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Inhibidores de la transferencia de la cadena de integrasa, su impacto en el tejido adiposo y en el aumento de peso en personas que viven con VIH: revisión narrativa

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ABSTRACT

Greater weight gain following initiation of antiretroviral therapy (ART) with integrase strand transfer inhibitors (INsTI) compared with that seen with other classes of antiretroviral drugs, is an increasingly recognized problem in people living with HIV (PLWH). The purpose of this narrative review is to highlight those clinical trials that have documented weight gain and associated factors among PLWH on INsTI-ART. This includes the underlying pathophysiological mechanisms, toxicity, impact on adipose

tissue, and how this tissue becomes metabolically dysfunctional, contributing to the emergence of insulin resistance and other comorbidities in PLWH. Considering the impact of the modern obesogenic environment and that PLWH on INsTI-ART are living longer, a coordinated approach by infectious disease specialists and other physicians to address the metabolic complications affecting this population, is imperative. The use of new anti-obesity drugs is becoming part of co-medication to limit weight gain in this population.

Keywords: Integrase Inhibitors. Weight gain. Adiposity. HIV.

RESUMEN

La mayor ganancia de peso tras el inicio de la terapia antirretroviral (TAR) con inhibidores de la transferencia de la integrasa (INsTI), en comparación con la observada con otras clases de fármacos antirretrovirales, es un problema cada vez más reconocido en las personas que viven con el VIH (PVV). El propósito de esta revisión narrativa es destacar los ensayos clínicos que han documentado el aumento de peso y los factores asociados en las PVV y que reciben INsTI-TAR. Esto incluye los mecanismos fisiopatológicos subyacentes, la toxicidad, el impacto en el tejido adiposo y cómo este tejido se vuelve metabólicamente disfuncional, contribuyendo a la aparición de resistencia a la insulina y otras comorbilidades entre las PVV. Considerando el impacto del entorno obesógeno moderno y que las PVV que reciben INsTI-TAR viven más tiempo; es imperativo un enfoque coordinado entre especialistas en enfermedades infecciosas y otros médicos para abordar las complicaciones metabólicas que afectan a esta población. El uso de nuevos fármacos antiobesidad se está convirtiendo en la actualidad en parte de la comedicación para limitar el aumento de peso en esta población.

Palabras clave: Inhibidores de la transferencia de la cadena de integrasa. Ganancia de peso. Adiposidad. VIH.

INTRODUCTION

Since 1996 the combined use of two or three active antiretroviral drugs (ARV) that interfering HIV viral lifecycle, has allowed suppression viral replication with immune restitution in people living with HIV (PLWH). This combination antiretroviral treatment (ART) has become the standard of care for PLWH, improving their morbidity and mortality (1). Currently, there are nine drug class of ARV: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease Inhibitors (PI), fusion inhibitors, integrase strand transfer inhibitors (INsTI), entry inhibitors, and nucleoside reverse transcriptase translocation inhibitors (NRTTI), HIV-1 attachment inhibitors and HIV-1 capsid inhibitors (2). INsTI are a class of ARV which block the integration of the viral DNA into host genome (3). Because its high genetic barrier, good tolerability, low toxicity, high potency to suppress HIV viral loads, inherent barrier to resistance, and their beneficial effects on plasma lipids; the INsTI are currently used as first-line treatment in HIV infections (4,5). Raltegravir (RAL) and elvitegravir (EVG) are the first generation of INsTI approved by FDA in 2007 and 2012 respectively (6), whereas that the second generation of INsTI, such as Dolutegravir (DTG), bictegravir (BIC) and cabotegravir (CAB) were approved in 2013, 2018 and 2020, respectively by FDA (7). Currently, World Health Organization and international guides for HIV treatment recommend the ARV regimens based on DTG and BIC as first line of ART (8,9).

