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Antiretroviral therapy and weight gain in naive HIV-1 infected patient: a narrative review

*Emilie Dupont[1,2] and Jean Cyr-Yombi[2]**

[1]Department of Infectious diseases, CHU UCL Namur, Yvoir; [2]Department of Internal Medecine and Infectious diseases, Cliniques Universitaires Saint-Luc (UCLouvain), Bruxelles. Belgium

Abstract

The prevalence of obesity has increased dramatically in recent decades worldwide. An increase in the prevalence of obesity has also been observed among people living with HIV (PLHIV) in high and low incomes countries. Antiretroviral therapy (ART), by controlling the viral load (VL) and restoring cellular immunity, has improved the health status and life expectancy in PLHIV. However, the risk of developing non-AIDS events (NAEs) remains higher than the general population. Therefore, specific attention is given to managing risk factors associated with NAEs during the follow-up of PLHIV, including obesity. Factors related to weight gain in PLHIV include demographic factors, HIV disease-related factors, and ART-associated factors. In naive PLHIV, weight gain after the initiation of ART is expected. The weight gains observed are generally not severe even if there appear to be risk factors such as the advanced stage of disease (low CD4 cells count and high VL), female sex, black race, and taking integrase strand transfer inhibitors (INSTI) associated or not with tenofovir alafenamide fumarate (TAF). The role of each antiretroviral drug per-se remains to clarify. As INSTI ± TAF has been associated with significant weight gain, further research is needed to identify the individual-level factors predictive of weight gain, the mechanisms of ART-associated weight gain and the clinical relevance of this weight gain. As PLHIV survive longer on effective ART, the prevention and management of NAEs will remain a challenge for healthcare providers.

Keywords

Weight gain. Obesity. Naive HIV-1 infected patients. Antiretroviral therapy. Integrase strand transfer inhibitors. Tenofovir alafenamide fumarate.

Introduction

The initiation of antiretroviral therapy (ART) has improved the health status and life expectancy of people living with HIV (PLHIV) by controlling the viral load (VL) and restoring cellular immunity. It has reduced the risk of developing HIV-related complications and improved life expectancy. On the other hand, the risk of developing non-AIDS events (NAEs) (neoplastic, cardiovascular, liver, bone, kidney, lung, and neurocognitive diseases) remains higher than the HIV-uninfected population[1-3]. PLHIV are exposed to chronic immune activation, toxicities of antiretroviral drugs (ARV), and higher and cumulative exposure to certain lifestyle risk factors, which partly explain this more increased risk of developing NAEs[4,5]. Therefore, particular attention is given to managing risk factors associated with NAEs, including obesity, during the follow-up of PLHIV, which is

Correspondence to:
*Jean Cyr Yombi
E-mail: jean.yombi@uclouvain.be

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becoming an aging population (> 50 years), exposed to several comorbidities that occur more frequently and earlier. Obesity is associated with metabolic abnormalities, including insulin resistance, dyslipidemia, and kidney disease leading to chronic diseases such as hypertension, diabetes, cardiovascular diseases, and some cancers[6]. Overweight and obesity can also promote the occurrence of osteoarticular, respiratory, obstetric, or psychological complications[6].

Overweight is a public health problem affecting more than 600 million adults worldwide[4,7] and overweight caused 4 million deaths worldwide (60% of which are obese) in 2015, and around 70% of deaths are due to cardiovascular diseases[7].

The prevalence of obesity has increased dramatically in recent decades. From 1975 to 2014, global rates of obesity increased from 3.2 to 10.8% in men and from 6.4 to 14.9% in women[6]. It has sometimes even reached > 30% for women, in some countries such as the United States of America (USA), where the overall prevalence is estimated at 36.2% in 2016[8]. If this trend continues, it is estimated that by 2025, 18% of men and 21% of women worldwide will be obese[6]. The worldwide economic burden of managing obesity and its complications has been estimated at roughly $2 trillion annually, nearly as much as smoking, armed conflict, and terrorism combined[6].

An increase in the prevalence of overweight and obesity has also been observed among PLHIV in high and low incomes countries[4,9,10]. A cross-sectional study including 53,825 PLHIV was conducted to determine the proportion of patients who were overweight or obese at enrollment to care and treatment centers from 2004 to 2011 in Africa. About 16% of women and 8% of men were overweight, while 7% and 2% were obese, respectively[11]. The English/Irish POPPY cohort (n = 1361)[10] reports an obesity prevalence of around 15% for PLHIV. The most affected sub-populations are women, African descent patients, and elderly patients, as observed in the general population[10].

