Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

Check for updates

AIDS Rev. 2022;26:14-26

Weight gain in HIV-infected patients

Antoni Pla Rodríguez[1], Isabel Serrano Lillo[1]*, Cristina Sánchez González[2], and María J. Galindo[3]*

[1]HIV MSL, Janssen-Cilag; [2]Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, Madrid; [3]Internal Medicine, Hospital Clínico Universitario de Valencia, Valencia, Spain

Abstract

Since its emergence, HIV has been linked to metabolic alterations with an impact on the distribution of fat and the weight of people living with HIV. While extreme weight loss and processes such as lipodystrophy were of concern at first, in recent years, and with the appearance of increasingly effective and better tolerated drugs, an abnormal weight gain is paradoxically taking place among people living with HIV. Although this weight gain is a multifactorial process in which lifestyle habits, physical exercise or diet have a great impact, antiretroviral treatment has been recently considered as one of the key causes of this increase according to different clinical trials and real-life cohorts. The use of integrase inhibitors, specifically dolutegravir or bictegravir, and being female and/or from African/American origin appear to contribute to weight gain. In contrast, drugs such as tenofovir disoproxil fumarate would be protective factors. Even though different mechanisms of action have been proposed by which these agents would cause weight gain, the exact processes remain unclarified. Efforts are currently focused on knowing not only these mechanisms, but, more importantly, on finding the clinical relevance that this abnormal weight gain could have in other pathologies such as diabetes or cardiovascular events.

Keywords

Weight gain. Antiretroviral treatment. Integrase inhibitor.

Introduction

The disease caused by HIV has been linked since its beginning to a general alteration of the metabolism, which was causative of the appreciable physical changes of HIV-positive people in the 1st year of the epidemic: lipid alterations manifested as abnormal fat distribution and reductions in body mass index (BMI) and weight. All these changes involved not only a worsening of the general health of HIV-positive people due to the clinical consequences derived from these alterations, but they could also have serious psychological and social consequences due to changes in physical appearance.

***Correspondence to:**
Antoni Pla Rodríguez
E-mail: aplarodr@ITS.JNJ.com
Isabel Serrano Lillo
E-mail: iserran4@ITS.JNJ.com

The cause of these initial alterations in the metabolism of HIV-positive people must be sought in (i) the pathology caused by the virus itself, in (ii) the initial lack of effective treatments to palliate this process, and later in (iii) the appearance of the first antiretrovirals, which caused toxicities mainly related with mitochondrial dysfunction.

Over time, more has been learned about the virus itself, and at the same time antiretroviral treatment (ART) has improved, being more effective and with fewer toxicities. Metabolic alterations and weight loss have gradually become less relevant. Although it may seem surprising, the current trend in people with newly diagnosed HIV and active ART today is precisely the

Received in original form: 16-11-2022
Accepted in final form: 21-11-2022
DOI: 10.24875/AIDSRev.M22000057

opposite: weight gain. Initially, it was argued that this increase could be due to the reduction in energy consumption, and consequent return to normality, associated with the suppression of viral replication and accelerated catabolism[1]. It could also result from resolution of opportunistic infections and gastrointestinal dysfunction that would negatively affect appetite and nutrient absorption, especially in patients with low CD4 counts[2]. However, this gain does not only occur in this group of naive patients, but also some people living with HIV (PLHIV) who have been in treatment for years continue to gain weight over the years at a higher rate than the general population[3].

This is not a minor issue, and it is included in a context in which excess weight and obesity constitute a global health problem, causing a significant increase in morbidity and mortality through augmented risk of cardiovascular disease, diabetes, chronic kidney disease, nonalcoholic steatohepatitis, and cancer[4,5]. In this sense, cardiovascular events and type 2 diabetes have become prominent causes of morbidity and mortality in HIV-positive people in recent years[6].

Even though in recent years many studies have been published in indexed journals and in the most relevant congresses in the field of HIV, there is still generally more ignorance than certainty on this subject. Is there really an abnormal weight gain in HIV-positive people relative to the general population? If so, which would be the mechanisms involved? What role does ART play? And, finally, what is the clinical relevance of this weight gain?

The aim of this review is to collect and analyze the most relevant information available in this regard to try to clarify the mechanisms involved in weight gain in HIV-positive people, and specifically the influence of ART on this process, as well as whether this responds to a normal or a pathological process, and finally the possible long-term clinical consequences.

There is abnormal weight gain in PLHIV associated with ART, especially with integrase inhibitors

Weight gain in HIV-positive people has been recently acquiring relevance because of the decrease in more serious adverse events (AE) caused by the existence of new, better-tolerated drugs[5,7,8]. In this sense, the increase in weight could partially reflect the better metabolic profile of the new antiretrovirals[9]. However, the detailed study of this process has revealed that said weight gain may not be a normal process within a general improvement in health but may sometimes be the consequence of etiopathogenic mechanisms linked to certain specific antiretrovirals[10,11]. It should be noted that the context in which this gain occurs must also be considered. For example, the situation that occurs in naive patients would be different from patients who change treatment, since while in the former it would make sense to gain weight as a process of improving their health, this would not be the case in the latter[8-12]. In addition, the patterns of weight gain and the type of fat that is gained are different in these two populations, as will be detailed later.