ANTIRETROVIRAL THERAPY AND TOXICITIES ON ADIPOSE TISSUE

With the introduction of combination ARTs in 1996, based on two first generation NRTIs (thymidine analogues stavudine and zidovudine) plus PI, fat partitioning disorders, such as lipoatrophy or subcutaneous fat tissue (SAT) loss, visceral fat hypertrophy with or without truncal fat accumulation (lipohypertrophy) and buffalo hump, were clinically manifest among PLWH (10). These fat partitioning disorders were not clinically isolated, because they were associated with dyslipidemia and insulin resistance (11). Lipohypertrophy involves visceral adipose tissue (VAT), whose increase in PLWH may contribute to increased inflammation and risk for cardiovascular disease (CVD) (Table I). In this context, CVD emerges as a result of persistent immune activation, endothelial dysfunction, elevated coagulation, and dyslipidemia (12). On the other hand, the VAT of PLWH under NRTI-ART is metabolically dysfunctional and can promote mitochondrial dysfunction and thus insulin resistance (13,14). VAT also includes epicardial fat, whose accumulation is associated with a higher risk of cardiovascular events in PLWH under ART (15). Interestingly, the VAT:SAT ratio is related with coronary plaque and calcified plaque segments. In contrast, increased SAT tended to be related to reduced coronary plaque among PLWH (16).

WEIGHT GAIN WITH INsTI: EVIDENCE AND STUDIES

Current ART is based on BIC and DTG co-administered with a backbone of two NNRTIs or one NRTI. While these ART regimens have shown therapeutically an excellent efficacy and tolerability, they also have seen associated with weight gain in PLWH (17,18).

One of the first studies that documented weigh gain in PLWH treated with INsTI was the metabolic substudy A5260s within the randomized study AIDS Clinical Trials Group (ACTG) A5257 (19). Initially, the central and peripheral fat changes from a total of 328 participants, after 96 weeks of treatment with 2 boosted PIs or with RAL as INsTI, were not

different. However, a gain in central fat and VAT was observed in the INsTI arm of this study. Bhagwat and cols. compared body changes at 96 weeks in 1809 PLWH randomized to 1 of 3 ART regimens: RAL; atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r), either alone or in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) (20). Importantly, the increase in waist circumference was greater in the group that received RAL, compared to the group that received DRV/r as PI ($p < 0.005$) (20).

In the European Network for AIDS Treatment 022 Study (NEAT022, NCT02098837), a randomized, non-inferiority, 96-week study in 420 participants, the impact of DTG (DTG-I group) and PI boosted with ritonavir (PI/r group) on lipid parameters were compared in PLWH with potential high CVD risk. While the DTG-I group showed a significant reduction in proatherogenic lipid fractions, PLWH with a previous pharmacological history of PI/r had modest gain weight after switching to a DTG-regimen at 48 weeks (21). The weight gain was also evidenced in the NAMSAL ANRS 12313 Study (NCT02777229). In this open-label, multicenter, randomized, phase-3 non-inferiority trial in 613 participants from Cameroun, an ART regimen based on NNRTI Efavirenz (EFV) combined with TDF and lamivudine (3TC) was compared with an INsTI DTG-regimen. Interestingly, a greater median increase in body weight was observed in the DTG group versus the EFV group. In addition, the weight gain was predominantly observed in women rather than men, and in participants from DTG group (22). The differential effects of EFV and DTG on weight gain were analyzed in a previous retrospective observational cohort study where a weight gain of +5.3 kg ($p = 0.001$) was evidenced at 18 months in 136 PLWH switched from EFV/TDF/FTC to an INsTI regimen (23).

Another pivotal study was the ADVANCED open-label, non-inferiority, phase-3 clinical trial (NCT03122262). In this study, 1053 individuals were randomized to compare noninferiority at 96 weeks between two INsTI

ART regimens: DTG/TDF/FTC, and DTG/tenofovir alafenamide/emtricitabine (DTG/TAF/FTC) with the EFV/TDF/FTC regimen. Both arms of the study with INsTI DTG regimens experienced substantial weight gain in comparison to the EFV/TDF/FTC arm. The most prominent weight gain was observed in the DTG/TAF/FTC group (7.1 kg ± 7.4), showing the contribution of the INsTI and additional effect of TAF (24).