Factors associated with weight gain in PLHIV include demographic characteristics (such as sex and race), HIV disease-related factors (such as disease stage and VL, and ART-associated factors (specific ARV). However, the role of each ARV per-se needed to be clarified[9]. Mechanism and characteristics associated with weight gain in PLHIV remain not completely understood[9]. This review aimed to expose and discuss weight gain in naive HIV-1 infected patients under ART to clarify prevalence and risk factors associated with weight gain, particularly the role of ART.

Materials and Methods

This review is based on large cohorts and randomized clinical trials (RCTs) published from 2015 to 2020 in the English language found in PubMed using keywords “weight gain” or “obesity” or “naive HIV-1 infected patients” or “antiretroviral therapy” or “integrase strand transfer inhibitors” or “tenofovir alafenamide fumarate.” We also used data from abstracts presented at major HIV/AIDS international conferences (European AIDS Clinical Society, Conference on Retroviruses and Opportunistic Infections, International AIDS Society, and HIV Glasgow conference). Our analysis intentionally targets naive patients, and the evaluation of weight gain for experienced patients will be the subject of further research. To try to obtain relevant data, we decide arbitrarily to include only a large cohort (n ≥ 500) and RCT (n = 400).

Weight gain in naive PLHIV

Weight gain was assessed in RCT[4,12-23] (Table S1) and cohorts studies[24-30] (Table S2) in naive PLHIV.

RCT in naive PLHIV

Advance[12] was a large open-label RCT carried out in South Africa comparing tenofovir alafenamide fumarate (TAF)/Emtricitabine (FTC)/Dolutegravir (DTG) versus tenofovir disoproxil fumarate (TDF)/FTC/DTG versus TDF/FTC/Efavirenz (EFV). The weight gain at 96 weeks (W) was significantly greater in the TAF/FTC/DTG group (+7.1 kg) compared to TDF/FTC/DTG (+4.3 kg) or TDF/FTC/EFV (+2.3 kg) and in women in the TAF group (+8.1 kg). Several independent predictors of treatment-emergent obesity were identified (TAF/FTC/DTG, baseline CD4 count, baseline VL, and baseline body mass index [BMI]). Authors also identified TAF/FTC/DTG, baseline CD4 count, baseline VL, baseline weight, female sex, and age) as independent risk factors for a 10% or greater weight gain[12]. Such weight gain is unlikely to be simply a “return to health” effect because viral suppression and CD4 recovery were similar across the groups, suggesting that weight gain is multifactorial[12].

Furthermore, a comparison was made with regimens containing TDF and EFV, probably attenuating the impact of weight gain[4,31-33]. Analysis of changes in body composition assessed by the DXA scan system shows that weight increases were predominantly fat rather than lean body mass and were

distributed in the trunk and limbs in participants in all three arms of the study. Increases in fat mass (trunk and limb) were significantly higher in women than men.

Increases in visceral adipose tissue (VAT) were higher in women than men, but these differences were not statistically significant and were higher in the TAF group regarding changes in mass and volume[12].

Namsal[13] was a RCT performed in Cameroon comparing DTG + TDF/Lamivudine (3TC) versus EFV + TDF/3TC. A greater weight gain was observed at 96W in the DTG versus EFV group (+5.0 kg vs. +3.0 kg). Weight gain ≥ 10% and incidence of obesity was higher in DTG group versus EFV group (23% vs. 16%), particularly in women and in patients with initial VL ≥ 100,000 copies/mL. Once again, the comparator was EFV which can mitigate, as we know, weight gain[31].

In Gemini I/II studies[14], comparing DTG/3TC versus DTG/TDF/FTC, patients receiving DTG/3TC gained slightly more weight (+3.7 kg) and higher BMI (1.2 kg/m^2) than those receiving DTG/TDF/FTC (+2.4 kg and +0.8 kg/m^2).

The Gilead 1490 study[15] compared TAF/FTC/DTG versus TAF/FTC/Bictegravir (BIC) showed a similar weight gain of 3.9 kg versus 3.5 kg, respectively, at 96W, suggesting a similar effect on weight gain from DTG and BIC. However, when abacavir (ABC) was used as the nucleoside reverse transcriptase inhibitors (NRTI) backbone in the Gilead 1489 study (DTG/ABC/3TC vs. BIC/FTC/TAF), observed weight gain was more modest in the DTG group (+2.4 kg at 96W)[16].

The Aria study[17] was a study devoted to women comparing DTG/ABC/3TC to atazanavir (ATV)/ritonavir (r) + TDF/FTC showing weight gain of 2.61 kg versus 1.41 kg and weight gain ≥ 10% in 18% versus 15% of participants in the DTG arm versus ATV arm at 48W. The odds of a 10% increase in weight were higher for the DTG group, black participants, participants with high VL, and lower for patients with high CD4 count and a baseline higher weight.

