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Antiretroviral therapy and weight gain in antiretroviral treatment-experienced HIV patients: A review

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Abstract

The risk of developing non-AIDS events (NAEs) remains higher in persons living with HIV-1 (PLWH) compared to the general population despite progress made in the treatment by antiretroviral (ARV). Particular attention is therefore given to the management of risk factors associated with NAEs during the follow-up of PLWH, including overweight. Factors associated with weight gain in PLWH are multifactorial and include demographics, HIV disease-related, lifestyle, cultural, and antiretroviral therapy (ART)-associated factors. All these confounding factors make it difficult to interpret the potential link between ARVs and weight gain. In antiretroviral treatment- experienced PLWH, confounding factors such as the return to normal health or the advanced stage of disease can be ruled out compared to naïve patients which somewhat facilitates the interpretation of weight gain. Weight gain after ART switch is modest, not generally a big concern in clinical practice in this population and correlated more strongly with baseline regimen, especially after the stop of TDF or EFV, than with sex-, race-, or HIV-related factors. It remains uncertain whether this is due to the loss of a weight suppressive effect of prior regimens with older agent such as TDF or EFV or a weight gain effect of the newer regimens especially TAF and/or INSTI, or both. The mechanisms linked to weight gain attributed to the new ARVs as well as its possible reversibility are not yet elucidated. Clinicians who switched ARV regimen of experienced PLWH should be aware of this side effect and of this potentially consequences on the global health.

Keywords

HIV. Antiretroviral. Weight gain. Obesity. Treatment-experienced patients.

Introduction

By controlling the viral load (VL) and restoring cellular immunity, the initiation of antiretroviral therapy (ART) has improved the health status and life expectancy of people living with HIV (PLWH) reducing dramatically HIV-related complications. On the other hand, the risk of developing non-AIDS events (neoplastic, cardiovascular, renal, liver, brain diseases, etc.) remains higher compared to the general population[1-3]. PLWH are exposed to chronic immune activation, toxicities of antiretroviral drugs (ARVs) and higher and cumulative exposure to certain lifestyle risk factors, which partly explain this higher risk of developing non-AIDS events (NAEs)[4,5]. Particular attention is there-

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fore given to the management of risk factors associated with NAEs during the follow-up of PLWH, including overweight that can also promote the occurrence of osteoarticular, respiratory, obstetric, or psychological complications[6].

Weight gain in PLWH can be multifactorial: return to normal health in naïve patients, ARV effect (better tolerance and direct effect potentially linked to the molecule), taking other drugs or toxicants, hormonal status, initial body mass index (BMI), age, healthy lifestyle, demographics and cultural differences, special situations (lockdown linked to COVID for example) and obesogenic environment marked by an increase in the prevalence of obesity worldwide[4,7,8]. In antiretroviral treatment experienced PLWH, confounding factors such as the return to normal health or the advanced stage of disease can be ruled out and make it more easier to interpret weight gain. Switch studies also make it possible to follow the modification of the weight associated with the switched molecule, insofar as it is the only modified variable and that we have the weight and baseline regimen data prior to the switch.

But the mechanisms linked to the possible weight gain attributed to the new ARVs as well as its possible reversibility are not yet elucidated[9-12]. The aim of this review is to discuss current knowledge regarding weight gain in antiretroviral treatment - experienced PLWH based on randomized controlled trials (RCTs) and large cohort studies recently published in the literature.

Materials and methods

This review is based on large cohort studies and RCTs published from 2015 to 2022 in the English language found in PubMed using keywords “weight gain” or “obesity” or “suppressed/experienced-treated HIV infected patients” or “ART” or “integrase strand transfer inhibitors” or “tenofovir alafenamide fumarate (TAF)” or “tenofovir disoproxil fumarate” or “efavirenz” or “protease inhibitors.” We also used data from abstracts presented at major HIV/AIDS international conferences (European AIDS Clinical Society (EACS), Conference on Retroviruses and Opportunistic Infections (CROI), International AIDS Society (IAS), and HIV Glasgow conference). Our analysis intentionally targets antiretroviral treatment-experienced HIV patients because the evaluation of weight gain for naïve patients has been the subject of a previous publication[8]. To try to obtain relevant data, we decide arbitrarily to include only large cohort studies (n ≥ 500) and RCTs (n = 400).

Weight gain in antiretroviral treatment- experienced PLWH

Weight gain has been evaluated in RCTs[13-23] and cohort studies[24-35] in antiretroviral treatment-experienced PLWH (see Supplemental Tables 1 and 2, respectively).