On the other hand, Sax and cols. (25) analyzed 8 Gilead Sciences–sponsored trials with 5680 participants that initiated ART in 2003-2015 to identify risk factors for weight gain after the initiation of ART. Longitudinal modeling of weight gain showed that the third antiretroviral class (INsTI, NNRTI, or PI) contributed to weight gain at 96 weeks in different grades. However, participants under second generation INsTI BIC or DTG experienced the most weight gain (BIC, 4.24 kg [95 % CI, 3.71-4.78]; DTG, 4.07 kg [95 % CI, 3.51-4.62], compared with modest weight gain in the EVG group (2.72 kg [95 % CI, 2.45-3.0]). Overall, 12.8 % of participants experienced weight gain ≥ 10 % basal body weight over 48 weeks. Interestingly, the factors associated with more extreme weight gain were female gender and black ethnical group, T CD4+ counts < 200/µL, and baseline HIV RNA viral load > 100,000 copies/mL (25).

On the other hand, data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) allowed to analyze the weight changes over time, and risk factors for weight gain, among over 20,000 treatment-naive PLWH who initiated ART — 49 % with NNRTI, 31 % with PI and 20 % with INsTI-based regimens. After following for 2 and 5 years, PLWH on INsTI-based regimens gained an estimated mean of +4.9 and +5.9 kg, respectively, compared to +4.9 and +5.5 kg among persons who received PI-based regimens, and +3.1 and +3.7 kg among NNRTI-based regimen recipients. In addition, RAL and DTG-ART regimens were associated with higher weight gain (+7.2 and 5.8 kg, respectively) than that observed in PLWH on EVG-based regimens (26).

It is noteworthy that the population analyzed in the majority of the above studies were predominantly from the USA, with Hispanic and other populations underrepresented.

Coelho and cols. analyzed almost 60,000 PLWH initiating ART in six countries in the Americas (Brazil, Honduras, Mexico, Peru, Haiti and USA), finding that greatest adjusted probability of becoming overweight or obese at 3-years post-ART initiation. Interestingly, 40 % of individuals with body mass index (BMI) of 30-34.9 kg/m² (obesity class 1) developed obesity class 2 (BMI, 35-39.9 kg/m²), while 16 % developed obesity class 3 (BMI ≥ 40 kg/m²) at 3 years post ART initiation. In addition, these percentage transitions besides lower baseline CD4 count and higher baseline HIV viral load were associated with a BMI increase over time in the adjusted model (27). The use of INsTI as the primary ART core drug constitutes the greatest risk factor for developing obesity (adjusted HR, 7.12, $p < 0.0001$) (28). While the studies described above have evidenced weight gain after ART-INsTI initiation (Table II), the body composition changes associated with the observed weight gain, in terms of increased subcutaneous fat, visceral fat, and lean mass, were not detailed.

Weight gain and TAF

Weight gain has also been reported in PLWH who switched from TDF to TAF-ART regimens, with a weight gain of +2.2 (IQR, -0.4 to +4.6) at week 48 (29). In addition, switching from TDF to TAF has been associated with a 0.45 kg/m^2 increase in BMI (30). On the contrary, TAF-to-TDF switching can prevent weight gain (31). However, in another study (Dutch ATHENA cohort), reversibility of weight gain of at least 7 % over the short-term was not observed after discontinuation of TAF or INsTI (32). Future studies are needed to show that TAF discontinuation may limit weight gain.

Mechanisms underlying gain weight in PLWH under INsTI-ART

Body weight in PLWH is influenced by an interplay of genetic and environmental factors and progression of disease (33). Before ART initiation, PLWH often experience a wasting syndrome characterized manly by involuntary weight loss of > 10 % of baseline body weight (34). Once initiated an effective ART, weight loss can be reversed and be viewed as beneficial after initiation of ART (34). In addition, suppression of viral replication and T CD4+ recovery allow weight regain. This condition is known as “return to health” and is a concept that describes the desirable weight gain following resolution of debilitating catabolic infection or illness that restores body fat and protein stores (35). However, it is important to distinguish the weight gain trajectories of the “return to health” phenomenon from excessive and clinically undesirable weight gain observed in PLWH with overweight and obesity, mainly characterized by central fat accumulation (36). PLWH who do not start their ART have more risk of develop adipose tissue dysfunction. In this regard, HIV viral proteins *Vpr*, *Nef*, *Tat* and *Gag* might alter adipogenesis, contributing to the onset of insulin resistance in adipocytes or inducing mitochondrial dysfunction by generation of mitochondrial reactive oxygen species (37-40). Furthermore, PLWH are prone to excess VAT accumulation in the intra-abdominal, pericardial, liver, and skeletal muscle depots (41). As was mentioned above, the VAT of PLWH under ART is metabolically dysfunctional. Adipose tissue from the SAT of PLWH receiving INsTI who underwent bariatric surgery presented perilobular and periadipocyte fibrosis and periadipocyte fibrosis in VAT. Interestingly, oxidative stress, mitochondrial dysfunction, and insulin resistance were also observed in the context of DTG and RAL use (42,43). In addition, adipocyte hypertrophy has been documented in the VAT of macaques treated with DTG, highlighting the plasticity of adipocytes to store caloric excess through hypertrophy and hyperplasia, and deposition of ectopic fat (42-44). INsTI-induced adipocyte