Adjusted mean change in BMI from baseline and treatment-emergent obesity was higher in the DTG arm (8%) versus ATV arm (6%). Among race subgroups, increases in adjusted mean weight were most prominent among women of African heritage in both treatment groups; however, the difference between groups was relatively small (0.99 kg).

The Flair study[18], which compares DTG/ABC/3TC to rilpivirine (RPV)/cabotegravir (CAB) (Per Os (PO) then long-acting (LA)) did not show a significant difference in terms of weight gain at 48W.

The AIDS Clinical Trials Group (ACTG) 5260 study[19] was a retrospective analysis of the ACTG 5257 study[20]. The study compared ATV/r versus darunavir (DRV)/r versus raltegravir (RAL) + TDF/FTC and showed at 96W that the patients with severe weight gain had a mean increase of 14.9 kg and those with extreme BMI gain had a mean increase of 4.4 kg/m^2. Predictors of severe weight/BMI gain in this population included a black descents, higher baseline disease severity, and use of RAL versus ATV/r. Results also suggested that treatment with protease inhibitors (PIs) versus RAL may be protective against severe weight/BMI gain. The odds of extreme weight gain were significantly lower for ATV/r versus RAL, while odds of severe BMI gain were substantially lower for DRV/r versus RAL.

Another sub-analysis of the ACTG 5257[21] investigated the modification of waist circumference (WC) between the three groups. All subgroups experienced an increase in WC à 96W, with the most significant increases appearing in the RAL group and the following subgroups: female, black, non-Hispanic, older, normal and obese BMI, VL ≥ 100000 copies/mL, and CD4+ < 350 cells/mm^3. The mean WC change was lower for DRV/r than RAL (-1.24 cm). A more considerable difference in WC change for DRV/r versus RAL was found for black individuals than other ethnicities/ethnicities. Change in WC for ATV/r versus RAL was more prominent for females than males. CD4 cells count and higher VL appeared to be strong predictors of more significant WC increases after adjusting for several variables, including BMI.

A pooled analysis of 3 RCT was performed in 2019 by Orkin et al.[22] to assess the effects of doravirine (DOR) on weight gain and BMI compared to DRV/r or EFV-based regimens. Their multivariate analysis did not show a significant association between ARV drugs, age, sex, race, weight, baseline BMI, and 10% weight gain at 48W and 96W. Weight changes were similar for DOR and DRV/r and lower EFV at 48W but at 96W, weight changes were similar for all groups. No significant differences between treatment groups were found in the proportion of participants with at least 10% weight gain or BMI class increase. In contrast, low CD4 cells count and high VL are significantly associated with weight gain ≥ 10% ($p < 0.001$) and with an increase in BMI ($p \leq 0.01$) at 96W[19].

In a pooled analysis, Bares et al.[23] resumed 3RCT (ACTG 5142, ACTG 5202, and ACTG 5257) from the AIDS Clinical Trials Group in patients in the USA, comparing the BMIs of 760 women and 3041 men in the first 96W following initiation of ART. Women gained an

average BMI of 1.91 kg/m^2 and men earned an average of 1.39 kg/m^2 ($p < 0.001$); the sex difference persisted within each pre-ART initiation BMI subgroup. After adjusting for pre-ART initiation, age, CD4+ count, VL, race/ethnicity, study, and ART regimen, the mean BMI change for women was 0.59 kg/m^2 more than for men ($p < 0.001$). Statistical interactions were observed between sex and pre-ART CD4+ count and VL and suggested that for subgroups with higher VL and lower CD4 at baseline, the estimated BMI changes in women are even more extensive than the average estimated difference. Most of the weight change observed over 96W occurred within the 1st year (y) of follow-up[23]. From subgroup analysis where additional characteristics were available, Bares et al.[23] found that the estimated sex difference was not modified by socioeconomic status, alcohol or illicit drug use, or metabolic syndrome. Still, current or former smoking status mitigated the estimated sex difference on BMI change.

In another pooled analysis of 8 Gilead RCT performed by Sax et al. (934: EFV + FTC/TDF vs EFV + Zidovudine (ZDV)/3TC; 236 - 0102: Elvitegravir(E)/Cobicistat (C)/FTC/TDF vs. EFV/FTC/TDF; 236 - 0103: E/C/FTC/TDF vs. ATV/r + FTC/TDF; 264 - 0110: RPV/FTC/TDF vs. EFV/FTC/TDF; 292 - 0104, 292 - 0111: E/C/FTV/TAF vs. E/C/FTC/TDF; 380 - 1489: BIC/FTC/TAF vs. ABC/DTG/3TC; 380 - 1490: BIC/FTC/TAF vs. DTG + FTC/TAF) involving 5680 treatment-naive PLHIV and over 10,000 person-years of follow- up (PYFU), weight gain was greater with the use of newer ART[4]. Pooled analysis revealed baseline demographic factors associated with weight gain, including lower CD4 cells count, higher VL, no injection drug use, female sex, and black descents. Integrase strand transfer inhibitors (INSTI) use was associated with more weight gain than were PI or non-nucleoside reverse-transcriptase inhibitors (NNRTIs), with DTG and BIC associated with more weight gain than Elvitegravir/cobicistat (EVG/c). Among the NNRTIs, RPV was associated with more weight gain than EFV. Among Nucleoside/nucleotide Reverse Transcriptase Inhibitors (NRTIs), TAF was associated with more weight gain than TDF, ABC, or ZDV.