RCTs in antiretroviral treatment experienced PLWH (Table S1)

Switch to Integrase Strand Transfer Inhibitor (INSTI)

NEAT 022[13] is a European multicentre RCT comparing switch (immediate or deferred switch at 48 weeks (W)) to a dolutegravir (DTG)-based regimen from a boosted protease inhibitor (bPI)-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. Initial backbone was similar for both groups (tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) ~ 65%; abacavir (ABC)/lamivudine (3TC) ~ 31%). A sub study of NEAT 022[14] shows that suppressed patients with immediate switch to DTG (n = 205) have a little, but statistically significant, weight gain (+ 0.82 kg) and BMI gain (+ 0.272 kg/m^2) compared with deferred patients (+ 0.25 kg and + 0.064 kg/m^2, respectively) at 48 W. After adjustment for baseline BMI, switching from darunavir (DRV) to DTG-regimen was the only independent factor associated with BMI gain (p = 0.018)[14].

BRAAVE[15] is a United States (US) multicentre RCT comparing suppressed patients who shift to bictegravir (BIC)/TAF/FTC (n = 330) versus no immediate shift (n = 165) in African-American population. At baseline, TAF/FTC was the most frequent backbone and INSTIs was the most frequent baseline 3nd agents. The results show a little weight gain in the immediate shift group at 24 W (+ 0.9 kg in BIC group vs. + 0.2 kg in no switch group) then remaining stable (+ 0.9 kg) at 48 W. In the men sub-analysis, median weight change at 24W was similar between groups but among women, a treatment difference was noted (+ 1.0 kg in BIC group vs. –0.4 kg in no immediate switch group). Participants who switched to BIC/FTC/TAF from a TDF-containing regimen had more median weight gain (+ 1.8 kg) compared with those taking TAF (+ 0.8 kg) and ABC (+ 0.7 kg) containing regimens.

TANGO[16] is an international multicentre phase 3 RCT comparing switch to DTG/3TC regimen versus stay on TAF-based regimen in suppressed PLWH. Weight gain was similar at 96 W in the two groups (+ 0.81 kg vs. + 0.76 kg) and weight gain ≥ 10% was low in both groups. However, a greater weight gain was observed in both groups if taking TAF pre-switch was < 1 year ago (+ 1.45 kg vs. + 1.35 kg). After 144 W, mean weight change was not statistically different between the 2 arms (+ 2.2 kg vs. + 1.7 kg)[17] suggesting that stopping TAF does not lead to a substantial change in weight. However, TAF ceased and DTG started together, so neither assessed alone. It should be noted that elvitegravir (EVG) was the most represented INSTI of the baseline regimen (~ 66% for each group), suggesting that weight gain on EVG is low or that its discontinuation could also contribute to weight gain.

SALSA[18] is an international multicentre phase 3 RCT comparing switch to DTG/3TC versus remain on the current ART regimen in suppressed PLWH. At screening, baseline 3nd agent class was ~ 50% NNRTI (mostly EFV) and ~ 40% INSTI (mostly DTG). The most commonly used NRTIs at baseline were FTC and TDF. TAF was the least represented which differentiates SALSA study from TANGO study. After 48 W, weight change was greater in the DTG/3TC group (+ 2.1 kg) but was similar in both groups for participants with baseline TAF use (+ 1.6 kg for dual therapy group and + 1.4 kg for maintain ART group) (like in TANGO study) and was greater in the DTG/3TC group for those with baseline TDF use (+ 2.4 kg), population not represented in TANGO study, suggesting that stopping TDF and/or starting DTG would promote weight gain. However, differences in the TANGO and SALSA study designs and diversity of participant demographics, influence ability to directly compare results between the two trials[16,18].

ATLAS[19] is an international multicentre phase 3 RCT comparing based-regimen (~ 60% of participants taking EFV/TDF/FTC baseline-regimen) versus shift to Long Acting (LA) Cabotegravir (CAB) + LA Rilpivirine (RPV) in suppressed PLWH showing that median weight gain was greater in LA group at 48 W (+ 1.8 kg vs. + 0.3 kg) but this effect could also be secondary to the interruption of TDF and EFV taken by a majority of switched patients rather than a direct effect of the new ARV regimen.

VISEND[20] is a trial from a Zambian population on NNRTI based-regimen (3TC/TDF + NVP or EFV) comparing two arms: arm A (patients with VL < 1000 copies/mL: switch to TAF/FTC/DTG (TAFED) or TDF/3TC/DTG [TLD]) and Arm B (patients with VL ≥ 1000 copies/mL: switch to TAF/FTC/DTG or TDF/FTC/DTG or AZT/3TC/LPV/r or ATV/r). In Arm B, weight gain after switch to DTG (+ 5.4 kg for TAFED and + 5.0 kg for TLD) was greater than to PIs (+ 2.0 kg for LPV/r group and + 2.8 kg for ATV/r group) at 48 W.

In Arm A, weight gain was less than Arm B at 48 W (+ 1.1 kg for TAFED and + 2.8 kg for TLD) but return to normal health can play a role for weight gain on patients in Arm B in whom the baseline VL was ≥ 1000 copies/mL.