hypertrophy creates a hypoxic environment, which in turn promotes fibrosis, alterations in adipokine secretion (increase in leptin and decrease in adiponectin levels) and changes in adipocyte size and numbers (45). Collectively these changes configure in the fat tissue a phenotype of aging adipose tissue (46).

Fat expansion and weight gain in PLWH under INsTI-ART are of concern, given their potential for increasing the prevalence of obesity and the risk of metabolic comorbidities and cancer. In this context, metabolic syndrome (including central obesity, insulin resistance, dyslipidemia and hypertension) occurs in 17-24 % of PLWH under ART. Considering the impact of the modern obesogenic environment, the prevalence of overweight and obesity in PLWH also will escalate at global level, contributing to morbidity and mortality through an increased risk of cardiovascular disease, diabetes, and metabolic disease as patients age (47,48). Weight gain in PLWH and high BMI are associated with an increased risk of diabetes, neurocognitive impairment, and other comorbid conditions; therefore, the avoidance of weight gain may reduce these risks (49,50). The increase in adipose tissue led to the emergence of a phenotype known as sarcopenic obesity (51). Whether INsTI are involved in the emergence of sarcopenic obesity over time requires more investigation.

NEW ANTI-OBESITY DRUGS

The pathophysiological basis of weight gain associated with InsTI, as explained above, should be considered in the context of personalized ART. This approach could help to stratify patients according to risk, predict disease progression, and select the most appropriate treatment, minimizing adverse side effects. To date, several strategies used in the general population to manage non-communicable AIDS conditions (hypertension, diabetes, dyslipidemia, cardiovascular diseases) can be take into consideration, in addition to lifestyle modification and specific

drugs (52). Despite the fact that effective interventions are lacking, improvements in diet may attenuate weight gain in PLWH under INsTIs and TAF-ART (53). Recently, tesamorelin (synthetic growth hormone-releasing hormone) an FDA-approved therapy to treat abdominal fat has been used to reduce VAT (abdominal and liver fat accumulation) in PLWH under INsTI-ART, with beneficial effects on body composition and glycemic control (54,55). On the other hand, semaglutide, a GLP-1 receptor agonist (GLP-1R), is highly effective for decreasing weight. In this regard, a randomized, double-blind, placebo-controlled phase-2b clinical trial was performed in 108 PLWH (56). A decrease by 30.8 % in abdominal visceral adipose tissue, 11.2 % in abdominal subcutaneous adipose tissue, and 18.9 % in total body fat was observed in the GLP-1 arm (56). Dual agonists as tirzepatide (GLP-1-GIP) and survodutide (GLP-1R/GCGRA) have also resulted in reductions in body weight of up to -11.2 kg (57). Another treatment for obesity is the use of triple agonists including GIP/GLP-1/GCGRA or retatrutide (LY3437943), which is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors (Table IV). Retatrutide is more potent at the human GIP receptor with an efficacy in terms of body-weight reductions of 5 % or more at 48 weeks in 64 to 100 % of participants. Interestingly retatrutide 12 mg resulted in a body weight reduction of 30 % in 26 % of participants (58). While tesamorelin and GLP-1 represent a promise in the therapy of lipohypertrophy in PLWH, future studies are needed to evaluate efficacy of dual agonists (GLP-1-GIP or GLP-1R/GCGRA), and triple agonists (GIP/GLP-1/GCGRA) in body weight reduction of PLWH, as well as their tolerability and drug interactions with ART.