Cohorts studies in naive PLHIV

A Brazilian retrospective cohort study[24] evaluated the prevalence of obesity before and the incidence of obesity after ART initiation to determine the risk factors in naive patients during a period of 4y median follow-up. A total of 1198 individuals (76.5%) gained weight over the study period, 688 (43.9%) increased their BMI category, and 286 (18.3%) developed obesity (overall incidence of obesity: 37.4/1000 PYFU). The median BMI increased from baseline to the end of the study from 22.3 to 24.7 kg/m^2 ($p < 0.0001$). In multivariate analysis, the risk factors significantly associated with obesity were young age, female sex, the highest initial BMIs, low CD4s, high VL, use of an INSTI, initial hypertension, and diabetes. Compared to patients on NNRTI or PI, patients on INSTI had 10 times the incidence of obesity, 4 times more annual gain in BMI, and almost two times more rapid onset of obesity (median time to obesity diagnosis was 1.9 years for patients on NNRTI or PI versus 1 year in patients on INSTI). Still, the number of patients on INSTI was meager (n = 14). Finally, the incidence of obesity and the annual gain in BMI in women taking INSTI were greater.

In 2019, Bourgi et al.[25] published the results of an 18-month retrospective cohort study conducted in Nashville, USA. The study had shown that all patients gained weight in the 1st year of treatment after initiation of ARV drugs, especially those with low baseline BMI, low CD4s, and high VL, but this weight gain subsequently slowed down. They did not observe a significant influence of sex or race on weight gain. The patients on DTG gained significantly more weight (+6.0 kg) than the patients on NNRTI (+2.6 kg) or EVG (+0.5 kg). However, they did not observe a significant difference in terms of incidence of obesity between groups. Patients on RAL gained significantly more weight (+3.4 kg) than those on EVG (+0.5 kg), and those on PI gained significantly more weight (+4.1 kg) than those on EVG (+0.5 kg). Note that the results were not adjusted according to the NRTI backbone and that most of the patients on DTG received an ABC/3TC-based regimen while the majority of patients on others INSTIs, NNRTI, and PI, the backbone was from TDF/FTC.

The NA-ACCORD cohort[26] observed that the use of an INSTI-based regimen was associated with more significant weight gain at 5 year after initiation of treatment (+5.9 kg) compared to NNRTI based regimen (+3.7 kg). On the other hand, the weight gain under the PIs-based regimen at 5 y (+5.5 kg) was similar to that under INSTIs based regimen. Among INSTIs, weight gain at 2 y was more significant in patients on DTG (+7.2 kg) compared to patients on RAL (+5.8 kg) and EVG (+4.1 kg). Among all ART initiators, the odds of a > 10% weight gain were substantially higher for PLHIV starting PI- and INSTI-based regimens compared to NNRTI-based regimens at both 2 y and 5 y. When restricting this analysis to participants starting

INSTI-based regimens, the odds of a > 10% weight gain at 2 y were significantly lower for patients receiving EVG than RAL.

Female sex, lower baseline weight, and lower baseline CD4 were associated with significantly higher odds of a > 10% weight gain at 2 and 5 y after ART initiation.

Rates of transition from overweight to obese after 3 years of ART use were more frequent for recipients of INSTI than those under PI and NNRTI[26]. In this cohort, the overwhelming majority of participants received ART containing TDF or ABC (< 1% of participants received an ART containing TAF)[26].

In the Dallas cohort[27], Bedimo et al. wanted to assess the effect of PIs and INSTIs on the change in BMI by gender and ethnicity. The BMI slope/y was steeper on INSTI than on NNRTI and PI. They observed that all PIs were associated with a more significant gain in BMI in women than in men, but with no difference by race. For INSTIs, EVG was associated with a greater increase in BMI but without a significant difference between sexes and ethnicities. DTG and RAL are associated with more significant BMI gain in females, and DTG is associated with more significant BMI gain in Blacks.

The retrospective study of an Italian cohort[28], evaluating the change in weight and BMI in naive patients under RAL versus DTG VS EVG/C versus DRV/r, showed after 12 months a small and comparable, but not significant, increase in body weight, BMI, and WC. Note the absence of TAF used as a backbone and the predominance of men.