Research on weight gain in HIV-positive patients began to gain relevance in 2018, when different publications and conference presentations appeared addressing this aspect. Perhaps one of the most relevant studies, since it is a randomized clinical trial, was the *post hoc* analysis of the NEAT-022 switch study[12]. Here, a significant weight gain was observed when switching from boosted protease inhibitors to dolutegravir (DTG) after 1 year of treatment[12], both in the early switch and in the late switch arm. Only a year later, weight gain was one of the most relevant and best studied aspects at the main international congresses held during 2019. Specifically, at CROI of that year, many related works were published, constituting said congress a kind of state-of-the-art at that time on weight gain. An increase in weight was observed in HIV-positive people in different cohorts and clinical trials, and it was stated that this phenomenon was more linked to integrase inhibitors than to other families[9,13-15]. When stratified among the different integrases, it was observed that this effect, despite being common to all of them, occurred more with DTG than with other inhibitors such as elvitegravir (EVG) or raltegravir (RAL). The ADVANCE study[16] provides additional data, showing that women treated with DTG and tenofovir alafenamide (TAF) have an increase in their weight of almost 10 kilos at week 96 of treatment[15-17], which suggests a greater role of weight gain in women when compared to men. During the same year, Andrew Hill publishes a review on the subject in which he analyzes the reason behind this weight gain[18]. One possibility is a “return to normality”, or to a healthy situation after a period of illness. Another is that an obesogenic context or environment for the general population has also an impact on the HIV population and other factors such as ART may influence, which is in line with everything published to date. In line with this, Hill proposes the following factors as promoters of weight gain: being a naive patient, being treated with DTG or bictegravir

(BIC), being a woman or black, and, to a lesser extent, being treated with protease inhibitors. On the contrary, the drug tenofovir disoproxil fumarate (TDF) would be a protective factor[8]. Other authors also focus on the integrase family as the main common link in these increases and publish articles on the matter[9-11, 13-17], even comparing the weight gain between integrases and other families such as protease inhibitors. For example, a retrospective, real-world analysis, showed that people living with HIV (PLWH) initiating BIC/FTC/TAF were more likely to experience BMI or weight increases than those initiating DRV/c/FTC/TAF, and tended to reach a threshold of increases ≥ 5% or ≥ 10% more quickly[5]. A summary of the most relevant studies presented in relation to weight gain and the impact of integrase inhibitors can be found in the Table 1[10].

All this published information had an immediate impact on the main ART guidelines, which considered weight gain as an important factor when choosing the appropriate ART. Today, the main Spanish national (GeSIDA) and international (DHHS, EACS) guidelines list weight gain as an AE common to the integrase family (DTG, BIC, EVG, and RAL).

More recently, Paul Sax published a meta-analysis analyzing the different clinical trials presented between 2003 and 2015, including more than 5,000 naive participants and 10,000 person-years of follow-up[9]. A clear increase in weight was observed at 96 weeks of treatment in all families of drugs, being greater in the group of integrase inhibitors when compared to other families such as protease inhibitors or non-nucleoside analogues. Furthermore, the increase occurred more strikingly with the integrase inhibitors DTG and BIC. In the family of nucleoside analogs, TAF was the drug with the most weight gain. In addition, women gained more weight compared to men and black subjects compared to white subjects, the effect being synergistic, so the greatest increase was seen in black women. Therefore, everything published in this article, which includes the most relevant clinical trials of the past two decades, confirms what had already been seen in the different real-life cohorts presented at the most recent congresses.

The same publication[9] mentioned that the mechanisms contributing to this weight gain are unknown. Yet, it pointed out that the "return to health" is the possible mechanism to recover previous weight levels due to naïve condition of the subjects included in the study. However, as previously mentioned, other studies suggest a different situation, in which this weight gain would not only be not beneficial but could also have detrimental effects on the health of HIV-positive people[19]. How is this apparent contradiction resolved? According to some authors, two clearly differentiated scenarios can be considered, depending on whether they are naive or switch patients[20].

The first scenario (i) would be the initiation of treatment in naive patients under 40 years of age. In this case, one could speak of a "return to health" process with a general gain in overall fat and lean mass. Patients with low CD4s, high viral loads and low BMI would gain more weight. For all these reasons, this scenario should not be worrying but rather beneficial for the patient, unless maintained for a long time[20].

The second scenario (ii) would be the one of patients in switch situations over 50 years of age. Here, a weight gain could not be explained as a "return to health" since they already started from a good and controlled basal situation. Weight gain would correspond to overall fat gain but maintained lean mass, and risk factors for further gain would be age and high BMI. This situation could have implications such as an increase in lipids or a worsening of insulin resistance. Therefore, this second scenario should be closely monitored as it could have deleterious consequences for the patient's health[20].

In both cases, the molecules related to this weight gain would be the integrase inhibitors (II; DTG, BIC, RAL, and EVG) and TAF. The risk would be increased in women compared to men. The race factor would only influence naive patients (black population at more risk than white people), but not so much in switch patients[20].

Another interesting study in this regard is the Kaiser Permanente cohort from the United States, published at the AIDS 2020 international conference[3]. This study retrospectively compared the rate of BMI increase in a HIV-positive population of more than 8000 people who started ART versus a general population of 129,966 HIV-negative individuals over twelve years. The findings suggest that the increase in BMI was produced at an accelerated rate in HIV-positive people, specifically three times faster[3]. However, it should be noted that HIV-positive people started from a lower BMI level than the non-HIV population (25.8-28.4 in HIV-positive vs. 28.7-29.4 in HIV-negative). Even more interesting is the stratification of the results according to the baseline BMI of the subjects. In the three scenarios studied (normal/low BMI: < 25 kg/m^2, overweight: 25-29.9 kg/m^2, and obesity: ≥ 30 kg/m^2), the increase in BMI was greater in the HIV-positive population than in the HIV-negative (0.31 kg/m^2/year vs. 0.2; $p < 0.01$ in normal/

Table 1. *Summary of studies that investigate weight gain with integrase inhibitors (adapted from Eckard et al. 2020)*[10]