FUTURE CONSIDERATIONS

The effectiveness of current ART regimens based on INsTI has allowed sustained and prolonged HIV viral suppression; however, their metabolic

impact in terms of weight gain, adiposity and non-communicable AIDS comorbidities will continue to be a global health concern. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has implemented the Global AIDS Strategy 95´- 95´- 95´aims to end the epidemic by 2030 — at least 95 % of all PLWH should be diagnosed, at least 95 % of them should be on ART, and at least 95 % of those on ART should be virologically suppressed (59). Moreover, with the inclusion of a fourth 95 ´ (quality-of-life (HRQoL), the new strategy adopts a more holistic approach in the HIV care cascade. In this context, despite being virologically suppressed, PLWH under current ART continue to experience metabolic complications such as overweight and obesity, which impact significantly their HRQoL (60). Given that excessive weight gain and obesity can exacerbate, accelerate, or accentuate multiple comorbidities in aging PLWH, maintenance of ideal body weight is the goal for reducing cardiovascular risk and improving diabetes (50,60). Thus, special attention to metabolic complications such as overweight or obesity and their prevention must be taken into consideration to reach the fourth 95 in the era of INsTI.

CONCLUSIONS

Currently, INsTI might contribute to weight gain and obesity in a low percentage of PLWH. The mechanisms involved in this weight gain include adipocyte hypertrophy, hypoxic environment and, importantly, periadipocyte fibrosis. This pro-fibrotic phenotype is associated with an insulin-resistant state in VAT, as well as altered adipokine secretion. While the success of INsTI-antiretroviral therapy has allowed sustained viral suppression, multiple interventions and a coordinated approach by infectious diseases specialists and other physicians are still required for metabolic complications.

REFERENCES

1. Gibas KM, Kelly SG, Arribas JR, Cahn P, Orkin C, Daar ES, et al. Two-drug regimens for HIV treatment. Lancet HIV 2022;9(12):e868-83. DOI: 10.1016/S2352-3018(22)00249-1
2. Cheney L, Barbaro JM, Berman JW. Antiretroviral Drugs Impact Autophagy with Toxic Outcomes. Cells 2021;10(4):909. DOI: 10.3390/cells10040909
3. Smith SJ, Zhao XZ, Passos DO, Lyumkis D, Burke TR Jr, Hughes SH. Integrase Strand Transfer Inhibitors Are Effective Anti-HIV Drugs. Viruses 2021;13(2):205. DOI: 10.3390/v13020205
4. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors. Curr Treat Options Infect Dis 2019;11(4):372-87. DOI: 10.1007/s40506-019-00203-7
5. Richetta C, Tu NQ, Delelis O. Different Pathways Conferring Integrase Strand-Transfer Inhibitors Resistance. Viruses 2022;14(12):2591. DOI: 10.3390/v14122591
6. Podany AT, Scarsi KK, Pham MM, Fletcher CV. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors: An Updated Review. Clin Pharmacokinet 2020;59(9):1085-107. DOI: 10.1007/s40262-020-00898-8
7. Mahajan PS, Burke TR Jr. Synthetic Approaches to a Key Pyridone-carboxylic Acid Precursor Common to the HIV-1 Integrase Strand Transfer Inhibitors Dolutegravir, Bictegravir, and Cabotegravir. Org Process Res Dev 2023;27(5):847-53. DOI: 10.1021/acs.oprd.3c00063
8. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2023 [Accessed on August 11, 2024]. Avalaible from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf

9. EACS Guidelines V12.0 2024 [Accessed on August 11, 2024]. Available in: https://www.eacsociety.org/guidelines/eacs-guidelines/
10. Lichtenstein KA, Delaney KM, Armon C, Ward DJ, Moorman AC, Wood KC, et al. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. J Acquir Immune Defic Syndr 2003;32(1):48-56. DOI: 10.1097/00126334-200301010-00007
11. Lagathu C, Béréziat V, Gorwood J, Fellahi S, Bastard JP, Vigouroux C, et al. Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment. Expert Opin Drug Saf 2019;18(9):829-40. DOI: 10.1080/14740338.2019.1644317
12. Beltrán LM, Rubio-Navarro A, Amaro-Villalobos JM, Egido J, García-Puig J, Moreno JA. Influence of immune activation and inflammatory response on cardiovascular risk associated with the human immunodeficiency virus. Vasc Health Risk Manag 2015;11:35-48. DOI: 10.2147/VHRM.S65885
13. Brown TT, Li X, Cole SR, Kingsley LA, Palella FJ, Riddler SA, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the Multicenter AIDS Cohort Study. AIDS 2005;19(13):1375-83. DOI: 10.1097/01.aids.0000181011.62385.91
14. Blümer RM, van Vonderen MG, Sutinen J, Hassink E, Ackermans M, van Agtmael MA, et al. Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. AIDS 2008;22(2):227-36. DOI: 10.1097/QAD.0b013e3282f33557
15. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-