Otherwise, higher weight gains were observed for women in arm B receiving DTG and TAF (+ 5.7 kg) versus PI-based regimens (+ 2.8 kg for LPV/r group and + 2.6 kg for ATV/r group) or TDF (+ 3.1 kg).

In the international multicentre RCT GS-US-380-4030 comparing a switch from based-regimen with DTG/FTC/TAF or TDF to BIC/FTC/TAF or DTG/FTC/TAF in suppressed PLWH[21], weight gain was greater for patients initially on TDF versus TAF (+ 2.2 kg vs. + 0.6 kg), with no differences between the BIC/FTC/TAF and DTG/FTC/TAF groups overall (+ 1.3 kg vs. + 1.1 kg).

Switch to non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

DRIVE-SHIFT[22] is an international multicentre phase 3 RCT comparing experienced-suppressed patients taking 2 NRTIs (~ 70% on TDF/FTC) + bPI (~ 70%, mostly DRV/r) or EVG/cobicistat (c) (~ 5%) or NNRTI ~ 24%, mostly EFV) after immediate or late switch (> 24 W) to DOR/3TC/TDF. Weight gain remained modest in both groups through at 144W (+ 1.4 kg vs. + 1.2 kg).

Globally, 40% of participants lost weight or had no change in weight, 30% gained < 5%, 20% gained 5-10% and 8% gained ≥ 10%. Most participants (~ 80%) remained in the same BMI category and 9% of obese patients at time of switch were no longer obese at 144 W. In both groups, there was no significantly difference in term of weight gain by sex or ethnicity. The adjusted mean weight gain at 144 W was similar for participants who switched from a bPI regimen and those who switched from an NNRTI regimen but was slightly lower for those who switched from EVG/c regimen but this latter group was relatively small and most had also received TAF in their previous regimen.

Pooled analysis

Erlandson et al.[23] evaluated the effects of demographic factors, clinical characteristics and ART on

weight gain in a pooled analysis of 12 Gilead prospective clinical trials wherein suppressed PLWH were randomized to switch or remain on a stable baseline regimen (SBR). Median weight gain was greater for switch participants at 48W (+ 1.6 kg) and at 96 W (+ 2 kg) compared with patients on SBR (+ 0.4 kg at 48 W and + 0.5 kg at 96 W). The proportion of obese participants increased from 21% to 25% at 96 W among switch participants but remained stable among SBR participants (21%). Baseline ART regimen was a significant predictor of weight gain after switch: the greatest risk was switch from EFV to RPV (+ 1.5 kg) or EVG/c (+ 0.9 kg) compared to staying on EFV and switch from TDF to TAF (+ 1.6 kg) compared to switch from ABC to TAF (data not available). Participants staying on TDF or ABC had similar weight changes to those who remained on TAF.

Weight change with switch from bPI to EVG/c or BIC did not differ significantly from staying on a bPI.

Among patients on INSTI-baseline regimen, switch from DTG to BIC was not significantly different from remaining on DTG in term of weight change. Switch from EVG/c to BIC was associated with greater weight gain (+ 0.7 kg) compared to no switch. Staying on DTG was associated with greater weight gain (+ 0.6 kg) than staying on EVG/c.

Among baseline demographic and clinical characteristics, only younger age and lower baseline weight or BMI were associated with any or ≥ 10% weight gain while race, ethnicity, sex, and CD4 count were not.

The interpretation of these results must nevertheless take into account the fact that the RCTs evaluate selected patients, without control compared to the general population, younger, and with fewer comorbidities compared to the population evaluated in the observational cohorts. In addition, the evolution of the weight before the switch is not available limiting the interpretation of the weight gain after the switch.

Cohorts studies in antiretroviral treatment-experienced PLWH (Table S2)

Switch TDF to TAF

In the US multicentric OPERA cohort[24], a database of electronic health records from > 100.000 PLWH, weight gain after switch from TDF to TAF in suppressed PLWH (n = 6919, only 12% of Black women) is similar in the 9 months following the switch among all patients who maintained the third agent (+ 2.43 kg/year), independently of the third agent (+ 2.64 kg/year for patients on INSTI (73% on EVG/c, associated with the least weight gain within its class); + 2.25 kg/year for patients on NNRTI (85% on RPV, associated with the most weight gain within its class); + 1.98 kg/year for patients on bPI [68% on DRV/r]).

They also observed a stabilization (0.24 kg/year) or even a decrease in weight after the first 9 months, variable depending on the associated ARVs (+ 0.29 kg/year for patients on INSTI; + 0.20 kg/year for patients on NNRTI; –0.11 kg/year for patients on bPI).

In patients who continued taking an INSTI after the switch, there was no significant difference in terms of weight gain between DTG, EVG (the most common), and raltegravir (RAL).