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings		
			Randomized-Controlled Trials				
ADVANCE Trial [18, 19]	96-week, randomized, open-label trial of DTG + FTC/TDF or FTC/TAF vs. EFV/FTC/TDF	South Africa	ART-naïve	1,053	Weight gain at 96 weeks: DTG+FTC/TAF: +8 kg DTG+FTC/TDF: +5 kg EFV/FTC/TDF: +2 kg	Treatment-emergent obesity at 96 weeks (% of participants): DTG+FTC/TAF: 19% DTG+FTC/TDF: 8% EFV/FTC/TDF: 4%	$p < 0.001$ between arms; $p < 0.01$ for DTG+FTC/TAF vs. other arms
NAMSAL Trial [18, 20]	48-week, randomized, open-label trial of DTG+3TC/TDF vs. EFV400/3TC/TDF	Cameroon	ART-naïve	613	Weight gain at 48 weeks: DTG: +5 kg EFV: +3 kg	Treatment-emergent obesity at 48 weeks (% of participants): DTG: 12% EFV: 5%	$p < 0.001$ between arms for weight gain; $p = 0.004$ for emergent obesity
Sax, et al. [5]	Pooled data from 8 phase 3, randomized-controlled trials	Multiple countries	ART-naïve	5,68	96-week LS mean weight gain: INSTI: +3.24 kg NNRTI: +1.93 kg PI: +1.72 kg ($p < 0.001$ INSTI vs. PI and NNRTI)		96-week LS mean weight gain: DTG: +4.07 kg BIC: +4.24 kg EVG: +2.72 kg ($p < 0.001$ DTG and BIC vs. EVG)
NEAT-022 [21]	Post-hoc analysis of NEAT-022, an open-label, randomized trials evaluating immediate (DTG-I) vs. delayed (DTG-D) switch from PI to DTG in participants ≥ 50 years old and Framingham risk score ≥ 10%	Multiple sites in Europe	ART-treated, virologically-suppressed	415	0–48-week weight change: DTG-I: +0.82 kg DTG-D: +0.25 kg ($p = 0.008$)		48–96-week weight gain: DTG-I: +0.03 kg DTG-D: +0.98 kg ($p = 0.002$)

(Continues)

Table 1. *Summary of studies that investigate weight gain with integrase inhibitors (adapted from Eckard et al. 2020)[10] (continued)*

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings
Wohl, et al. [22]	96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG/ABC/3TC	Multiple countries	ART-naïve	631	Weight gain at 96 weeks: DTG: +2.4 kg BIC: +3.6 kg
Stellbrink, et al. [23]	96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG+FTC/TAF	Multiple countries	ART-naïve	327	Weight gain at 96 weeks: DTG: +3.9 kg BIC: 3.5 kg
HPTN 077 [24]	Post-hoc analysis of HPTN 077, a phase 2a study investigating CAB vs. placebo randomized 3:1 for HIV prevention; participants given ≥ 1 injection and with paired week 0 and week 41 data included	U.S.	HIV-uninfected	177	Weight gain at 96 weeks: CAB: +1.1 kg Placebo: +1.0 kg (P = 0.66)
		Observational Cohort Data and Retrospective Studies			
TRIO Health Network [17]	Retrospective analysis of observational cohort data obtained from electronic health records and prescription data of patients who switched to an INSTI	U.S.	ART-treated, virologically-suppressed	3,468	INSTI use was significantly associated with ≥ 3% weight gain in bivariate analysis but was no longer significant in multivariate analysis

(Continues)

Table 1. *Summary of studies that investigate weight gain with integrase inhibitors (adapted from Eckard et al. 2020)[10] (continued)*

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings
U.S. Military HIV NHS [25]	Observational cohort data from U.S. male military personnel; changes in BMI over 2 years after ART initiation with PIs, NNRTIs, or INSTIs	U.S.	Virologically-suppressed	496	BMI increases higher for INSTIs (and PIs) compared to NNRTIs when baseline BMI ≥ 25 kg/m2; no difference in BMI increases among ART classes if baseline BMI < 25 kg/m2 or if not stratified by baseline BMI
Khan, et al. [26]	Retrospective chart review of patients initiating INSTI-based regimen	India	ART-naïve and treated	331	Average weight gain at 3 months: +3.69 kg; 19.5% of patients gained > 4 kg
WIHS [27]	Observational cohort data of women who switched to or added an INSTI vs. women who stayed on non-INSTI; changes in weight/BMI/body composition 6–12 mo. before and 6–18 mo. after switch/addition of INSTI vs. stayed on non-INSTI	U.S.	ART-treated	1,118	+2.4 kg weight gain with INSTIs vs. +0.2 kg with non-INSTIs ($p < 0.0001$); 22% of patients with ≥ 7% weight gain with INSTI vs. 14% with non-INSTI ($p < 0.0001$); +1.7% body fat increase with INSTI vs. 0.3% with non-INSTI ($p < 0.001$); greater increases in waist, hip, arm, and thigh circumference (but not waist-to-hip ratio) with INSTI; no differences among individual INSTIs
Bernstein, et al. [28]	Retrospective chart review of patients who switched from PIs or NNRTIs to INSTIs vs. stayed on NNRTIs; changes in weight ~18 mo. before and after switch	U.S.	ART-treated, virologically-suppressed	260	More weight gain after switch to INSTIs vs. staying on NNRTIs (+2.73 kg vs. +0.45 kg; $p = 0.004$); weight gain pre-switch greater than post-switch for patients on INSTIs (–0.32 kg vs. +2.68 kg; $p = 0.0001$); no difference in weight gain among different INSTI regimens

(Continues)

Table 1. *Summary of studies that investigate weight gain with integrase inhibitors (adapted from Eckard et al. 2020)[10] (continued)*