infected men. AIDS 2010;24(2):243-53. DOI: 10.1097/QAD.0b013e328333ea9e

16. Bogorodskaya M, Fitch KV, Lu M, Torriani M, Zanni MV, Looby SE, et al. Measures of Adipose Tissue Redistribution and Atherosclerotic Coronary Plaque in HIV. Obesity (Silver Spring) 2020;28(4):749-55. DOI: 10.1002/oby.22742
17. Sax PE, DeJesus E, Crofoot G, Ward D, Benson P, Dretler R, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. Lancet HIV 2017;4(4):e154-60. DOI: 10.1016/S2352-3018(17)30016-4
18. 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(9):e471-7. DOI: 10.1093/cid/ciaa177
19. McComsey GA, Moser C, Currier J, Ribaudo HJ, Paczuski P, Dubé MP, et al. Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors: ACTG A5260s. Clin Infect Dis 2016;62(7):853-62. DOI: 10.1093/cid/ciw017
20. Bhagwat P, Ofotokun I, McComsey GA, Brown TT, Moser C, Sugar CA, et al. Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race. Open Forum Infect Dis 2018;5(11):ofy201. DOI: 10.1093/ofid/ofy201.
21. Gatell JM, Assoumou L, Moyle G, Waters L, Johnson M, Domingo P, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. AIDS 2017;31(18):2503-14. DOI: 10.1097/QAD.0000000000001675
22. Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, Boyer S, et al. Dolutegravir-Based or Low-

Dose Efavirenz-Based Regimen for the Treatment of HIV-1. N Engl J Med 2019;381(9):816-26. DOI: 10.1056/NEJMoa1904340

23. Norwood J, Turner M, Bofill C, Rebeiro P, Shepherd B, Bebawy S, et al. Brief Report: Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor-Based Regimens. J Acquir Immune Defic Syndr 2017;76(5):527-31. DOI: 10.1097/QAI.0000000000001525

24. 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(10):e666-76. DOI: 10.1016/S2352-3018(20)30241-1

25. 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(6):1379-89. DOI: 10.1093/cid/ciz999

26. Bourgi K, Jenkins CA, Rebeiro PF, Palella F, Moore RD, Altoff KN, et al. 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(4):e25484. DOI: 10.1002/jia2.25484

27. Coelho LE, Jenkins CA, Shepherd BE, Pape JW, Mejia Cordero F, Padgett D, et al. Weight gain post-ART in HIV+ Latinos/as differs in the USA, Haiti, and Latin America. Lancet Reg Health Am 2022;8:100173. DOI: 10.1016/j.lana.2021.100173

28. Bakal DR, Coelho LE, Luz PM, Clark JL, De Boni RB, Cardoso SW, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. J