For patients who also switched to an INSTI in addition to TAF, weight gain at 9 months was greater for those on BIC (+ 4.47 kg), followed by patients on DTG (+ 3.09 kg) then finally those under EVG/c (+ 2.55 kg) but without statistically significant difference.

Among people switching to EVG/c or DTG, weight stabilized after the 9-month post-switch period.

Weight gain of patients already on EVG vs those who switched to EVG is identical in the 9 months after the switch.

This study could not differentiate between the impacts on weight of removing TDF versus adding TAF given the lack of direct comparison with a group of patients maintaining TDF but by modelling weight over time on TDF, a baseline could be established for how much weight gain is expected without TAF. Therefore, the pronounced acceleration of weight gain observed immediately following switch can be interpreted in the context of weight changes that occurred over the 5 years before switch.

Thus, these results suggest an independent effect of TAF on early and rapid weight gain 9 months after the switch, followed by a slowing, stabilization (or reduction) in weight gain depending on the maintained antiretroviral or new INSTI, similarly to weight change seen before switch to TAF, in both PLWH who maintained other ARVs and in PLWH who switched from a bPI or NNRTI to an INSTI.

It should be noted that the evolution of VL and therapeutic compliance after the switch is not taken into account in this study, potentially influencing weight changes.

Data from another US multicentric cohort evaluating weight change in antiretroviral treatment-experienced PLWH on INSTI+NRTIs switched from ABC (n = 142) or TDF to TAF (n = 828) show that switch from TDF to TAF led to higher risk of > 3% weight gain after 1 year

compared to switching from ABC to TAF, even after controlling for demographic factors, BMI, CD4s, and INSTI anchor drug, suggesting a suppressive effect of TDF on weight[25].

Switch to INSTI ± TAF

Lake et al.[26] have evaluated changes in weight in antiretroviral treatment-experienced PLWH from 2 observational study among AIDS Clinical Trials Group (ACTG), before and after switch to INSTI (n = 691). They observed that women, black patients and patients ≥ 60 years old gained more weight within 2 years after the switch compared to the weight taken 2 years before the switch. In the models adjusted for women, factors associated with greater weight gain are the white or black ethnicity, age ≥ 60 years and the BMI ≥ 30 kg/m^2 at the time of the switch. For men, age ≥ 60 years was the most important factor linked to weight gain. Switched patients to DTG gained more weight following the switch (+ 1 kg/year) compared to patients switched to RAL (+ 0.5 kg/year) or EVG (–0.2 kg/year). Weight gain following switch to INSTIs also varied by pre-switch ART class and by NRTI at time of switch. Switch from NNRTI to DTG or EVG was associated with significant increases in annualized weight gain (+ 1.2 kg/year and + 1.3 kg/year, respectively) whereas switch from NNRTI to RAL was not (–0.2 kg/year). For patients switched from bPI, only switch to DTG was associated with significant increases in weight gain (+ 0.9 kg/year). Switch to any INSTI + ABC or TAF was associated with a similar increase in annualized weight gain (+ 0.9 kg/year and + 0.8 kg/year, respectively), while switch to INSTI + TDF showed no weight gain (–0.2 kg/year), suggesting once again a suppressive effect of TDF on weight.

Koethe et al. analyzed PLWH from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)[27] who switched from NNRTI or PI based-regimen to an INSTI before the introduction of TAF (n = 870). They observed greater weight gain in patients who switched from an NNRTI-based regimen (+ 0.63 kg/year) compared to those on PI (+ 0.34 kg/year). Among those who switched from an NNRTI, women, non-white ethnicity patients, patients aged ≥ 50 years and patients switched to DTG had greater annual weight gain.

The cohort analyzed by Kerchberger et al.[28] specifically assesses experienced-treated US women living with HIV (WLWH) switched to INSTI (n = 234), mostly to DTG (+ TAF for 12%) compared to women maintaining ART without INSTI (n = 884), mostly on TDF + NNRTI or bPI (TAF for 8.7%). Compared to patients not taking INSTIs, WLWH on INSTI have greater weight gain (+ 2.4 kg vs. + 0.2 kg) and BMI (+ 0.9 kg/m^2 vs. + 0.1 kg/m^2). Weight gain ≥ 7% was observed in 22% of patients on INSTI versus 14% in patients without INSTI. In the switch group, weight gain is greater in patients aged ≥ 50 years, black women, in patients with BMI < 30 kg/m^2, in patients with undetectable VL and in patients with CD4s ≥ 350 cells/mm^3, but without significant difference according to INSTI (DTG, RAL or EVG).

Analysis of a cohort from Taiwan (n = 693)[29] assessed weight gain at 48W after switch to EVG/c/FTC/TAF. No significant weight gain after switch was observed among patients who had received INSTI-containing ART before switching (+ 1.37 kg) but the correlation was statistically significant for patients who had received NNRTI (+ 2.07 kg) or PI (+ 1.5 kg) prior switching.