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings		
OPERA Cohort [29]	Observational cohort data obtained from electronic health records; changes in BMI after switch to DTG, EVG, RAL, RPV, or DRV/r	U.S.	ART-treated, virologically-suppressed	10,653	Small absolute increases in BMI with all agents (statistically significant for DTG, EVG, RPV); adjusted BMI increases statistically less with EVG, RAL, and DRV/r vs. DTG at 6 months, but only DRV/r vs. DTG significant at 12 and 24 months		
Zimmerman, et al. [30]	Retrospective chart review of patients who switched from non-INSTIs to INSTIs; weight gain 1 year after switch	U.S.	ART-treated, virologically-suppressed	90	More weight gain after switch to INSTIs (+2.2 kg; $P < 0.001$); 26% of patients gained ≥ 4.5 kg; weight gain greater when switching from NNRTIs (+2.7 kg) vs. PIs (+1.8 kg) but was not statistically significant; weight gain was greater with EVG (+2.7 kg) vs. DTG (+1.8 kg) but was not statistically significant		
Bourgi, et al. [31]	Retrospective observational cohort study of ART-naïve participants who initiated INSTIs, PIs, or NNRTIs; adjusted average weight gain after 6 and 18 mo.	U.S.	ART-naïve	1,152	Weight gain after 6 mo.: DTG: +2.9 kg RAL: +3.0 kg EVG: +0.6 kg NNRTI: +1.1 kg PI: +2.6 kg	Weight gain after 18 mo.: DTG: +6.0 kg RAL: +3.4 kg EVG: +0.5 kg NNRTI: +2.6 kg PI: +4.1 kg	$p < 0.05$ for DTG, RAL, and PIs vs. EVG at both time points; $p < 0.05$ for DTG vs. NNRTIs at 18 mo.
NA-ACCORD [32]	Observational cohort study from 17 NA-ACCORD sites; changes in weight after 2 and 5 years with INSTI, PIs, or NNRTIs; changes in weight after 2 years with DTG, RAL, or EVG	U.S.	ART-naïve	24,001	Weight gain after 2 years: INSTI: +4.9 kg PI: +4.4 kg NNRTI: +3.3 kg	Weight gain after 5 years: INSTI: +6.0 kg PI: +5.1 kg NNRTI: +4.3 kg	Weight gain after 2 years: DTG: +6.0 kg RAL: +4.9 kg EVG: +3.8 kg

(Continues)

Table 1. *Summary of studies that investigate weight gain with integrase inhibitors (adapted from Eckard et al. 2020)[10] (continued)*

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings
Lake, et al. [33]	Observational cohort study of participants previously enrolled in ACTG protocols A5001 and A5322; annual rate of weight change 2 years before and 2 years after switch to INSTI	U.S.	ART-treated, virologically-suppressed	691	Difference in weight gain pre-/post-switch: DTG: +1.0 kg/year (p = 0.0009) EVG: +0.5 kg/year (p = 0.11) RAL: −0.2 kg/year (p = 0.37)
HOPS [34]	Retrospective observational cohort study from 9 U.S. HIV clinics of patients who were switched to INSTI vs. non-INSTI	U.S.	ART-treated, virologically-suppressed	653	DTG and RAL (but not EVG) were associated with increases in BMI after switch; greater increases were seen with DTG vs. RAL, DTG vs. EVG, and RAL vs. EVG

low BMI; 0.18 vs. 0.09; p < 0.001 in overweight; and 0.07 vs. −0.02, p = 0.9 in obese)[3].

Taking these results into account, and if the "return to health" hypothesis was valid, the greatest increase in the HIV-positive population with a normal or low BMI could be considered as this return to normality. However, it should be noted that HIV-positive people who began the 12-year period with a BMI below that of HIV-negative people (21.6 vs. 22.0) ended the period with a higher BMI (25.1 vs. 24.2). If it was just a "return to health", one might expect populations to even out over time but not HIV-positive individuals to outperform the general population in BMI. In addition, in the other two scenarios, overweight and obesity, this theory loses its strength since it is not based on a normal situation but rather excessive weight, so a greater increase in BMI cannot be explained as something positive. On the contrary, this BMI could be indicative of a metabolic situation potentially harmful in the long term[20], what demonstrates that there must be physiological mechanisms that trigger this greater weight gain in HIV-positive people. Despite the power of this study, which includes a very large population and a 12-year follow-up, it should be noted as possible limitations that (i) only BMI was measured (and not the type of mass gained, without differentiating mass lean fat or muscle), (ii) the existence of possible confounding factors, and (iii) the fact that women were underrepresented (only 15% of people included).

Switching to TAF from TDF also contributes to weight gain

As previously mentioned, TDF seems to have a protective role against weight gain[8]. This raises the question of what happens to people on treatment who substitutes TDF for TAF. The OPERA Cohort of the United States[21] showed that there is an initial increase in the first 9 months after the change in all families of antiretrovirals, being more notable in integrase inhibitors and non-analogues and less in protease inhibitors. From the 9th month on, the initial increase slows down and tends to stabilize to return to the levels before the change, even decreasing these levels with the use of protease inhibitors.

Regarding TAF, some authors[9] suggest that it has a clear impact on weight gain, while others question whether TAF really plays a key role in this process[21,22], or is it rather the withdrawal of TDF and consequently the loss of its protective role the cause of the weight

