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Weight gain in HIV-infected individuals using distinct antiretroviral drugs

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Abstract

Following the initiation of antiretroviral therapy, most HIV-infected individuals experience significant weight gain. It was originally thought to result from reduced energy consumption associated with suppression of overt virus replication. However, recent evidence suggests that is not simply a back to normal phenomenon. Indeed, a differential influence on weight has been noticed for distinct antiretroviral drugs, some of which may produce abnormal body weight gain and metabolic disturbances. Treatment with integrase inhibitors in particular leads to significant increases in body mass index. By contrast, protease inhibitors might protect from undesirable weight gain. Ultimately, the development of overweight and obesity in an aging HIV population may increase the risk of cardiovascular events and should be prevented. In this scenario, the differential influence on weight gain using distinct antiretroviral agents might provide an opportunity for personalized medicine, adapting the most convenient drug regimen to each patient. **(AIDS Rev. 2020;22:158-167)**

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Key words

Body weight gain. Metabolic syndrome. Dyslipidemia. Body mass index. Antiretroviral drugs. Dolutegravir. Darunavir. Tenofovir alafenamide. Tenofovir disoproxil fumarate.

Introduction

Excess weight and obesity are an escalating global health concern. It causes substantial morbidity and mortality through an increased risk of cardiovascular disease (CVD), diabetes, chronic kidney disease, non-alcoholic steatohepatitis, and cancer[1].

In human immunodeficiency virus (HIV) disease, antiretroviral therapy (ART) is associated with weight gain, a finding that was initially thought to represent a return-to-health phenomenon, due to alleviation of HIV-associated inflammation and accelerated catabolism[2]. In addition, it could result from resolution of opportunistic infections and gastrointestinal dysfunction that could adversely affect appetite and nutrient absorption, especially in patients with low CD4 counts[3].

Given the high success of HIV therapy, the aging HIV population on long-term ART has increasingly been under the obesogenic influence of the current environment (Fig. 1)[4]. Not surprisingly, CVD events and type 2 diabetes have become leading causes of morbidity and mortality in persons living with HIV (PLWH)[5,6]. Furthermore, following the success of antiviral therapy for curing hepatitis C, fatty liver disease is emerging

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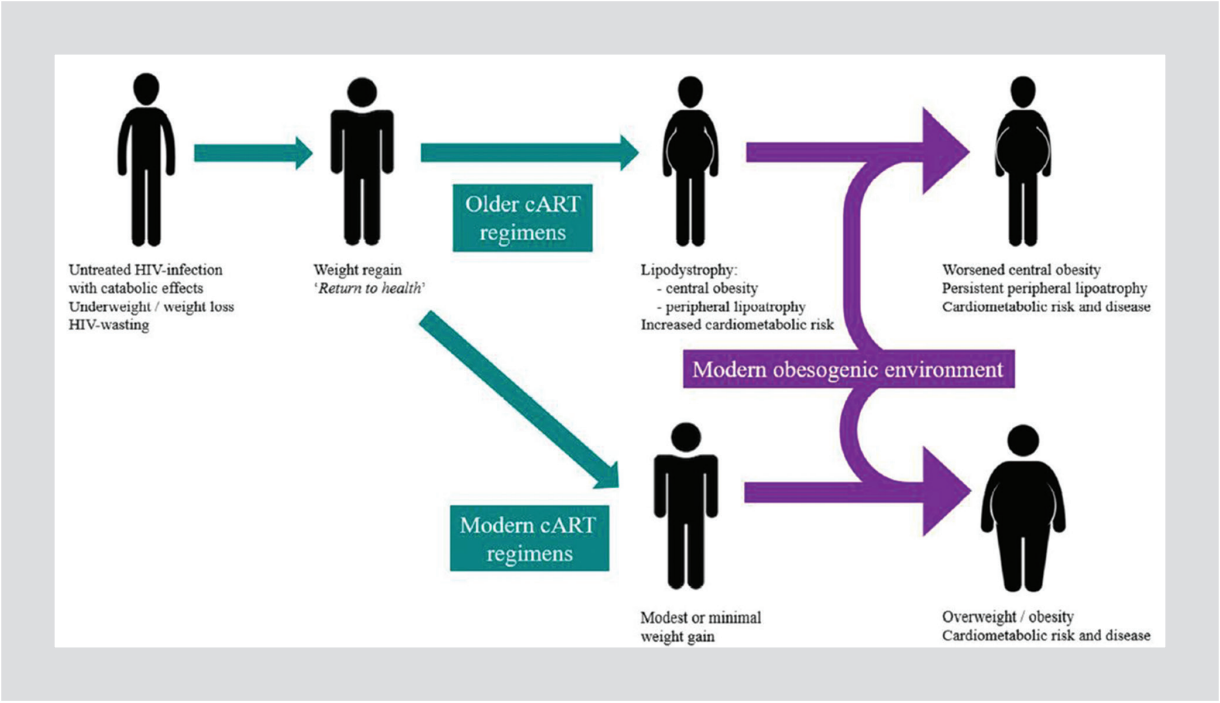

Figure 1. *Interactions between HIV infection, antiretrovirals, and weight gain. Adapted from Kumar* et al., *2018*[4].

as the most common cause of liver cirrhosis and hepatocellular carcinoma in this population (Fig. 2)[7].