In the KAISER-permanent cohort[29], changes in BMI between PLHIV starting treatment (n = 8256) and non-HIV patients (n = 129,966) in the same category in terms of age, sex, and race were assessed. At the first study visit, a higher proportion of people with than without HIV had a normal BMI, similar ratios with and without HIV were overweight, and a lower proportion with HIV was obese. After 12 years of follow-up, they observed a faster increase in BMI in PLHIV than uninfected people regardless of the initial BMI, but the mean BMIs at 12 years were similar for both groups. The rate of weight gain was significantly greater in PLHIV than in HIV-negative people for all baseline weight categories apart from obese people. The study could not consider the effects of diet or exercise, and the findings have limited applicability to women due to the small proportion in the Kaiser cohort.

Data from the Veterans Aging Cohort Study[30], a US observational study of PLHIV demographically matched 1:2 to uninfected controls, show that weight gain exceeding 5 pounds (= 2.27 kg) was typical in naive PLHIV. Still, more PLHIV gained weight (48%) than uninfected (31%), and median weight gain was more remarkable in PLVIH 1y after starting ART. Among PLHIV, a lower baseline BMI was associated with a higher probability of weight gain. Two-thirds of those with baseline BMI < 18.5 kg/m^2 gained weight in the 12 months after ART initiation, as did half of the standard weight and more than 40% of those overweight or obese at baseline. At every level of BMI, weight gain was more common, and the amount of weight gained was greater in PLHIV than uninfected.

Table 3 summarizes the risk factors highlighted in the cohorts and the RCTs that seem to promote obesity or weight gain > 10%.

Potential mechanisms that may explain abnormal weight gain in PLHIV

The mechanism that may explain weight gain and PLHIV obesity is complex and multifactorial.

Environment

Changes in the food environment and food systems are likely to be significant drivers in the general population as in PLHIV[7]. Increased availability, accessibility, and affordability of energy-dense foods, along with intense marketing of such foods, could explain excess energy intake and weight gain among different populations[7]. Although we do not have reliable data on the impact of poor diet on weight gain in PLHIV, it would be surprising if this well-known impact in the general population differed in PLHIV. Food insecurity leading to poor dietary behavior ultimately responsible for increased BMI and obesity was also demonstrated in a Caribbean population of PLHIV[34].

The reduced opportunities for physical activity that have followed urbanization and other changes in the built environment have also been considered potential drivers[7]. It highlights the need to implement multi-component interventions to reduce high BMI prevalence and disease burden[7]. Medication that promotes weight gain or socioeconomic status may also influence weight, as in the general population, and is often overlooked in studies[4]. Sax et al.[4], in their pooled analysis of 8 RCTs, observed that the median weights and BMIs at the baseline were currently greater, approaching overweight and that the weight gain documented in the 2 y of starting ART was not higher than that reported in the general population. The English/Irish POPPY cohort (n = 1361) reports an obesity

Table 3. Risk factors for weight and BMI gains

	RCT		COHORTS	
	ART	**Others factors**	**ART**	**Others factors**
Weight gain > 10%	NRTI TAF > ZDV or ABC or TDF[4] INSTI DTG/TDF/3TC > EFV/TDF/3TC[13] DTG/ABC/3TC > ATV/r/TDF/FTC in women[17] BIC or DTG > EFV[4] EVG/c > EFV[4] INSTI + TAF DTG/TAF/FTC > DTG/TDF/FTC or EFV/TDF/FTC[12] NNRTI DRV/r > DOR > EFV[21] RPV > EFV[4]	Low baseline CD4 count[12,17,22] High baseline VL[12,13,17,22] Baseline weight[12] Women[12] DTG + women[13] Black descents[17] Age[12]	INSTI PI or INSTI > NNRTI[26] RAL > EVG[26]	Low baseline CD4 count[26] Low baseline weight[26] Women[26]
Obesity (BMI ≥ 30 kg/m^2)	INSTI + TAF TAF/FTC/DTG[12] DTG/TAF/FTC > DTG/TDF/FTC[13] DTG/ABC/3TC > ATV/r/TDF/FTC[17]	Baseline CD4[12] Baseline VL[12] Baseline BMI[12] Women + DTG/TAF/FTC[13]	INSTI INSTI > NNRTI or PI[24] INSTI > PI or NNRTI[26]	Low baseline CD4 count[24] High baseline VL[24] High baseline BMI[24] Women[24] Women + INSTI[24] Young age[24] Baseline hypertension[24] Baseline diabete[24]

ART: anti retroviral therapy; RCT: randomized controlled trials; BMI: body mass index; VL: viral load; NRTI: nucleoside (tide) reverse-transcriptase inhibitor; TAF: tenofovir alafenamide fumarate; TDF: tenofovir disoproxil fumarate; ZDV: zidovudine; ABC: abacavir; FTC: emtricitabine; 3TC: lamivudine; INSTI: integrase strand transfer inhibitor; RAL: raltegravir; DTG: dolutegravir; EVG: elvitegravir; BIC: bictegravir; c: cobicistat; NNRTI: non-nucleoside reverse-transcriptase; EFV: efavirenz; RPV: rilpivirine; DOR: doravirine; PI: protease inhibitor; DRV: darunavir; ATV: atazanavir; r: ritonavir.

prevalence of around 15% for PLHIV[10]. The most affected sub-populations are women, African descent patients, and elderly patients, as observed in the general population[10].