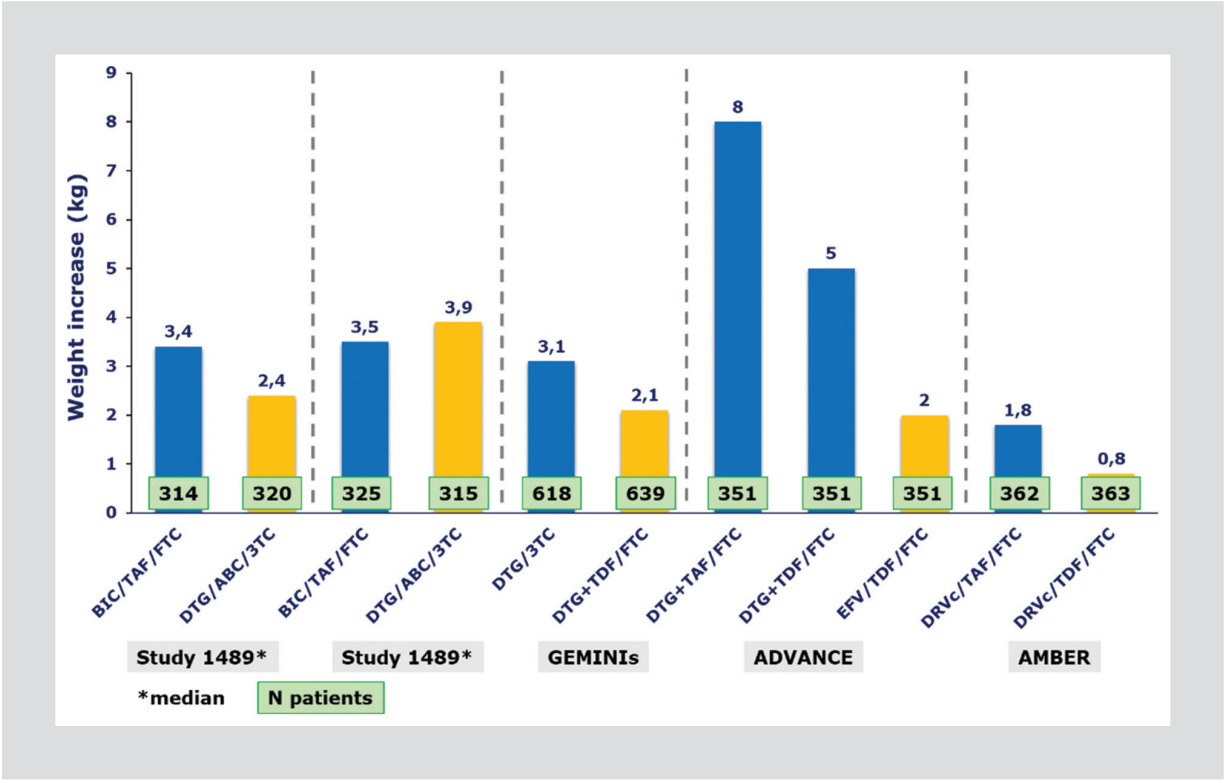

Figure 1. *Weight increase (kg) in naive patients at 48 weeks in different phase III clinical trials (adapted from Buzon-Martin, 2020)[23].*

increase in people with TAF by comparison. For example, when comparing different clinical trials published in recent years[23], it is suggested that the arms with TAF generate a greater increase in weight than the ones with TDF (Fig. 1). However, in switch studies in which TAF is compared to another therapy that does not include TDF either, for example, in the TANGO[24] study in which patients from regimens with TAF (mainly EVG/c/TAF/FTC) are switched to DTG/3TC, the weight remains relatively constant at 48 weeks. On the contrary, this does not happen in study 1489 that compares DTG or BIC plus TAF/FTC in naive patients (Fig. 1)[23,25].

In the McComsey study[26] presented at IDWeek 2020, the percentage of patients who experienced a weight gain greater than 3% when switching from ABC to TAF was found to be less than the percentage of patients who switched from TDF. These findings highlight the loss of the protective effect of TDF and subsequent weight gain associated with its elimination, rather than the effect of the new antiretroviral. The study authors conclude that the risk of weight gain is greater when switching from TDF to TAF than from ABC to TAF, and that is maintained considering the third agent (integrase inhibitor) included in the antiretroviral regimen. They also suggest that the differences observed in weight gain between TDF and TAF in multiple studies would be motivated by the elimination of the suppressive effect of TDF.

In this regard, it is worth highlighting a couple of pre-exposure prophylaxis (PrEP) studies carried out in the general population since this way all factors related to HIV are excluded and only the drug influence is considered. The DISCOVER clinical trial, conducted in more than 5000 HIV-negative people, showed a weight gain of 1.1kg in the TAF/FTC arm compared to the TDF/FTC arm, with no change in weight and with a decrease in lipid parameters (CT, LDL, and HDL)[27]. It is worth putting this study in context by comparing it with the iPrEx[28], which compares the effect of taking TDF/FTC versus placebo in almost 500 participants. The placebo arm increased their weight by 0.5 kg at week 48, while the treated group not only did not gain, but also decreased their weight by 0.3 kg. Again, the protective effect of TDF seems to prevail rather than a deleterious effect of TAF.

While within the family of integrase inhibitors several possible mechanisms have already been postulated as

