Weight and antiretrovirals: a novel episode of a long series

Jacqueline Capeau

Weight and antiretrovirals: a novel episode of a long series

Jacqueline Capeau

Sorbonne Université, Faculty of Medicine, Inserm UMR_S938, Saint-Antoine Research Centre, FRM EQU201903007868, ICAN, RHU CARMMA ANR-15-RHUS-003, Paris, France

Jacqueline Capeau, MD, PhD, Faculty of Medicine Sorbonne University, 27 rue Chaligny, 75012 Paris, FRANCE

Email: Jacqueline.capeau@inserm.fr

In the Lancet HIV, L Bansi-Matharu and colleagues[1] report data from real life settings, obtained in the prospective RESPOND international Cohort Study, on the effect of different contemporary antiretrovirals (ARV) on body mass index (BMI) or, similarly, weight. They observe that, compared to lamivudine, use of dolutegravir (DTG) raltegravir (RAL) and TAF (tenofovir alafenamide) are associated with significant (>7%) BMI increase. This has been previously reported in a number of studies, performed in either ART-naïve or ART-experienced persons living with HIV (PLWH)[2-4]. The assets of this study are: i) the international recruitment and real-life settings, ii) the large number of included subjects (over 14,000) allowing evaluation of all contemporary ARV (but not bictegravir since recent calendar years are missing), iii) the independent association of DTG and TAF with BMI increase, the magnitude of the association being greater for both ARV when used concomitantly and iv) the weight gain trajectory, mainly during the first two years after ARV initiation.

In RESPOND[1], 54% PLWH presented >7% BMI increase on the median term, suggesting a very common effect. However, I think that the weight gaining effect of integrase strand transfer inhibitors (INSTI) and TAF affect a minority of PLWH, more often black persons and women, while most treated PLWH present no, or a moderate, gain[5,6]. We need to consider that weight gain could result from numerous factors others than ARV and HIV, including age, western diet, sedentary way of life, use of corticoids or antipsychotics, tobacco stopping. In addition, it could result from confinement due to COVID-19 (but this is not accurate in RESPOND[1] since patients were evaluated from 2012 up to December 2018). For the clinician, it is important to identify at-risk subjects to propose adequate follow-up.

In RESPOND[1], the authors also evaluate the 5.1% PLWH who gained more than 30% BMI, which is a considerable gain. Affected PLWH are those with low pre-ARV BMI and CD4 number, suggesting a gain mainly linked to the return to health process. Weight gain in PLWH with low CD4 and high VL, generally reported in ART-naïve subjects, is a surrogate marker for the success of ART[3]. Nevertheless, DTG, RAL and TAF present an additional effect, over the return to health process.

Increased weight in INSTI/TAF-treated subjects results essentially from increased fat mass. Relationships between HIV, ARV and fat amount/repartition could be considered as a series with multiple seasons. It began with the lipoatrophic effect of thymidine analogues (stavudine, zidovudine), then with truncal fat accumulation when thymidine analogues were withdrawn, without clearly ascertaining which ARV were involved into this fat gain[7]. The discovery that HIV is present within fat reservoirs and involved into fat alterations was a novel episode[8] as was the worldwide rising prevalence of obesity also affecting PLWH[6].

The unexpected fat gaining effect of some INSTIs and TAF is worrisome given the overall good tolerance and efficiency of these ARVs which were positioned to treat both naive and controlled patients. They induce global fat increase, affecting both limbs and trunk, subcutaneous and visceral fat, while efavirenz and TDF revealed inhibitory effects on weight gain[6].

The weight gain trajectory is an important issue for the patients' follow-up. Some previous data suggested a transient effect of DTG and TAF on weight. Accordingly, in RESPOND[1], most of the weight gain occurred during the first two years after ARV initiation. Also, the use of elvitegravir (and cobicistat) was not associated with BMI gain[1], excluding a class effect. The mechanisms involved are only poorly understood at present, probably multifactorial, including personal factors. DTG and RAL could directly affect adipose tissue[9] but the effect of TAF is not known.

Gaining weight has an overall deleterious impact on cardiometabolic features, favoring atherosclerotic cardiovascular diseases, insulin resistance and diabetes, hypertension and non-alcoholic fatty liver disease. Observing a global rather that a truncal fat gain is reassuring with regard to these complications. Data are still scarce and contradictory. In ART-naive

patients initiated with DTG or TAF, the young age at ART initiation precludes solid estimations. In ART-controlled patients switched to an INSTI and/or TAF, it is too early to evaluate atherosclerotic risk. Data regarding diabetes are conflictual[10]. Taken as a whole, I think that an increased risk is associated with weight gain, as expected, but that an additional effect of INSTI and/or TAF is not proven.

In conclusion, a moderate weight gain with some recent and efficient INSTI and TAF is a common situation and does not preclude their use. A minority of PLWH present a worrying weight gain requiring a careful follow-up, life-style recommendations and eventually ARV switch.

Declaration of interests

JC reports grants paid to the institution from ViiV Healthcare and MSD and personal fees for educational presentations from ViiV Healthcare, MSD and Gilead outside the submitted comment.

References

1. Bansi-Matharu L, Phillips A, Oprea O, et al. Association between contemporary antiretrovirals and increase in body mass index: results from the prospective RESPOND Cohort Study. *Lancet HIV* 2021.
2. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. *N Engl J Med* 2019; **381**(9): 803-15.
3. Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. *Clin Infect Dis* 2019.
4. Lake JE, Wu K, Bares SH, et al. Risk Factors for Weight Gain Following Switch to Integrase Inhibitor-Based Antiretroviral Therapy. *Clin Infect Dis* 2020.
5. Kileel E, Lo J, Malvestutto C, et al. Assessment of obesity and metabolic profile by integrase inhibitor use in REPRIEVE. CROI 2021; 2021; virtual; 2021.
6. Lake JE, Trevillyan J. Impact of Integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV. *Curr Opin HIV AIDS* 2021; **16**(3): 148-51.
7. Erlandson KM, Zhang L, Lake JE, et al. Changes in weight and weight distribution across the lifespan among HIV-infected and -uninfected men and women. *Medicine (Baltimore)* 2016; **95**(46): e5399.
8. Koethe JR, Lagathu C, Lake JE, et al. HIV and antiretroviral therapy-related fat alterations. *Nat Rev Dis Primers* 2020; **6**(1): 48.
9. Gorwood J, Bourgeois C, Pourcher V, et al. Integrase inhibitors dolutegravir and raltegravir exert proadipogenic and profibrotic effects and induce insulin resistance in adipose tissue and adipocytes. *HIV Med* 2019; **20**(SI): 8-9.

10. Capeau J, Lagathu C, Bereziat V, Feve B. Recent data on adipose tissue, insulin resistance, diabetes and dyslipidaemia in antiretroviral therapy controlled HIV-infected persons. *Curr Opin HIV AIDS* 2021; **16**(3): 141-7.