New insights into the pathogenesis of body weight gain associated to ART

Especially in the subset of patients with advanced HIV disease, weight gain after initiating ART has been shown to reflect a return-to-health phenomenon. In contrast, in persons with early stage HIV disease and in those with normal or above normal body mass index (BMI), it might contribute to excess weight gain.

The pattern of more weight gain with newer ART regimens might partially reflect the advent of better tolerated, easier to take regimens[8]. If individual agents contribute to weight gain aside from tolerability, the mechanisms by which they do so should be understood. Domingo et al. have recently hypothesized that integrase strand transfer inhibitors (INSTIs) might interfere with the melanocortin signaling pathway in the central nervous system, mimicking what happens with disturbances caused by melanocortin receptor mutations in the general population and by antipsychotic therapy in psychiatric patients. In this way, INSTI might produce weight gain influencing food intake behavior and metabolic energy balance[9].

Concerns on abnormal body weight gains using INSTI have been acknowledged in both drug-naïve and treatment-experienced patients, including those switched from other drug class regimens, suggesting that this drug class might cause weight gain beyond any consideration on return to normality[10,11]. Indeed, weight gain with INSTI seems to be more pronounced in women, Afro-Americans, and older persons. Furthermore, it occurs along with increases in waist circumference suggesting that there is increase in fat mass.

The mechanism that underlies this unique effect of INSTI on weight gain is still unclear, although the interference with the melanocortin signaling system mentioned above, a well-known neurogenic regulator of catabolism, is being considered carefully[9,12]. However, alternative mechanisms were postulated at Conference on Retroviruses and Opportunistic Infections (CROI) 2020, including the involvement of polymorphisms at the resistin gene, whose protein is involved in the adipose metabolism[13].

Body weight across ART randomized clinical trials

A decade ago, the SPRING-1 study, a Phase IIb trial for dolutegravir (DTG), noticed that body weight increases were more pronounced with all doses of

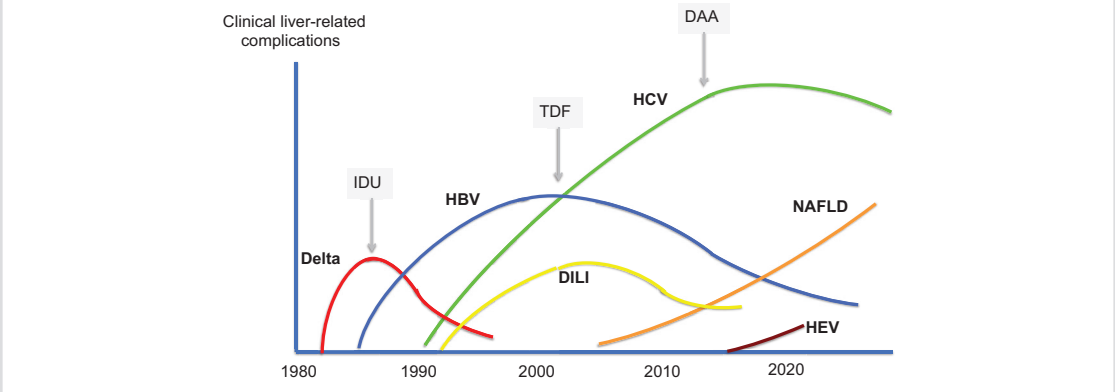

Figure 2. *Time trends in liver disease etiologies in persons living with HIV. Adapted from Soriano* et al., *2013*[7].