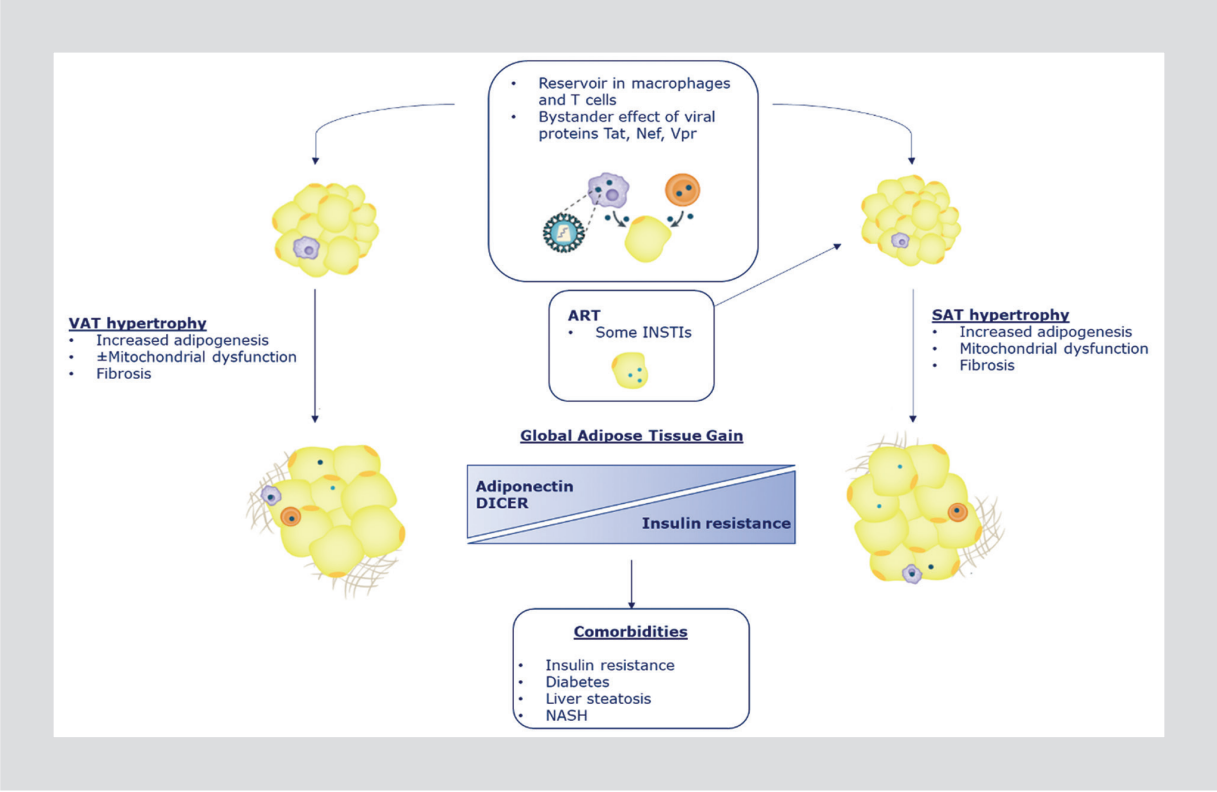

Figure 2. *Physiopathological mechanisms involved in white adipose tissue dysfunction related to HIV infection and ART with integrase inhibitors (adapted from Koethe et al. 2020)*[31].

responsible for weight gain, the etiology of the possible weight gain caused by TAF still needs to be studied in detail. In any case, and regardless of whether TAF has a direct effect on weight gain, as a conclusion derived from all the studies presented, special attention should be paid to the weight of people with HIV in treatment with TAF, particularly if the third agent is an integrase inhibitor.

Weight gain could have detrimental long-term health consequences

The most clinically relevant aspect of weight gain is undoubtedly the pathological consequences that may result from it. Various studies point to possible complications at the cardiovascular level, diabetes, or other metabolic alterations because of this process[5]. In the ADVANCE study[16,19], it was shown that people on treatment with DTG+TAF/FTC, who are the ones who gained the most weight, had greater increases in visceral and subcutaneous fat and an increased risk of developing diabetes at 10 years compared to the rest of groups at week 96[16]. DTG+TAF/FTC was also associated with an increased risk of metabolic syndrome or cardiovascular event versus the efavirenz group. These data were later confirmed at 144 weeks[19].

We must not only look at weight gain, but also at the characteristics of the fat that is gained. The Modena cohort[29] focused on patients who gained more than 5% weight from the first visit on, differentiating between patients who had never taken an integrase inhibitor and patients who changed their treatment and started using an integrase inhibitor. After a 4-year follow-up period, it was concluded that patients who switched to integrase inhibitors experienced greater increases in BMI than those who never took integrase inhibitors. These differences were mainly caused by subcutaneous fat, with no changes in ectopic deposits[29]. Differences in visceral fat density did not suggest metabolically abnormal fat gain, which contrasts with results previously reported in the ADVANCE study. Interestingly, a recent study published at CROI 2022 showed that risk factors associated with liver steatosis included exposure to TAF but not to integrase inhibitors[30].

All these data stand out the necessity of having more long-term information to definitively clarify this issue. It should not be forgotten that most of the AE attributed to antiretrovirals were discovered only after long periods