The Trio Health HIV Research Network electronic medical records (n = 2272) show that the mean increase in weight at 1 year after switch to INSTI ± TAF was 1.3 kg. Weight gain ≥ 10% was more common in those taking DTG compared to BIC, in women, patients underweight or normal BMI at baseline, those switching from a prior non-INSTI regimen and those switching from TDF to TAF.

It should be noted that a greater proportion of patients taking DTG were women or African Americans, while a switch from TDF to TAF was more frequent in patients on EVG.

However, there were no differences in weight gain by INSTI in multivariable analysis adjusted for baseline characteristics (age, gender, race, baseline BMI, and baseline CD4), for prior treatment and for TDF-to-TAF switching. In sensitivity analysis, there were also no differences in weight gain by INSTI type for prior treatment with TDF compared to prior treatment without TDF[30].

Results from the Italian GEPPO cohort (Geriatric Patients Living With HIV/AIDS), compared switch from INSTI naive patients ≥ 65 year to DTG versus no switch (n = 568), did not show a significant weight gain in the both group at the end of follow-up. This finding emerged also when comparing 3 versus 2 drug regimen and TAF versus TDF exposed[31]. The possible protective mechanisms for weight gain in the elderly PLWH could not be clearly identified in this study, in the same way that the mechanisms linked to weight gain in younger PLWH still remain unclear to this day. However, a geriatric population has certain particularities compared to the general population since it may suffer from cardio-metabolic comorbidities

requiring lifestyle interventions or from concomitant neoplastic pathologies that may contribute to weight loss. Furthermore, the population studied in this study is predominantly male and the population switched to DTG was more vulnerable in terms of comorbidities at baseline, which could possibly explain a lower weight gain. Moreover, in the geriatric and as well as in the oncological setting, the lack of weight gain does not automatically exclude fat accumulation while losing lean mass. Anthropometric measurements by Dexa-scan would therefore be more appropriate compared to the use of weight measurements. Finally, the significant weight gain cutoff used in this study corresponds to weight gain > 5%, unlike other studies that do not use a cutoff or lower cut-offs.

The analysis of US data from the multicenter HIV Outpatient Study (HOPS)[32] reported weight changes in an initial INSTI-naive population before and after switch to INSTI-based or not INSTI-based regimen (n = 653). Pre-switch BMI trajectory slopes were greater for patients who subsequently switched to non-INSTI regimen than INSTI-regimen. However, switched patients to INSTI-based regimen have a greater weight (+ 1.2 kg) and BMI gains after switch than patients on non-INSTI-based regimen (+ 0.3 kg). Women and Hispanic ethnicity were associated with greater BMI gain ($p < 0.01$) and among INSTI, switch to DTG was associated with greater increase of BMI than other INSTIs ($p = 0.03$ vs. RAL and $p = 0.003$ vs. EVG).

Further data from this cohort on switched patients to INSTI ± TAF[33] showed that BMI increases was faster during the 8 months immediately after switch to INSTI than non-INSTI group, regardless of whether the new regimen contained TAF or not and there were no significant differences by INSTI types. After the first 8 months on INSTI-based regimen, weight change was similar than patients on non-INSTI based regimen but weight change among patients on INSTI+TAF remained greater than participants on INSTI-regimen without TAF. There was no difference in term of BMI change after adjustment for age, gender, race and baseline BMI.

In the Swiss HIV Cohort Study[34], median weight change after switch to DTG-containing regimens is modest at 18 months after switch (+ 0.72 kg/year) compared to pre-switch period (+ 0.47 kg/year). Men gained more weight than women although the weight change remained modest (+ 0.81 kg/year vs. 0.41 kg/year) but weight gain > 5% was more likely for women, black participants, and current smokers. Weight gain after switch to DTG + TAF was higher (+ 1.4 kg/year) but the number of patients in this group is too small (n = 72).

INSTI use

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)[35] enrolled a global international cohort of ART-experienced PLWH, aged 40-75 year, with low-to-moderate traditional cardiovascular risk, and assessed specifically the effect of INSTI use on weight among participants in regions where at least 5% of the enrolled population were using INSTI-based regimens. The use of INSTI-based regimens was associated with higher mean BMI (+ 1.6 kg/m^2), higher WC (+ 3.6 cm) and 63% higher odds of obesity and this association were more pronounced in women. The greatest differences were seen in the tails of the BMI and WC distributions.

Table 1 summarizes the factors promoting weight gain, BMI and metabolic changes highlighted in the cohorts and RCTs described above.

Potential mechanisms that may explain abnormal weight gain in experienced-suppressed PLWH

The mechanisms that may explain weight gain and obesity on PLWH are complex and multifactorial.