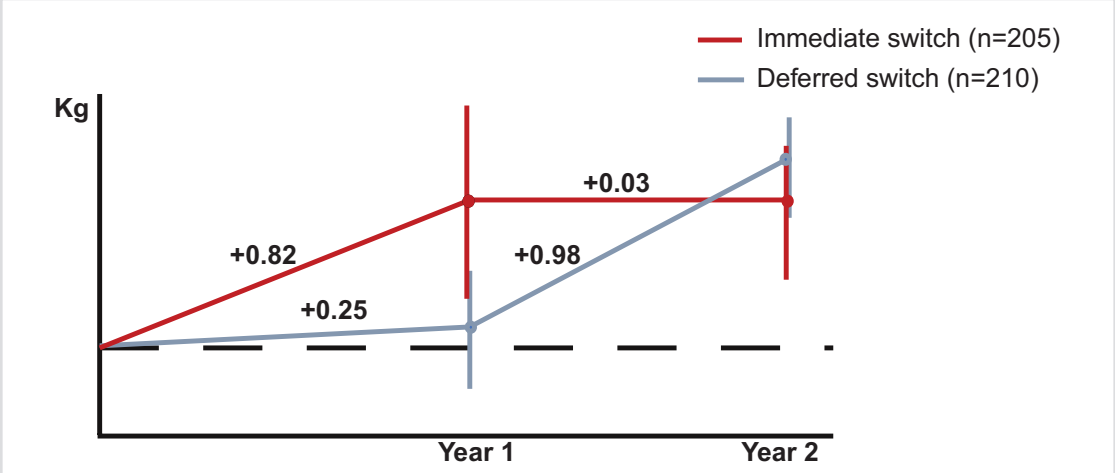

Figure 3. *Body changes in the NEAT-022 trial. Adapted from Waters* et al., *2018*[18].

DTG than with efavirenz (EFV)[14]. Unfortunately, weight was not analyzed in registrational Phase III trials for DTG. Years later, several cohort studies confirmed this association between INSTI and weight gain[15,16]. Furthermore, it could be particularly significant in women treated with the coformulation of DTG/3TC/Antecedent-Behavior-Consequence (ABC)[17].

A *post hoc* analysis of the European NEAT-022 switch trial was one of the first studies to highlight the importance of collecting body weight changes when assessing distinct ART regimens[18]. In the NEAT-022 trials, 415 PLWH suppressed under a boosted protease inhibitor (bPI) and having high CVD risk was randomized to switch to DTG immediately or deferring it 1 year. The study was planned for 2 years. Body weight increased in both arms at 1 year, but it was more pronounced in the immediate DTG switch arm. However, the deferred DTG arm depicted a similar body weight gain at 2 years (Fig. 3). Interestingly, more significant increases in body weight were noticed in patients switched any time from darunavir (DRV) to DTG than in those switched from atazanavir or lopinavir[18].

A recent pooled analysis has assessed weight gain in eight Gilead-sponsored Phase III trials with a follow-

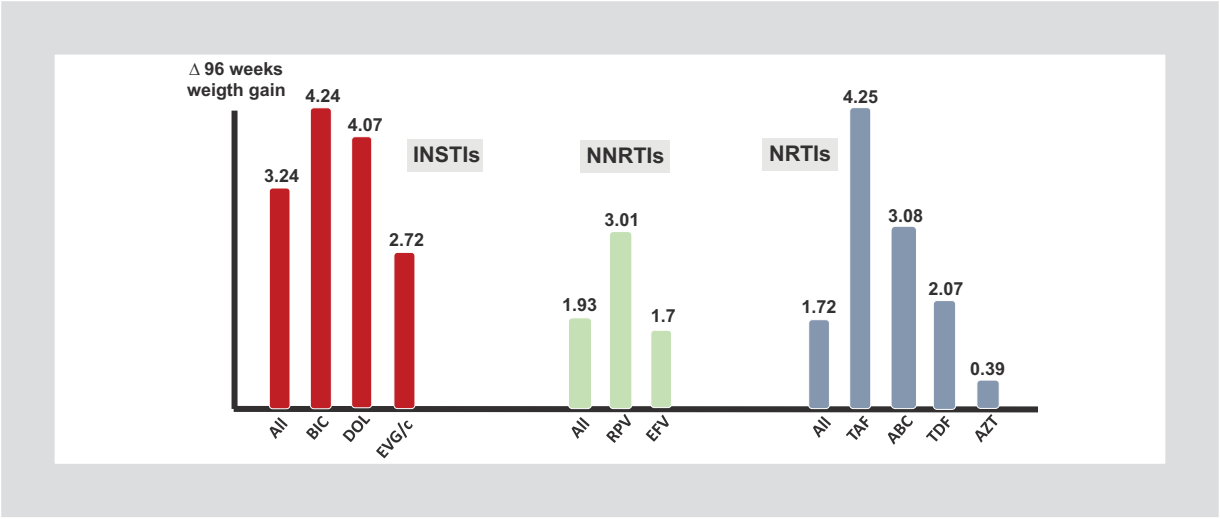

Figure 4. *Weight gain using distinct antiretroviral agents in Gilead Phase 3 trials in drug-naive persons living with human immunodeficiency virus. Adapted from Sax* et al., *2020*[8].

