications should be adopted with the integration of lifestyle interventions, including dietary counselling and exercise promotion, although long exposure to HIV and antiretroviral drugs might require more efforts to reach tailored goals.

Limitations of the study are the retrospective design, which cannot exclude residual confounding biases, and the lack of data on reasons for switching. Nevertheless, it provided an excellent opportunity to investigate weight changes in a large sample size in a real-world setting.

In conclusion, merely switching ART after an increase in weight did not have any effect on weight change in our cohort. Due to the impact that being overweight or obese has on individual health, a multidisciplinary strategy may be required to lower the risk of comorbidities.

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