Contrary to naive patients, the return to the normal state of health manifested by moderate weight gain following the introduction of ART and stabilizing over time[8] is no longer considered in antiretroviral treatment-experienced PLWH. On the other hand, other factors also favoring weight gain remain common, such as the patient environment (lifestyle, obesogenic environment, changes in the food environment, and reduction of physical activity followed urbanization), others medications or toxic substances, socioeconomic status, chronic exposure to HIV, improvement of the tolerance of ARVs and the potential metabolic impact of taking long-term ARVs[7,8].

The mechanisms linked to weight gain associated with ARVs have not yet been elucidated, but a few hypotheses have already been mentioned in ART-experienced PLWH and are described below.

Suppressive effect of TDF

Weight gain after switch from TDF to TAF was observed in several studies[15,20,21,23-25,31] but it remains unknown whether these observations result from removal of a weight-suppressive effect of TDF or (TAF ± INSTI)-associated weight increase or a combination of this both effects. The potential for TDF to suppress weight gain is also supported by studies in naive PLWH

Table 1. Risk factors for weight and BMI gain for experienced patients

	(RCTs	Cohorts studies
Weight gain	– bPI → DTG [14]	– bPI → DTG [26] – bPI → EVG/c/FTC/TAF [29]
	– TDF → BIC/FTC/TAF (vs TAF/ABC → BIC/FTC/TAF) [15 – TDF DTG/3TC [18] – TDF/FTC/EFV → LA RPV+ LA CAB [19 – 3TC/TDF + NVP or EFV → TAF+DTG [20] – TDF → TAF (vs ABC → TAF) [23]	– TDF → TAF + maintaining 3dr agent (mostly EVG, RPV, DRV) at 9 months [24]
	– EFV → RPV vs staying EFV [23] – EFV → EVG/c vs staying EFV [23]	– NNRTI → DTG or EVG [26,27] – NNRTI → INSTI [27] – NNRTI → EVG/c/FTC/TAF [29] – [NNRTI + women] to INSTI [27] – [NNRTI + non-white ethnicity] → INSTI [27] – [NNRTI + ≥ 50y] → INSTI [27]
	– EVGc → BIC vs staying on EVG/c [23] – staying DTG vs staying EVGc [23]	– TDF → TAF at 9 months [24] – TDF → TAF vs ABC → TAF at 1y [25] – non-INSTI → INSTI [32] – non-INSTI → INSTI + TAF [33] – switch to DTG [26] – switch to INSTI+ [ABC or TAF] 26] – switch to [INSTI + black patients] [26] – switch to [INSTI + age ≥ 60y] 26] – switch to [INSTI + women] 26, 28] – switch to [INSTI + women + ≥ 50y [28] – switch to [INSTI + women + white/black] [26] – switch to [INSTI + women + age ≥ 60y] [26] – switch to [INSTI + women + BMI > 30kg/m2] [26] – switch to [INSTI + Black women] 28] – switch to [INSTI + women + BMI < 30kg/m2] [28] – switch to [INSTI + women + undetectable VL] [28] – switch to [INSTI + women + CD4s ≥ 350cells/mm3] [28] – switch to [INSTI + men+ age ≥ 60 y] [26] – switch to [DTG + Black] 34] – switch to [DTG + Women] 34] – switch to [DTG + smokers] 34]
Weight gain ≥ 10%	– younger age [23 – lower baseline weight or BMI [23]	– TDF → TAF + INSTI [30 – switch to DTG (vs BIC) [30] – switch to [INSTI + women] 30] – switch to [INSTI + underweight or normal BMI] [30] – non-INSTI based regimen → INSTI [30]
BMI gain	– DRV/r → DTG [14]	– switch to [INSTI + women] 28] – non-INSTI [INSTI + women] [32] – non-INSTI DTG [32] – non-INSTI INSTI +/– TAF ≤ 8 months post-switch [33] – INSTI based-regimen (vs non-INSTI) [35] – [INSTI based-regimen (vs non-INSTI) + women][35]

RCTs: Randomized Controlled Trials; BMI: Body Mass Index; y: year(s); bPI: boosted Protease Inhibitor; r: ritonavir; c: cobicistat; FTC: Emtricitabine; TAF: Tenofovir Alafenamide Fumarate; TDF: Tenofovir Disoproxil Fumarate; 3TC: Lamivudine; ABC: Abacavir; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NVP: Nevirapine; EFV: Efavirenz; RPV: Rilpivirine; INSTI: Integrase Strand Transfer Inhibitor; DTG: Dolutegravir; BIC: Bictegravir; EVG/c: Elvitegravir/cobicistat; LA: Long Acting; CAB: Cabotegravir.

like in GEMINI 1 and 2, where dual therapy group with DTG/3TC gained more weight than tritherapy group with DTG/TDF/FTC (3.7 kg vs. 2.4 kg at 144 W)[36], and in preexposure prophylaxis (PrEP) trials, suggesting an initial weight-suppressive effect of TDF in a setting where confounding effects of HIV are absent[37-39].