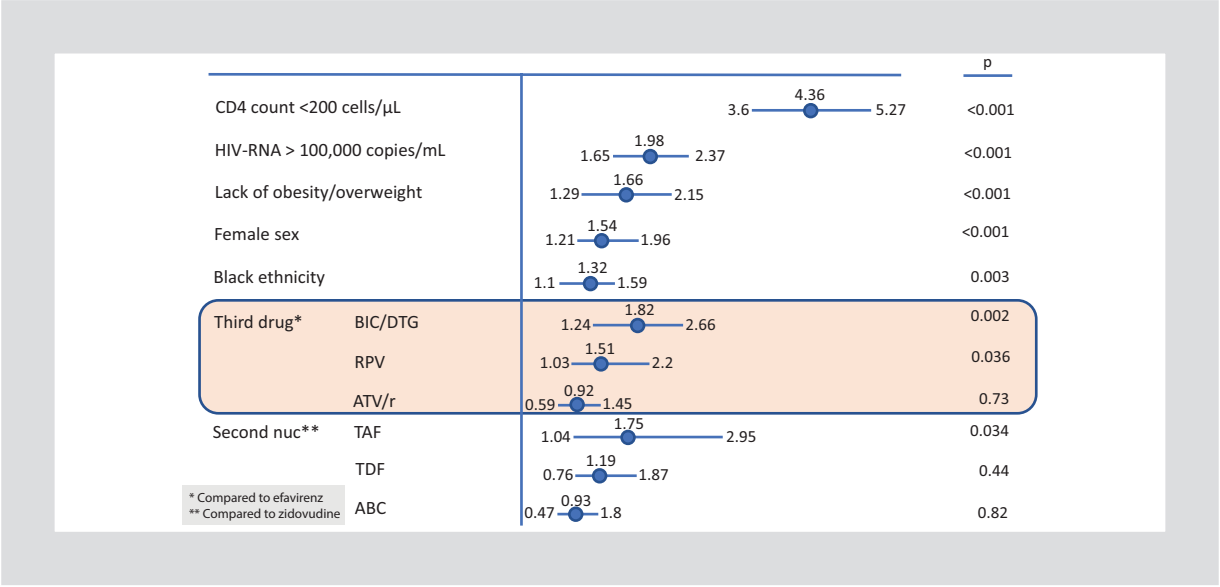

Figure 5. *Risk factors for significant (> 10%) weight gain in persons living with human immunodeficiency virus after initiating antiretroviral therapy. Adapted from Sax* et al., *2020*[8].

up of at least 96 weeks (Fig. 4)[8]. A total of 5680 treatment-naïve PLWH that initiated ART were examined. Overall, at ART initiation, median BMI was 24.8 kg/m^2, 16.3% were obese, and 31.4% were overweight. The 96-week median weight gain was 2.0 kg (IQR –1.0, 5.8). The greatest rate of weight gain occurred during the initial 48 weeks. It should be noted that weight gain was not observed in all participants; up to 30.2% lost weight. Figure 5 shows the impact of distinct variables on significant (> 10%) weight gain after initiating ART.

The degree of weight gain in the Gilead trials could mirror the obesity trend observed in the general population in North America. Indeed, the average American aged 20-40 gained nearly 1 kg/year in the NHANES CARDIA study[19], being Black race and female sex associated with greater weight gain. Regardless the disproportionate high prevalence of obesity among Black women in the general US population, other analyses of ACTG trials have shown that weight gain under ART is particularly pronounced using INSTI[20].

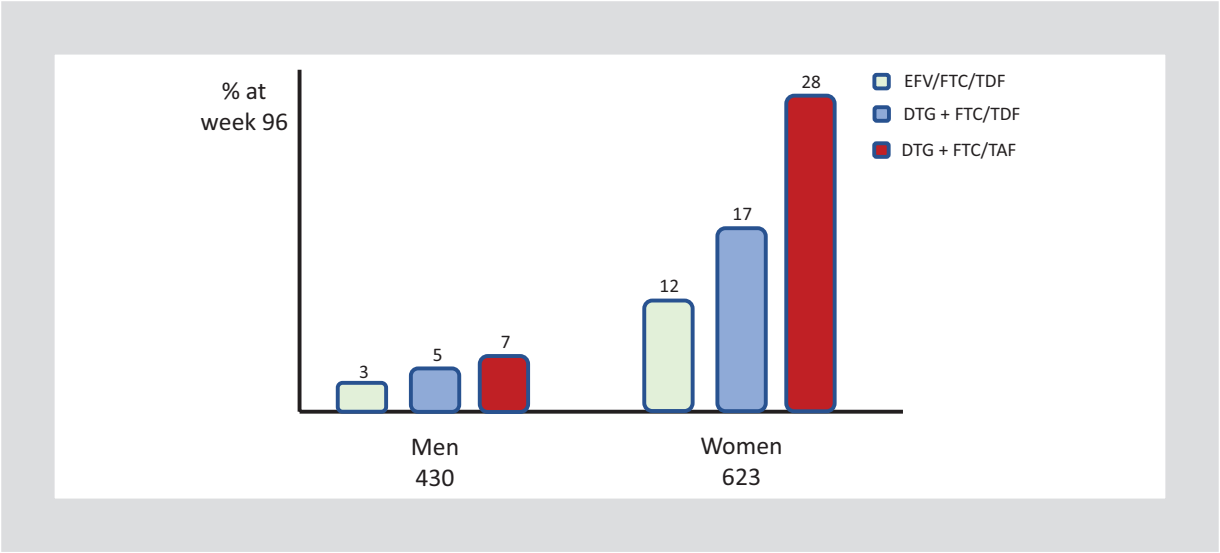

Figure 6. *Predicted risk at 10 years in the ADVANCE trial. Adapted from Venter et al., 2019[23] and Hill* et al., *2020[24].*