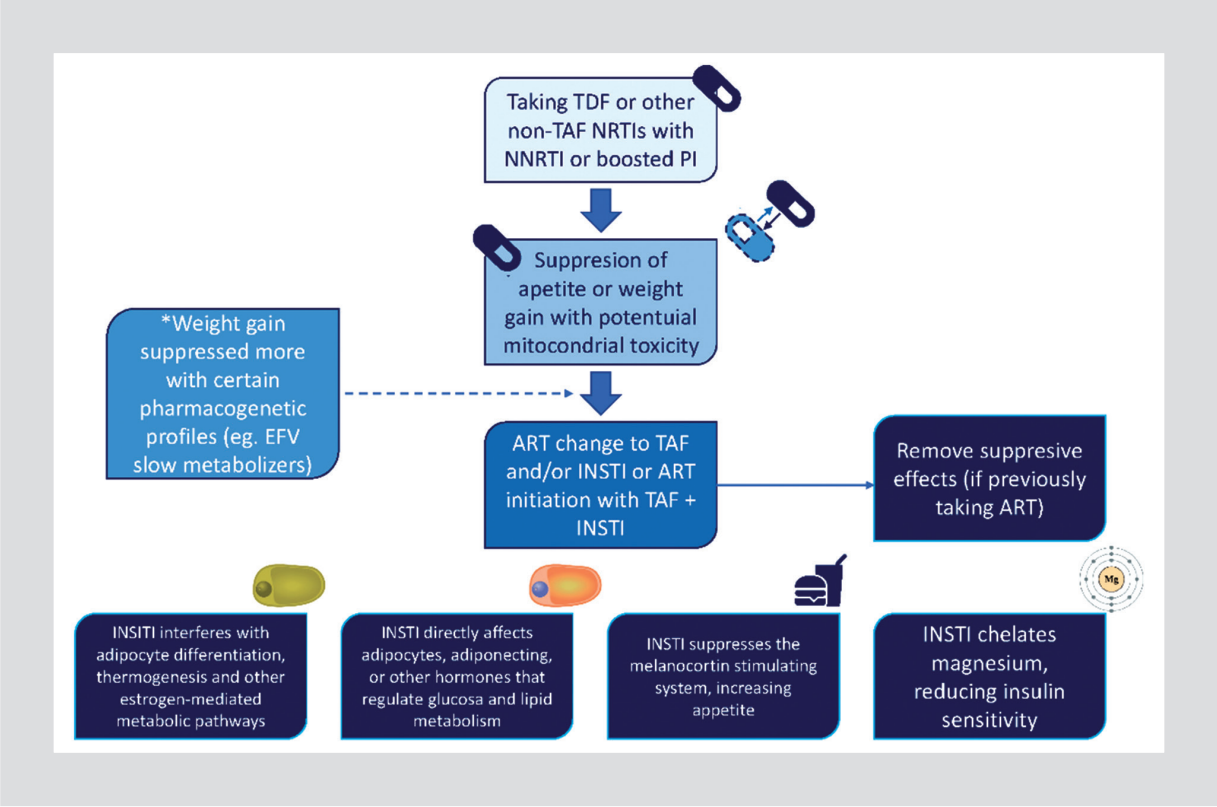

Figure 3. *Proposed mechanisms of TAF- and INSTI-mediated excess weight gain.*
(INSTI, Integrase Strand Transfer Inhibitor; NNRTI, Non-nucleoside Reverse transcriptase Inhibitor; NRTI, Nucleoside Reverse Transcriptase Inhibitor; adapted from Wood BR and Huhn D. Open Forum Infect Dis. 2021;8)[8].

of use after marketed. Something that would greatly help in this matter would be to know the molecular mechanisms involved in weight gain associated with ART.

Some studies have highlighted the role of integrase inhibitors in increasing adipogenesis, specifically in the hypertrophy of both subcutaneous and visceral adipose tissue, in addition to their influence on other processes such as cytokine secretion or bacterial translocation[31]. This would trigger a general gain in the amount of adipose tissue promoting, among other results, insulin resistance, diabetes, hepatic steatosis, and non-alcoholic steatohepatitis (Fig. 2).

On the other hand, some authors[32] hypothesize that integrase inhibitors could interfere with the melanocortin signaling pathway in the central nervous system, mimicking what happens with alterations due to mutations in the melanocortin receptor in the general population and by the antipsychotic therapy in psychiatric patients. All this would translate into an increase in appetite with the consequent weight gain[32]. Finally, in the 2020 CROI, other alternatives were postulated, such as the involvement of polymorphisms in the *RESISTIN* gene, whose protein is related to adipose metabolism[33]. All these mechanisms still need to be confirmed and could be amplified in switch patients by the removal of drugs, such as TDF or non-TAF NRTIs with an NNRTI such as EFV or protease inhibitors, that have been linked to suppression of appetite or weight gain (Fig. 3)[8].

Interestingly, cabotegravir (CAB) oral form has demonstrated to increase weight[34] similar to other integrase inhibitors, but this does not occur when administered intramuscularly as injectable long-acting CAB in combination with long-acting rilpivirine (RPV, an NNRTI)[9]. Multiple studies comparing this dosage (long-acting CAB+RPV) with current ART[35-38] or placebo[39], demonstrate minimal weight changes when using CAB+RPV and suggest a favorable metabolic profile for this long-acting regimen. The mechanism by which injectable long-acting CAB+RPV does not have an impact on weight needs further examination.

Ultimately, several issues related to weight gain in HIV-positive people remain unresolved. The first of them is how to act in this situation. Beyond the use of lipolytic drugs or changes in lifestyle, a series of rec-

ommendations should be proposed to treat patients who gain more weight over the years. The second question that could arise is whether this weight gain is a reversible process, or at least could be slowed down. To resolve these issues, more studies will be needed that actively intervene on the parameters that cause weight gain, related, or not to ART.

Conclusions

Weight gain with age is a normal physiological phenomenon in the general population. Even though there is a process of weight gain in HIV-positive population after the start of ART, this gain is sometimes excessive and continues over the years above the average of the uninfected population. Weight gain in HIV-positive people must be considered during their treatment, since there is sufficient evidence suggesting that, in certain scenarios, it constitutes an abnormal process rather than a "return to health" and that could have long-term clinical repercussions, such as the development of metabolic syndrome, diabetes, or cardiovascular events.

Although more research is needed on the etiology of this process, ART has a considerable impact on this aspect. It is well known that certain drugs contribute more than others: the effect is greater with integrase inhibitors (DTG, BIC, EVG, and RAL) than with protease inhibitors, and higher with TAF versus TDF possibly, and at least in part, due to the protective role of the latter. The mechanisms involved in this process are multifactorial and different antiretrovirals could have a direct effect on increased adipogenesis, hypertrophy of subcutaneous and visceral adipose tissues, bacterial translocation, and signaling pathways involved in the regulation of appetite.

There are currently no relevant clinical trials or cohort studies that shed light on how to act in the face of weight gain, or that clarify whether the effect of certain antiretrovirals reverses, or at least ceases, when treatment is changed. It would be advisable to carry out these studies to try to stop, slow down and/or anticipate the appearance of long-term clinical consequences that could derive from excessive weight gain.