Suppressive effect of EFV

From some trials, it appears that EFV suppresses weight gain and this influences weight change after switch to a different NNRTI or an INSTI[19,23]. In pooled study of Erlandson[23], significant weight gain was associated with switching from EFV to RPV, but maybe because oral RPV need to be taken with food. However, switch of EFV was the only third-agent switch associated with ≥ 10% weight gain[23]. The mechanism linked to the suppressive effect of EFV on weight remains unclear. Leonard et al.[40] have analyzed 2 cohorts to study pharmacogenetics of weight gain following switch from EFV to INSTI-based regimens at 48W. In the observational cohort (n = 61), they have observed that cytochrome P450 2B6 (*CYP2B6*) slow metabolizers experienced significantly greater weight gain after the switch for EVG and RAL (median weight gain: + 2.0 kg for slow metabolizer vs. + 0.1 kg for normal metabolizer) but not for DTG. In the clinical trials cohort (n = 462), *CYP2B6* slow metabolizers had lesser weight gain among participants receiving EFV + TDF (p = 0.001), but not those receiving EFV + ABC (p = 0.65). The impact of *CYP2B6* on weight change has also been seen in a sub-analysis of the ADVANCE study (TAF/FTC/DTG vs. TDF/FTC/DTG vs. TDF/FTC/EFV in naive patients) where the differences in weight gain between EFV group (+ 2.3 kg) and DTG groups (+ 7.1 kg for TAF/FTC/DTG group and + 4.3 kg for TDF/FTC/DTG group) are driven by reduced weight gain in patients with *CYP2B6* intermediate or slow metabolizer genotypes[41]. Participants with a slow EFV metabolizer genotype (found more often in African population) lost weight, while those with an extensive EFV metabolizer genotype gained a similar amount of weight as those in the DTG/FTC/TDF arm[41].

Furthermore, they were able to observe that the association between *CYP2B6* metabolizer genotype and fat distribution in women was more marked for peripheral fat than for central fat, probably due to the concentration-dependent effect of EFV on mitochondrial toxicity and adipocyte differentiation. These observations limited to women could be explained by higher plasma concentrations of EFV but this effect could be evaluated in men in larger studies with longer follow-up.

TAF effect on weight gain

The weight gain potentially associated after a switch to TAF is difficult to interpret given the frequent association of TAF with an INSTI in switch-regimen, especially if the baseline regimen contained TDF. In TANGO, weight gain is similar for switched experienced-treated patients from TAF-containing regimens to DTG/3TC versuss staying on TAF[16,17] although these observations are confounded by a high proportion of study participants also switching from non-DTG-containing regimens at baseline.

In the pooled study of Erlandson[23] switch from ABC to TAF was associated with smaller but statistically significant weight gain but ABC/3TC/DTG was associated with more frequent gastrointestinal adverse events than BIC/FTC/TAF in one of the RCT included in their analysis. However, results from HOPS cohort evaluating weight change among naive-INSTI experienced patients switched to INSTI ± TAF based regimen showed that switched patients to INSTI + TAF continue to gain weight more than 8 months after the switch compared to INSTI without TAF regimen[33].

The evaluation of weight gain in seronegative patients on TDF/FTC versus TAF/FTC for PrEP in the DISCOVER study[38] showed greater weight gain for patients on TAF (+ 1.7 kg) versus TDF (+ 0.5 kg) at 96 W but which remains similar to the weight gain observed in young seronegative US adults not taking PrEP[42].

INSTI effect on weight gain

Weight gain on INSTI-regimen have been acknowledged in both, naive and experienced-treated patients including those switched from other drug class regimens, suggesting that this drug class might cause weight gain beyond any consideration on return to normal health[12,13,15,18-20,23,24,26-30,32,35]. But according to some studies, there was also no observed weight difference among experienced patients on INSTI[16,17,31]. The interpretation of data in experienced patients must nevertheless be nuanced according to pre-switch ART, which can also contribute to undocumented weight change before and after switch ART, often represented by INSTI+TAF-based regimen.

Female and black patients

In experienced-treated patients, the results of the RCTs and the cohorts evaluated for this review are also divergent in term of the impact of sex and ethnic-

ity on weight gain. Some studies found that female sex[26-28,30,32,35] particularly black female[28,34] are at risk of increases weight but the mechanism remain understood. Jung et al.[43] have tested in a mouse model the effects of INSTIs (DTG and BIC) and NNRTI (DOR) on mitochondrial function and adipocyte differentiation on female pre-adipocyte cells. DTG and BIC mildly induced differentiation into white adipocytes and significantly suppressed differentiation into brown adipocytes compared to no treatment group. INSTIs also caused downregulation of enzymes responsible for thermogenesis in brown adipocytes and affected other mitochondrial enzymes. DTG specifically inhibited cellular oxygen consumption and energy expenditure and interfered with estrogen-mediated metabolic pathways. DOR had no effect on mitochondrial activity or fat cell differentiation. It would therefore be interesting to have more data on body and weight measurements in women on INSTIs to assess the clinical repercussions of these *in vitro* modifications on fat cells.