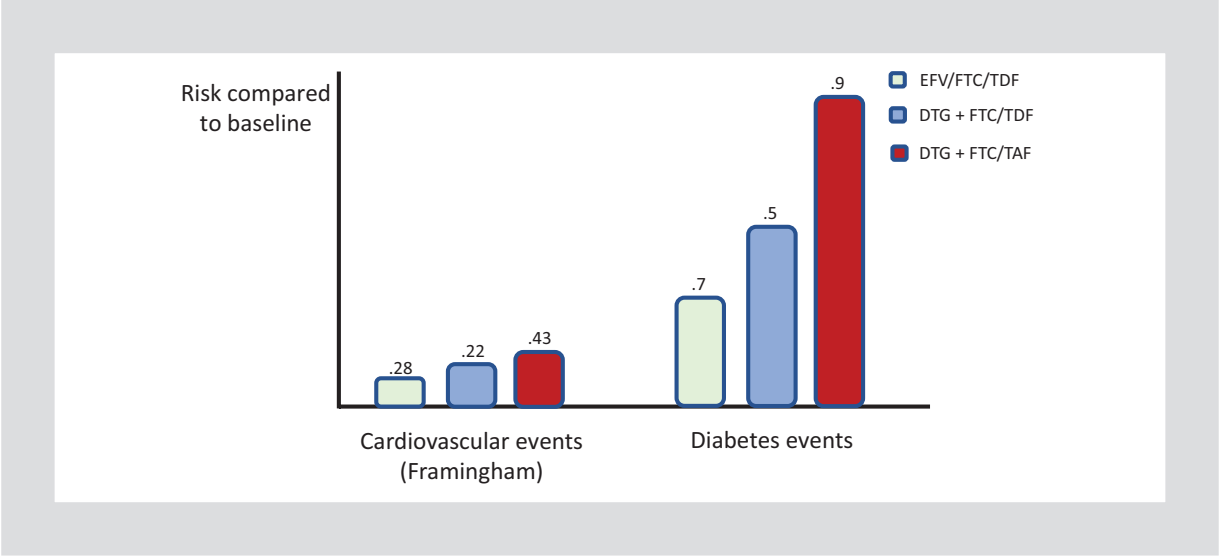

Figure 7. *Changes in body weight and body mass index at the DISCOVER trial. Adapted from Ogbuagu* et al., *2020[36].*

AT CROI 2020, body changes associated with ART were examined at two trials performed in African pregnant women. In the DOLPHIN study, 250 drug-naïve HIV-infected women in late pregnancy in South Africa and Uganda initiated DTG or EFV along with two nucleosides. At 6 weeks postpartum, a mean body weight loss of 6.1 Kg was recognized. However, the mean body weight was 4.35 Kg greater in women that received DTG than EFV[21].

In the Tshilo Dikotla study conducted in Botswana, 284 HIV-infected pregnant women received DTG to EFV along with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF). They were compared with 122 HIV-negative pregnant women. At 18 months postpartum, women on DTG had by average 5 Kg above those on EFV or HIV negatives[22].

The ADVANCE trial

Two large African Phase III trials have recently reported data on body weight gains using distinct antiretroviral agents. In the ADVANCE trial conducted in South Africa, 1053 drug-naïve PLWH were randomized 1:1:1 into three treatment arms: DTG/TDF/FTC, DTG/Tenofovir