References

1. Bailin SS, Gabriel CL, Wanjalla CN, Koethe JR. Obesity and weight gain in persons with HIV. Curr HIV/AIDS Rep. 2020;17:138-50.
2. Kimokoti RW, Hamer DH. Nutrition, health, and aging in Sub-Saharan Africa. Nutr Rev. 2008;66:611-23.
3. Silverberg M, Leyden W, Alexeeff S, Lam J, Anderson A, Hechter R, et al. Changes in Body Mass Index over Time in Persons with and without HIV. AIDS 2020. In: 23rd International AIDS Conference Virtual. Abstract OAB0603.
4. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309: 71-82.
5. Emond B, Rossi C, Côté-Sergent A, Bookhart B, Anderson D, Lefebvre P, et al. Body mass index increase and weight gain among people living with HIV-1 initiated on single-tablet darunavir/cobicistat/emtricitabine/tenofovir alafenamide or bictegravir/emtricitabine/tenofovir alafenamide in the United States. Curr Med Res Opin. 2022;38:287-98.
6. Pettit AC, Giganti MJ, Ingle SM, May MT, Shepherd BE, Gill MJ, et al. Increased non-AIDS mortality among persons with AIDS-defining events after antiretroviral therapy initiation. J Int AIDS Soc. 2018;21:e25031.
7. Chen YW, Anderson D, Pericone CD, Donga P. Real-world assessment of weight change in African American females and hispanics with HIV-1 after initiating integrase strand-transfer inhibitors or protease inhibitors. J Health Econ Outcomes Res. 2022;9:1-10.
8. Wood BR, Huhn GD. Excess weight gain with integrase inhibitors and tenofovir alafenamide: what is the mechanism and does it matter? Open Forum Infect Dis. 2021;8:ofab542.
9. Sax PE, Erlandson KM, Lake JE, Mccomsey GA, Orkin C, Esser S, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71:1379-89.
10. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis. 2020;33:10-9.
11. Lake JE, Wu K, Bares SH, Debroy P, Godfrey C, Koethe JR, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. Clin Infect Dis. 2020;71:e471-7.
12. Waters L, Assoumou L, Rusconi S, Domingo P, Gompels M, de Wit S, et al. Switch to dolutegravir (DTG) from a boosted protease inhibitor (PI/r) associated with significant weight gain Over 48 weeks in NEAT-022, a randomized 96-week Trial. United Kingdom: HIV Glasgow; 2018.
13. Bourgi K, Jenkins CA, Rebeiro PF, Palella F, Moore RD, Altoff KN, et al. North American AIDS cohort collaboration on research and design (NA-ACCORD). Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. J Int AIDS Soc. 2020;23: e25484.
14. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis. 2020;70:1267-74.
15. Venter WD, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med 2019;381:803-15.
16. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020;7:e666-76.
17. Esber AL, Chang D, Iroezindu M, Bahemana E, Kibuuka H, Owuoth J, et al. Weight gain during the dolutegravir transition in the African Cohort Study. J Int AIDS Soc. 2022;25:e25899.
18. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad. 2019;5:41-3.
19. Hill A, Kaitlyn M. Risks of Metabolic Syndrome, Diabetes, and Cardiovascular Disease in the ADVANCE Trial. Boston, MA: CROI; 2020. p.81.
20. Capeau J. Themed discussion: In: Fat in focus. Boston, MA: CROI; 2020.
21. Mallon PW Mallon, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021;24:e25702.
22. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, et al. Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials. Clin Infect Dis. 2021;73:1440-51.
23. Buzon-Martin L. Weight gain in HIV-infected individuals using distinct antiretroviral drugs. AIDS Rev. 2020;22:158-67.
24. Van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Sogorb JP, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus Type 1: phase 3, randomized, noninferiority TANGO study. Clin Infect Dis. 2020;71(8):1920-9.
25. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063-72.
26. McComsey G. Weight Change in Suppressed People with HIV (PWH) Switched from Either Tenofovir Disoproxil Fumarate (TDF) or Abacavir (ABC) to Tenofovir Alafenamide (TAF). IDWeek. In: Conference Reports for NATAP; 2020.

27. Ogbuagu O, Ruane PJ, Podzamczer D, Salazar LC, Henry K, Asmuth DM, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet HIV. 2021;8:e397-407.
28. Glidden DV, Mulligan K, McMahan V, Anderson PL, Guanira J, Chariyalertsak S, et al. Metabolic effects of preexposure prophylaxis with coformulated tenofovir disoproxil fumarate and emtricitabine. Clin Infect Dis. 2018;67:411-9.
29. Guaraldi G, Draisci S, Milic J, Carli F, Besutti G, Bassoli C, et al. Fat Distribution and Density in People Living with HIV with ≥5% Weight Gain. HIV Glasgow. In: Conference Reports for NATAP; 2020, Abstract 0111.
30. Riebensahm C, Berzigotti A, Surial B, GÃnthard HF, Tarr P, Furrer H, et al. Determinants of Liver Steatosis in People Living with HIV on Antiretroviral Therapy. Seattle: CROI; 2022.
31. Koethe JR, Lagathu C, Lake JE, Domingo P, Calmy A, Falutz J, et al. HIV and antiretroviral therapy-related fat alterations. Nat Rev Dis Primers. 2020;6:54.
32. Domingo P, Villarroya F, Giralt M, Domingo JC. Potential role of the melanocortin signaling system interference in the excess weight gain associated to some antiretroviral drugs in people living with HIV. Int J Obes (Lond). 2020;44:1970-3.
33. Minami R, Takahama S, Koyama K, Yamamoto M. Resistin Gene Polymorphism Related to Weight Gain and Psychiatric Symptoms on in STI. Boston, MA: CROI; 2020.
34. Margolis D, Sutton K, De Vente J, et al. Long-term efficacy, safety, and durability of CAB and RPV as two drug oral maintenance therapy: LATTE week 312results. Open Forum Infect Dis. 2019;6:S66-7.
35. Swindells S, Andrade-Villanueva JF, Richmond GJ, Rizzardini G, Baumgarten A, Masiá M, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med. 2020;382:1112-3.
36. Orkin C, Arasteh K, Górgolas M, Hernández-Mora MG, Pokrovsky V, Overton ET, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med. 2020;382:1124-35.
37. Overton ET, Richmond G, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet. 2021;396:1994-2005.
38. Patel P, D'Amico R, Thiagarajah S, Wu S, Elliot E, Polli JW, et al. Weight and Lipid Changes in Phase 3 Cabotegravir and Rilpivirine Long-acting Trials. In: Conference on Retroviruses and Opportunistic Infections; 2021.
39. Landovitz RJ, Zangeneh SZ, Chau G, Grinsztejn B, Eron JJ, Dawood H, et al. Cabotegravir is not associated with weight gain in human immunodeficiency virus-uninfected individuals in HPTN 077. Clin Infect Dis. 2020;70:319-22.