Effect on adipose tissue

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]. Current evidence mainly suggests that fat gains with INSTI are widespread in both, ART-naive and switch studies but the underlying mechanisms are unclear. Reassuringly, this fat gain differs from lipodystrophy syndrome that is typically associated with long-lasting metabolic complications[46]. INSTIs could also cause changes in the structure of adipocytes favoring the development of obesity and insulin resistance[47,48].

Adiponectin, a chemokine produced by adipose tissue for regulation of glucose and lipid, decreased following the switch to DTG, which can lead to insulin resistance and weight gain[49]. However, the correct interpretation of the modification of adiponectin levels remains controversial in the literature and requires further exploration[10].

Effect on "regulatory" receptors

The melanocortin 4 receptor (MC4R) is a receptor involved in the regulation of calorie intake by modulating the signal of leptin in the central nervous system. The impact of INSTIs on this receptor remains unclear and would only be significant at supratherapeutic dosages[50,51]. The regulation of body weight can also be modified via manipulation of other signaling pathways (MC1R, neuropeptide-Y receptors, ghrelin receptor, and glucagon-like peptide-1) leads to weight gain. Whether INSTIs are able to affect these receptors is unclear and these hypotheses remain to be directly tested[51].

Genetic polymorphism

A Japanese team found an association between a certain polymorphism in the resistin (a pro-inflammatory adipokine influencing insulin sensitivity in peripheral tissues and in the central nervous system) gene (RETN-420C/G) and BMI gain (+ 0.86 kg/m^2) and psychiatric symptoms in INSTI-naive patients (n = 220) after 6 months of treatment[52]. Therefore, patients gaining weight could be screened for significant psychiatric effects and vice versa. However, this is a small study and this data are limited to a Japanese population. Further investigations in other ethnic groups would be interesting to validate these data.

Impact of weight gain on management of experienced patient in practice

It seems reasonable to pay attention to weight gain after a change of ART in experienced PLWH despite the fact that gain is not generally a big concern in clinical practice in this Population. The weight gain remains modest and often stabilizes over time[23], like similar plateau observed in naive patients[4,53] or following TAF switch[24], except for patients with weight gain ≥ 10%[23]. In contrast, other studies on switch to INSTI in experienced patients showed continued weight gain ≥ 2 year post-switch[26-28] or BMI gain 8 months post-switch to INSTI + TAF[32].

In the event of objective excess weight gain, an assessment of the patient as a whole (co-morbidities, drug treatment excluding TAR, 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). The reduction of the contributing factors highlighted during this evaluation must remain the basis of any management, therefore involving multidisciplinary management, before considering a possible shift to another ART. 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," especially that the weight gains are modest.

Avoiding the TAF ± INSTI combination by switch to TDF should help to mitigate weight gain. While there is sugges-

tion that this may come at a compromise to patients bone mineral density and renal markers, a recent meta-analysis found there were no differences in clinical safety endpoints between TAF and TDF[54]. Weight gain cannot be considered as a side effect in elderly patients on INSTIs according to the Geppo cohort and these could also be a good alternative in dual therapy to avoid TDF and ABC in this patients with comorbidities[31]. DOR has not been associated with weight gain[22], appears to have no effect on adipose tissue[43] and has a favorable lipid profile[55].

Conclusions

Weight gain in experienced PLWH, like in naive patients, can be multifactorial making difficult to interpret the role of each factor. Modest weight gain is common after ART switch and is correlated more strongly with baseline regimen, especially switch off of TDF or EFV, than with sex-, race-, or HIV-related factors.

It remains uncertain whether this is due to the loss of a weight suppressive effect of prior regimens with older agent such as TDF or EFV or a weight gain effect of the newer regimen or the both effects.

Further research including demographics/lifestyle/comorbidities and co-medication factors, single-variable ART switch studies and HIV-negative studies may help disentangle these complex observations.

More research and reporting of weight and body measurements data are required to widen the evidence base and to establish clinical significance.

Further studies focusing on pharmacogenomics of ART metabolism and individual genetic factors associated with weight gain may provide additional insights into the mechanisms of ART-associated weight gain.

There are therefore no absolute contraindications to shift PLWH to INSTIs or TAF based regimens if indicated but it remains important that clinicians prescribing news ARVs, alone of in association, must be aware of this side effect in experienced -suppressed PLWH. As PLWH survive longer on effective ART, the prevention and management of NAEs will remain a challenge for health providers. Close monitoring of weight and counseling to maintain a healthy diet and remain physically active, as well as optimize other lifestyle factors, is imperative for all patients on ART.

Supplementary data

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