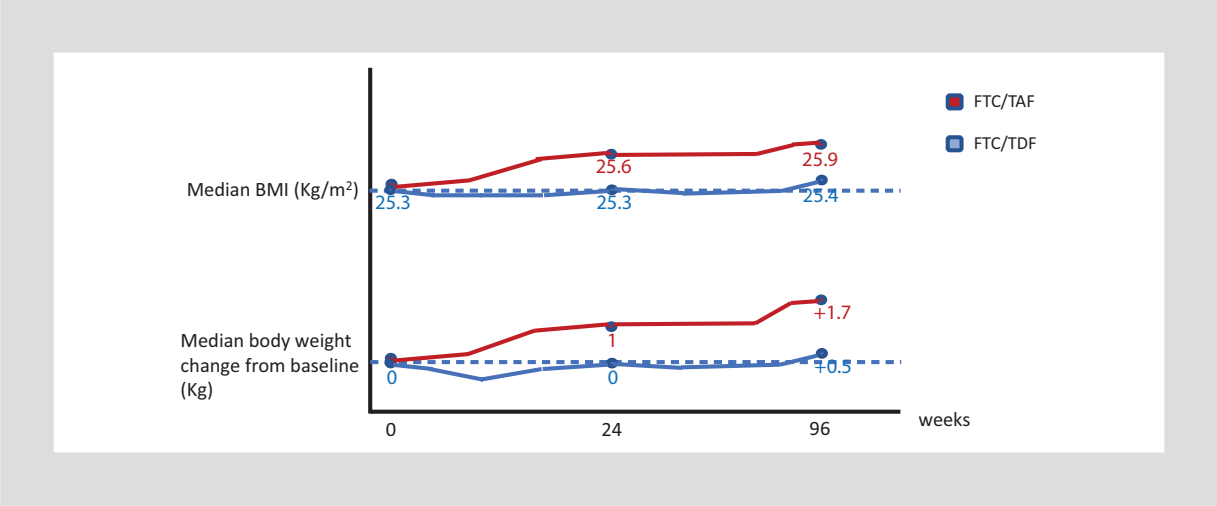

Figure 8. *Treatment-emergent obesity in the ADVANCE trial. Adapted from Venter et al., 2019[23] and Hill* et al., *2020[24].*

Alafenamide (TAF)/FTC, and EFV/TDF/FTC. Overall, 60% were female, almost all Black, and with a median age of 31 years old. Baseline obesity was 14%. Participants in the two DTG arms achieved viral load suppression faster than those in the EFV arm, although the proportion of patients with plasma HIV-RNA < 50 copies/mL was similar across all arms. Overall, very few participants in any arm experienced virological failure. However, the emergence of obesity was a remarkable finding in the subset of patients treated with DTG and TAF (Fig. 6), suggesting that the obesogenic effect of these agents might be additive if not synergistic[23].

Updated figures for metabolic outcomes at 96 weeks were presented at CROI 2020[24]. Rates of the metabolic syndrome increased in parallel. Accordingly, the 10-year predicted risks of CVD and diabetes increased significantly (Fig. 7).

The NAMSAL study

The French ANRS conducted in Cameroon a trial in drug-naïve PLWH. A total of 613 adults received at least one dose of two regimens, either DTG/3TC/TDF or EFV400/3TC/TDF[25]. At week 48, undetectable viremia was observed in 231/31 (74.5%) on DTG and in 209/303 (69.0%) on EFV400, a difference that was non-inferior. Interestingly, more weight gain was observed in the DTG group than in the EFV400 group (median weight gain, 5.0 kg vs. 3.0 kg; incidence of obesity, 12.3% vs. 5.4%). Updated figures at 96 weeks for significant weight gain (> 10%) were 45% on DTG and 33% on EFV[26].

Body weight gain using ART in cohort/observational studies

Besides collecting evidence from randomized trials, information derived from cohorts and observational studies may be valuable for obtaining further insights into the association of weight gain and ART modalities.

The HIV Outpatient Study reported body weight changes in a large population of US PLWH with virological suppression that was switched to other regimens. Among 653 patients, 368 switched to INSTI experienced a greater weight gain compared to 285 switched to other drug classes. The effect was more pronounced in women and in those switched to DTG (whereas it was not significant for elvitegravir)[27].

Another large retrospective study conducted at multiple clinics in the USA examined weight gain in 2080 drug-naïve PLWH that initiated distinct INSTI along with TDF, TAF, or ABC[28]. Overall individuals treated with DTG or BIC along with TAF were those experiencing more pronounced body weight changes at 6 months[28].

A Spanish study examined 219 drug-naive PLWH that consecutively initiated ART at one reference clinic. Patients that received INSTI experienced at 1 year a significant increase in systolic blood pressure that was correlated with weight gain. In addition, this subset of patients experienced an increase in LDL cholesterol[29].

The D:A:D cohort study

The gain in the BMI observed immediately after ART initiation was analyzed in 9321 HIV-infected persons