Return to normal health

An excess of weight gain must be distinguished from the weight gain attributed to the return to normal health in naive HIV-infected patients, particularly in patients with advanced disease with low CD4 cells count, high VL, and weight loss initial disease-related[4,12,13,17,21-26,35]. This weight gain is most often modest, although we do not have the initial weight data in most studies, making it difficult to assess accurately. This return to a normal state of health is also associated with a reduction in short-term mortality, particularly in initially "underweight"[29]. Still, it could also contribute to excessive weight gain in individuals with early-stage HIV disease and those with normal or above-normal BMI[4]. In the Strategic Timing of Antiretroviral Therapy (START) study[36] comparing two strategies for initiating ART (immediate initiation vs. deferred initiation until the CD4+ count declined to 350 cells/mm^3 or the development of an AIDS-related event or another condition that dictated the use of ART), after a median follow-up of 3 y, the mean change in weight from baseline was 1.13% in the immediately treated arm versus 1.92% in the delayed arm ($p < 0.001$). The factors associated with less weight gain in the immediately treated group versus the delayed group were the high CD4 cells count ($p < 0.001$), the female sex ($p = 0.048$), and the patients living in a "low-middle income country" ($p = 0.019$).

Improvement of the tolerance of ARVs and the prognosis of PLHIV

Resolving opportunistic infections and digestive dysfunctions on ART may contribute to weight gain by improving appetite and absorption[4]. The weight

Table 4. Important factors for interpretation of weight/BMI gain and goal of future studies

Important factors for interpretation of weight/BMI gain	Goal of futures studies
NRTI, NNRTI and booster used in ART regimen	Comparative studies with identical backbone Compare ART with backbone/NNRTI less likely to influence weight gain (TAF vs. TDF; EFV) Independent backbone assessment (TDF vs. TAF in PrEP studies) Compare booster VS no booster with identical backbone less likely to influence weight gain
Demographics factors (race, sex, local prevalence of obesity, cultural habits, …) Actually, populations studied are mainly white and male	Adequate representation of the demographic of PLWH globally Additional studies on female and African populations Studies comparing men and women would make it possible to assess the possible influence of sex
Presence of confounding factors	Confounding factors should be taken into account: lifestyle, others medications promoting weight gain, pregnancy,… Studies on experienced populations make it possible to avoid attributing weight gain to the return to normal health Additional studies in patients taking PrEP can eliminate confounding factors linked to HIV or other ARVs
Regularity in measures of weight/BMI parameters in cohorts and in retrospective analysis of RCT	Strict protocol for weight/BMI measurements to be defined Interest in defining a significant weight gain threshold from which it would be reasonable to change treatment
Assessment of other markers of weight gain (biological markers, others anthropometric measurements, …) and assessment of metabolic consequences (fat distribution, diabetes, lipid profile, cardiovascular diseases, …)	A broader assessment of weight gain (distribution of fat, density, anthropometric measurements) would make it possible to refine the data and specify the subsequent metabolic risk Longer-term studies would make it possible to assess the possible metabolic consequences

gain attributed to the new molecules could also be partly explained by their effectiveness and better tolerance[4,37]. Moreover, INSTIs such as DTG, BIC, and RAL do not require boosting with cobicistat or ritonavir, associated with nausea and diarrhea[4]. Among NNRTIs, RPV is better tolerated than EFV and should be taken with food, resulting in higher caloric intake. In the case of NRTIs, early trials demonstrated more gastrointestinal toxicity with ZDV than newer NRTIs, including ABC and TDF[4]. However, in a sensitivity analysis of Advance study[12], eliminating patients with insomnia and gastrointestinal adverse effects (e.g., nausea) did not affect differences in weight gain. Moreover, other well-tolerated ARV, such as DOR, has not been associated with extreme weight gain[38].

Female and black patients

The data diverge, but according to some studies, women and black people are more at risk of gaining weight, increasing their BMI or their WC when they are exposed to INSTI or TAF[4,12,13,17,19,21,23,24,26,27], but the underlying mechanism remain unknown. Nevertheless, these populations remain under-represented in most available studies where white males are predominant. The weight increases could also reflect the high prevalence of obesity in black women, cultural differences, or other confounding factors such as hormonal status, other medications, or poor food hygiene. During midlife, women gain approximately 0.7 kg/y, independent of initial body weight or ethnicity[37]. This increase in body weight is believed to be multifactorial, potentially involving hormonal changes[37]. In the Advance study[12], women gain more weight and faster than men in all three groups, potentially reflecting gender-related differences in obesity in South Africa, which has the highest prevalence of female obesity globally[39].

Given that INSTIs are first-line therapy in the United States and European nations, it is anticipated that more women will be started on or switched to INSTIs in the future. The public health implications of usual, aging-related weight gain, compounded by the potential of INSTI-associated weight gain, are critically important

to recognize, as WomenLHIV are living longer with ART and as INSTI use increases globally[37]. In the pooled analysis performed by Sax et al., 4 female sex and black descents were associated with ≥10% weight gain (female vs. male: OR 1.54 ($p < 0.001$); black vs. non-black: OR 1.32 ($p = 0.003$)) in naive population. More black women experienced ≥10% weight gain than non-black women (19.7% vs. 12.4%; $p < 0.001$). In the pooled analysis performed by Bares et al.[23], women gained an average of 1.91 kg/m^2, and men gained an average of 1.39 kg/m^2 ($p < 0.001$). Statistical interactions were observed between sex and pre-ART CD4 cells count and VL and suggested that for subgroups with higher VL and lower CD4 cells count at baseline, the estimated BMI changes in women are even larger than the average estimated difference[23].

However, women, in general, have lower total muscle mass than men, and BMI may therefore underestimate the sex differences in changes in adiposity following the initiation of ART[23].

Weight gain and ARVs

Even if a weight gain attributed to TAF and INSTI (DTG, BIC), particularly in the female and black populations, is confirmed, the results observed in weight gain in the RCTs and the cohorts remain very heterogeneous. Several elements must be considered for their interpretation and to obtain better quality data (Table 4).

The mechanisms linked to the weight gain associated with ARV have not yet been elucidated. Nevertheless, a few hypotheses have already been mentioned, and some are developed below.

Effect on adipose tissue

Evaluating the amount and distribution of fat makes it possible to differentiate between lipohypertrophy, an accumulation of subcutaneous adipose tissue, and lipodystrophy, the VAT accumulation associated with using first ARVs. Current evidence mainly suggests that fat gains with INSTI are widespread. Reassuringly, this differs from lipodystrophy syndrome that is typically associated with long-lasting metabolic complications[40].

The evaluation of the quality of the fat through density measurements with the CT-scan (DXA-scan) makes it possible to distinguish the fat with low density linked to larger adipocytes and an increase in the fat content corresponding to the associated lipohypertrophy with the lower metabolic risk and higher density fat linked to inflammation and fibrosis leading to lipodystrophy associated with a higher risk of secondary metabolic abnormalities[41]. INSTIs could also cause changes in the structure of adipocytes favoring the development of obesity and insulin resistance[42,43].

The persistent HIV-infected macrophages in adipose tissue could enhance local inflammation and cause expansion of fat tissues[44]. In addition, HIV can also promote the aging of adipose tissue and alter its function, contributing to insulin resistance[45].

Effect on "regulatory" receptors

The melanocortin four receptor (MC4R) regulates calorie intake by modulating leptin's signal in the central nervous system. There seem to be interactions between DTG and MC4R, but a study by McMahon et al.[9] showed that all tested INSTIs (BIC, DTG, CAB, RAL, and EVG) could antagonize the MC4R receptor to some degree. Still, importantly, inhibition occurs only at drug concentrations substantially more significant than the therapeutic plasma concentrations of each drug[9]. For instance, DTG is associated with more substantial weight gain than EVG. However, EVG was approximately 25-fold more potent in MC4R antagonism than DTG in their experiments[9]. These findings suggest that it is unlikely that MC4R opposition contributes to the weight gain associated with INSTI use in clinical practice[9]. Bodyweight regulation can also be modified via manipulating other signaling pathways independent of MC4R. In nonclinical models, activation of the melanin-concentrating hormone receptor-1, neuropeptide-Y receptors, or ghrelin receptor leads to weight gain[9]. Whether INSTIs can activate these receptors are unknown[9]. The glucagon-like peptide-1 (GLP-1) pathway, wherein synthetic peptide agonists of the GLP-1 receptor drive weight loss, is currently approved to treat diabetes and obesity[9]. In nonclinical models, blockade, or loss of GLP-1 receptors do not promote weight gain[9]. However, it remains possible that INSTIs may affect the GLP-1 receptor or its ligands in a clinical setting to the extent it may increase body weight. These hypotheses remain to be directly tested[9].