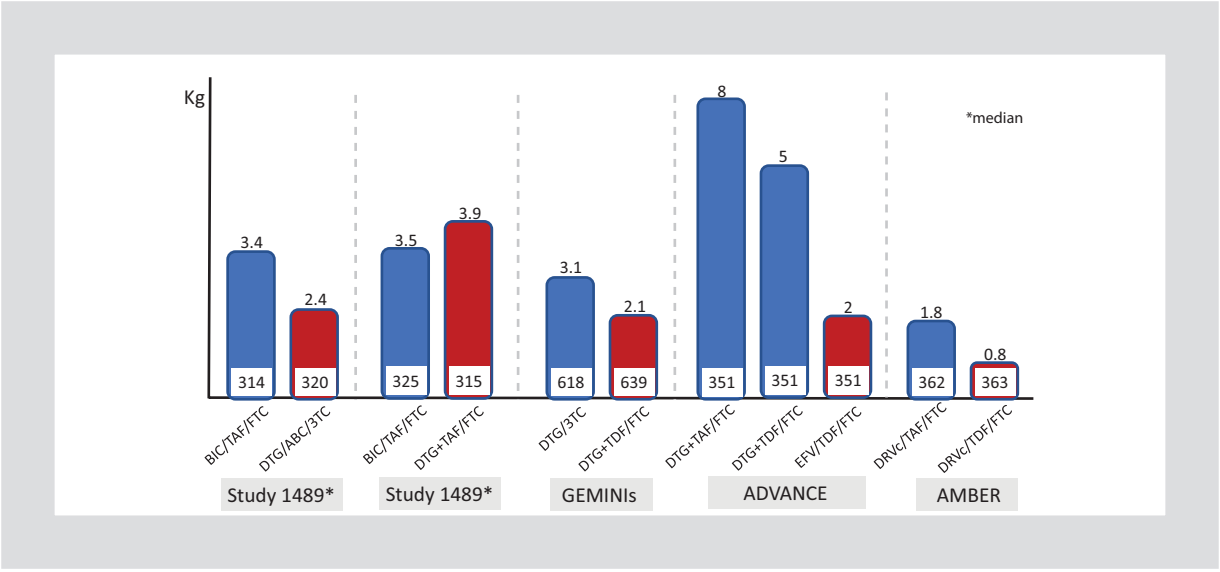

Figure 9. *Mean weight gain at 48 weeks from baseline in major Phase III trials in drug-naive persons living with HIV.*

followed for an average of 4.5 years. A total of 97 cardiovascular events (composite of myocardial infarction/stroke/coronary procedure) were recorded[5]. In fully adjusted analyses, the IRR/unit gain in BMI (95% confidence interval) in the 1st year of ART, by pre-ART BMI category, was underweight, 0.90 (0.60-1.37); normal, 1.18 (1.05-1.33); overweight, 0.87 (0.70-1.10), and obese, 0.95 (0.71-1.28) (p = 0.04 in all cases). In summary, short-term gain in BMI following ART initiation appeared to increase the longer term risk of CVD, but only in those with pre-ART BMI in the normal range.

An updated assessment of the risk of CVD after BMI changes on ART was presented looking at the large D:A:D study[30]. A total of 43,011 PLWH on ART were analyzed. After multiple adjustments, only the risk of diabetes was significantly increased in patients with BMI gains above 2 points[30].

Body weight gain associated with ART in special situations

The assessment of changes in body weight using antiretrovirals as pre-exposure prophylaxis (PrEP), as dual combinations or under modified long-acting formulations may provide valuable information on the effect of distinct antiretroviral agents in distinct scenarios. Preliminary data in all these circumstances support concerns on abnormal body weight gains using INSTIs extends to new regimens or formulations with drugs in this class, such as dual regimens (i.e., DTG + 3TC)[31] or in less extent with long-acting cabotegravir[32-35].

Overall, the effect of ART drugs on weight gain is confounded by HIV disease factors. This variable could be avoided by studying weight changes in PrEP trials. The DISCOVER trial is a Phase III study that examined the safety of PrEP with daily FTC/TAF versus FTC/TDF in more than 5000 HIV-negative individuals in North America and Europe[36]. Weight gain at week 48 was 1.1 kg in the TAF/FTC arm with no change in the TDF/FTC arm[36]. At 96 weeks, regimens performed similarly well in terms of conferring HIV protection. However, body weight and BMI differed significantly (Fig. 8)[36]. Similar trends were seen for metabolic parameters, with decreases in total, LDL and HDL cholesterol more pronounced with FTC/TDF than FTC/TAF.

Body weight changes with other antiretrovirals

The COVID-19 crisis hits the annual venue of CROI in Boston on March 2020. The conference shift from its original face-to-face format to be online. Several new studies addressed the issue of body weight changes associated with ART. However, the focus of attention at this year's virtual CROI 2020 switched to antiretrovirals other than INSTI and to the long-term consequences of ART-associated body weight gain differentially seen with some antiretrovirals.

The removal of TDF rather than the introduction of TAF seems to result in weight gain. This is the major finding of an Italian study that examined 252 PLWH suppressed on RPV/FTC/TDF that were switched to RPV/FTC/TAF[37].