Plasma DTG concentrations

A theory is that weight gain may be linked to higher drug exposure, especially for INSTI, as increased DTG plasma drug levels have been associated with neuropsychiatric effects[37]. A sub-analysis of advance study[46] showed that the differences in weight gain between EFV and DTG are driven by reduced weight gain in patients

with cytochrome P450 2B6 intermediate or slow metabolizer genotypes. Indeed, participants with a slow EFV metabolizer genotype (found more often in the African population) lost weight. In contrast, those with an extensive EFV metabolizer genotype gained a similar amount of weight as those in the DTG/FTC/TDF arm[46].

Others mechanisms

Gut microbiome disturbance and immunologic alterations also contribute to the weight gain associated with INSTIs[47].

Impact of weight gain/BMI or obesity on several outcomes

Immune cells are abundant in adipose tissue, and obesity inducing their activation causes changes in their number and activity, leading to chronic inflammation and dysregulation of the immune system leading to metabolic or vascular complications and an increased risk of cancer or infectious diseases[6].

The impact of weight gain in the general population is multiple and well documented (cardio-metabolic diseases, gastroenterological, respiratory, orthopedic, renal, oncological, obstetrical, immune, and psycho-social complications). However, data on the impact of long-term weight gain in PLHIV have still limited actually[35].

Impact of weight gain on the management of PLHIV in clinical practice

It seems reasonable to pay attention to weight gain in PLHIV, especially when starting a new ART. The naive patient should be warned that weight gain is expected following a return to normal health. In the event of objective weight gain, an assessment of the patient as a whole (comorbidities, drug treatment excluding ARV, lifestyle, stage of the disease, etc.) must be carried out systematically as well as the monitoring of any consequences (metabolic, cardiovascular, and impact on therapeutic compliance). Reducing the contributing factors highlighted during this evaluation must remain the basis of any management involving multidisciplinary management before considering a possible shift to another ART. Expert opinions diverge, but there is not enough evidence to change treatments quickly, especially if it is well-tolerated and has no consequences.

Nevertheless, this can be considered if we observe a disproportionate weight gain without any other convincing explanation, but there is not yet a well-defined "trigger." We avoid the TAF± INSTI (especially DTG), particularly in black female patients. Combination by using other molecules should help to mitigate weight gain. TDF could be an alternative given its favorable impact on weight and lipid profile[48]. While there is a suggestion that this may come at a compromise to patients bone mineral density and renal markers, a recent meta-analysis found no differences in clinical safety endpoints between TAF and TDF[49]. DOR is a novel NNRTI that has not been associated with weight gain, which presents a favorable lipid profile and a high genetic barrier[38]. Consequently, it may mark a therapy option, particularly for those with cardiometabolic risk factors or high BMI before starting ART. Future research should directly compare weight gain between DOR and the newer INSTIs, particularly in Black female populations.

Conclusions

Weight gain in PLHIV can be multifactorial: return to normal health (particularly in patients with low initial CD4 cells count and high VLs), ART (better tolerance and direct effect potentially linked to the molecule), the backbone or booster used, taking other drugs (anti-depressants, hormones, and corticosteroids), taking toxicants (cannabis, etc.), hormonal status (menopause, pregnancy, thyroid disorders, etc.), initial BMI, age, healthy lifestyle (diet, sporting activity, smoking, alcohol consumption, etc.), demography, cultural differences (a sign of good health, wealth, beliefs, socioeconomic importance, etc.), and special situations (weight gain attributed to the lockdown linked to COVID), all of which is part of a current obesogenic environment marked by an increase in the prevalence of obesity worldwide. These confounding factors make it difficult to interpret the potential link between ARVs and weight gain. Weight gain after the initiation of ART is expected. The weight gains observed are generally not severe, with stabilization sometimes observed over time, even if there appear to be risk factors such as the advanced stage of disease, female sex, black descents, and taking INSTI ± TAF.

The mechanisms linked to the possible weight gain of the news ARVs and their potential reversibility are not yet elucidated. It should be noted that the clinical relevance of this weight gain is still unclear.

Further research is needed in this area to identify the individual-level factors predictive of INSTI ± TAF. Associated significant weight gain and further studies focusing on pharmacogenomics of ART metabolism and individual genetic factors related to weight gain

may provide additional insights into the mechanisms of ART-associated weight gain.

There are, therefore, no absolute contraindications to prescribing INSTIs ± TAF. Still, it remains vital that prescribing clinicians must be aware of this side effect, particularly in patients who are already obese or at already higher cardiovascular risk. As PLHIV survive longer on effective ART, the prevention and management of NAEs will remain a challenge for health providers.

SUPPLEMENTARY DATA

Supplementary data are available at AIDS review online (10.24875/AIDSRev.21000092). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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