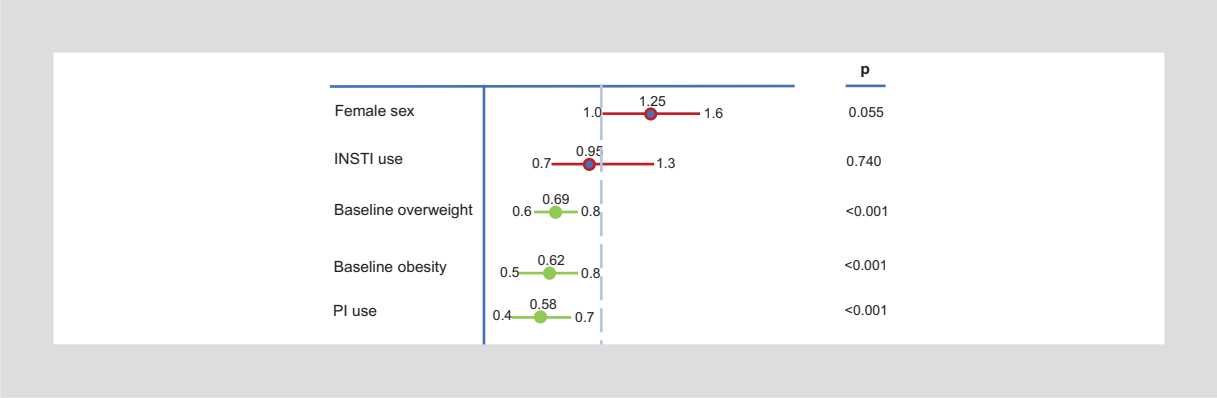

Figure 10. *Variables associated with body weight > 3% after antiretroviral therapy switching in the Trio Network. Adapted from McComsey* et al., *2020*[42].

Their mean baseline weight was 73.8 (± 14.3) Kg and remained stable for 6 months before switching. However, 3 and 6 months after switching rose to 77.7 (± 12.3) and 75.5 (± 14.5) Kg. The appreciation of consequences of these changes on the atherosclerotic risk score has been highlighted in a recent study[38].

A retrospective German study examined 1 year body weight changes in all patients treated with TDF and those switched from TDF to TAF. Mean increase in weight was + 0.55% in the 1st year on TDF versus 3.2% in those switched to TAF. Increases above 10% were recognized in 19% of patients in the last group[39].

Altogether, individuals taking TAF or INSTI experience more pronounced weight gain that the general population, which contrasts with the weight suppressive effect of TDF. Of note, ART-associated weight gain is generalized, with increases in subcutaneous fat, visceral fat, and lean mass. Thus, there is a need for increased clinical attention to the maintenance of healthy body weight, lifestyle modification, and exercise at ART initiation when using INSTI plus TAF.

Attention to abnormal body weight gain has been focused during the last couple of years on INSTI. No similar finding had been observed using neither NNRTI nor bPI. Whereas older PI such as indinavir and lopinavir had been associated with lipodystrophy[40], new agents within this family such as atazanavir and DRV have rarely been associated with body shape changes[41]. However, few data have been reported impact on body weight and BMI using these drugs. A protector role for bPI against overweight and obesity in PLWH had already been previously noticed comparing older Phase III trials (Fig. 9).

Data from the TRIO Network were presented at CROI 2019[42]. The BMI from 3468 PLWH having viral suppression at 9 US clinics was assessed 19 months after switching to a new ART regimen. Overall, 30% experienced > 3% weight gain. In a multivariable analysis, baseline overweight/obesity and PI use (mostly DRV) were significant protectors against body weight gain > 3% (Fig. 10).

At CROI 2020, an updated analysis of the TRIO Network examined 387 PLWH switched to INSTI regimens[43]. At 1 year, 27% had experienced a weight gain > 5%. Interestingly, switching from prior PI use (mostly DRV) was significantly associated with significant weight gains on INSTIs.

At the virtual IAC 2020, the results of a large retrospective real-world study conducted at the USA comparing patients that initiated INSTI versus bPI during the past 2.5 years was reported[44]. Briefly, significant changes in weight/BMI were examined retrospectively in all PLWH that initiated either INSTI (n = 383) or bPI (n = 372). DRV represented nearly 90% of bPI and BIC nearly 60% of INSTI. After an average of 13 months, mean weight increase was +1.47 in the INSTI group versus 0.03 (p = 0.006) in the PI group. Figures for mean BMI gain were +0.48 versus +0.01 Kg/m^2, respectively. Clinically significant variations were considered for individual changes >5% and were significant comparing both weight and BMI, regardless the inclusion of TAF in patients on bPI[44].

Altogether, the information currently available suggest that INSTI, perhaps influencing the neurogenic pathways of food intake and catabolism, lead to increased body weight. Rather than be specific of one agent, it seems to be a class side effect. The mid- and long-term consequences of induced overweight and/or obesity in the HIV population, which already suffers

from an increased cardiovascular risk, need to be assessed more carefully.

Conclusions

Weight gain is a physiologic phenomenon while aging. Although weight gain recovery following initiation of ART in PLWH often reflects a "return to normal" phenomenon, it is more pronounced using INSTI. Furthermore, it is more easily recognized in the subset of patients with low CD4 counts and/or high plasma viral load. The recognition of abnormal body weight gain associated with INSTI, mostly DTG and BIC and in less extent with EVG/c, must be considered as a drug-related side effect. Given that overweight and obesity are associated with an increased risk of diabetes and CVD events, it seems warranted to consider body weight gain using different ART regimens in all therapeutic decisions in PLWH. It would represent a further step toward the implementation of precision medicine in PLWH, acknowledging that distinct patient's profiles would require different treatment strategies.

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