Antimicrob Chemother 2018;73(8):2177-85. DOI: 10.1093/jac/dky145

29. Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, et al. Switching to Bictegravir, Emtricitabine, and Tenofovir Alafenamide in Virologically Suppressed Adults With Human Immunodeficiency Virus. Clin Infect Dis 2021;73(2):e485-93. DOI: 10.1093/cid/ciaa988
30. Schafer JJ, Sassa KN, O'Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in Body Mass Index and Atherosclerotic Disease Risk Score After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide. Open Forum Infect Dis 2019; 6(10): ofz414. DOI: 10.1093/ofid/ofz414
31. Kauppinen KJ, Aho I, Sutinen J. Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain. AIDS 2022;36(10):1337-44. DOI: 10.1097/QAD.0000000000003245
32. Verburgh ML, Wit FWNM, Boyd A, Reiss P, Van der Valk M; ATHENA national observational cohort. No evidence of rapid reversibility of tenofovir alafenamide and/or integrase strand transfer inhibitor-associated weight gain. AIDS 2023;37(12):1843-50. DOI: 10.1097/QAD.0000000000003654
33. Wohl DA, Koethe JR, Sax PE, McComsey GA, Kuritzkes DR, Moyle G, et al. Antiretrovirals and Weight Change: Weighing the Evidence. Clin Infect Dis 2024;12:ciae191. DOI: 10.1093/cid/ciae191
34. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. Clin Infect Dis 2006;42(6):836-42. DOI: 10.1086/500398

35. Tate T, Willig AL, Willig JH, Raper JL, Moneyham L, Kempf MC, et al. HIV infection and obesity: where did all the wasting go? Antivir Ther 2012;17(7):1281-9. DOI: 10.3851/IMP2348
36. Kumar S, Samaras K. The Impact of Weight Gain During HIV Treatment on Risk of Pre-diabetes, Diabetes Mellitus, Cardiovascular Disease, and Mortality. Front Endocrinol (Lausanne) 2018;9:705. DOI: 10.3389/fendo.2018.00705
37. Otake K, Omoto S, Yamamoto T, Okuyama H, Okada H, Okada N, et al. HIV-1 Nef protein in the nucleus influences adipogenesis as well as viral transcription through the peroxisome proliferator-activated receptors. AIDS 2004;18(2):189-98. DOI: 10.1097/00002030-200401230-00007
38. Agarwal N, Iyer D, Patel SG, Sekhar RV, Phillips TM, Schubert U, et al. HIV-1 Vpr induces adipose dysfunction in vivo through reciprocal effects on PPAR/GR co-regulation. Sci Transl Med 2013;5(213):213ra164. DOI: 10.1126/scitranslmed.3007148
39. Pérez-Matute P, Pérez-Martínez L, Blanco JR, Oteo JA. Role of mitochondria in HIV infection and associated metabolic disorders: focus on nonalcoholic fatty liver disease and lipodystrophy syndrome. Oxid Med Cell Longev 2013;2013:493413. DOI: 10.1155/2013/493413
40. Gorwood J, Ejlalmanesh T, Bourgeois C, Mantecon M, Rose C, Atlan M,et al. SIV Infection and the HIV Proteins Tat and Nef Induce Senescence in Adipose Tissue and Human Adipose Stem Cells, Resulting in Adipocyte Dysfunction. Cells 2020;9(4):854. DOI: 10.3390/cells9040854
41. Bailin SS, Gabriel CL, Fan R, Ye F, Nair S, Terry JG, et al. Relationship of Subcutaneous Adipose Tissue Inflammation-Related Gene Expression With Ectopic Lipid Deposition in Persons With HIV. J Acquir Immune Defic Syndr 2022;90(2):175-83. DOI: 10.1097/QAI.0000000000002926

42. Gorwood J, Bourgeois C, Pourcher V, Pourcher G, Charlotte F, Mantecon M, et al. The Integrase Inhibitors Dolutegravir and Raltegravir Exert Proadipogenic and Profibrotic Effects and Induce Insulin Resistance in Human/Simian Adipose Tissue and Human Adipocytes. Clin Infect Dis 2020;71(10):e549-60. DOI: 10.1093/cid/ciaa259
43. Ghaben AL, Scherer PE. Adipogenesis and metabolic health. Nat Rev Mol Cell Biol 2019;20(4):242-58. DOI: 10.1038/s41580-018-0093-z
44. Bailin SS, Gabriel CL, Wanjalla CN, Koethe JR. Obesity and Weight Gain in Persons with HIV. Curr HIV/AIDS Rep 2020;17(2):138-50. DOI: 10.1007/s11904-020-00483-5
45. Ngono Ayissi K, Gorwood J, Le Pelletier L, Bourgeois C, Beaupère C, Auclair M, et al. Inhibition of Adipose Tissue Beiging by HIV Integrase Inhibitors, Dolutegravir and Bictegravir, Is Associated with Adipocyte Hypertrophy, Hypoxia, Elevated Fibrosis, and Insulin Resistance in Simian Adipose Tissue and Human Adipocytes. Cells 2022;11(11):1841. DOI: 10.3390/cells11111841
46. Ahmed B, Farb MG, Gokce N. Cardiometabolic implications of adipose tissue aging. Obes Rev 2024;30:e13806. DOI: 10.1111/obr.13806
47. Zhao H, Goetz MB. Complications of HIV infection in an ageing population: challenges in managing older patients on long-term combination antiretroviral therapy. J Antimicrob Chemother 2011;66(6):1210-4. DOI: 10.1093/jac/dkr058
48. Bailin SS, Gabriel CL, Wanjalla CN, Koethe JR. Obesity and Weight Gain in Persons with HIV. Curr HIV/AIDS Rep 2020;17(2):138-50. DOI: 10.1007/s11904-020-00483-5
49. Kim DJ, Westfall AO, Chamot E, Willig AL, Mugavero MJ, Ritchie C, et al. Multimorbidity patterns in HIV-infected patients:

the role of obesity in chronic disease clustering. J Acquir Immune Defic Syndr 2012;61(5):600-5. DOI: 10.1097/QAI.0b013e31827303d5

50. Sattler FR, He J, Letendre S, Wilson C, Sanders C, Heaton R, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. J Acquir Immune Defic Syndr 2015;68(3):281-8. DOI: 10.1097/QAI.0000000000000458

51. Milic J, Calza S, Cantergiani S, Albertini M, Gallerani A, Menozzi M, et al. Sarcopenic Obesity Phenotypes in Patients With HIV: Implications for Cardiovascular Prevention and Rehabilitation. Can J Cardiol 2023;39(11S):S359-67. DOI: 10.1016/j.cjca.2023.08.027

52. Capeau J, Lagathu C, Ngono Ayissi K, Fève B, Béréziat V. HIV and adipose tissue: A long history linked to therapeutic classes of antiretrovirals. Ann Endocrinol (Paris) 2024;85(3):255-8. DOI: 10.1016/j.ando.2024.05.005

53. Patel YS, Doshi AD, Levesque AE, Lindor S, Moranville RD, Okere SC, et al. Weight Gain in People with HIV: The Role of Demographics, Antiretroviral Therapy, and Lifestyle Factors on Weight. AIDS Res Hum Retroviruses 2023;39(12):652-61. DOI: 10.1089/AID.2023.0008

54. Russo SC, Ockene MW, Arpante AK, Johnson JE, Lee H, Toribio M, et al. Efficacy and safety of tesamorelin in people with HIV on integrase inhibitors. AIDS 2024;38(12):1758-64. DOI: 10.1097/QAD.0000000000003965

55. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, et al. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. JAMA 2014;312(4):380-9. DOI: 10.1001/jama.2014.8334

56. Eckard AR, Wu Q, Sattar A, Ansari-Gilani K, Labbato D, Foster T, et al. Once-weekly semaglutide in people with HIV-associated lipohypertrophy: a randomised, double-blind, placebo-controlled phase 2b single-centre clinical trial. Lancet Diabetes Endocrinol 2024;12(8):523-34. DOI: 10.1016/S2213-8587(24)00150-5
57. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med 2021;385(6):503-15. DOI: 10.1056/NEJMoa2107519
58. Jastreboff AM, Kaplan LM, Frías JP, Wu Q, Du Y, Gurbuz S, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med 2023;389(6):514-26. DOI: 10.1056/NEJMoa2301972
59. UNAIDS. Understanding measures of progress towards the 95–95–95 HIV testing, treatment and viral suppression targets. 2024. Updated March 11, 2024 [Accessed on August 11, 2024]. Available from: https://www.unaids.org/sites/default/files/media_asset/progress-towards-95-95-95_es.pdf
60. Bavaro DF, Laghetti P, Poliseno M, De Gennaro N, Di Gennaro F, Saracino A. A Step Closer to the "Fourth 90": A Practical Narrative Review of Diagnosis and Management of Nutritional Issues of People Living with HIV. Diagnostics (Basel) 2021;11(11):2047. DOI: 10.3390/diagnostics11112047

Table I. Antiretroviral therapy and toxicities on adipose tissue

Fat portioning disorder	**Adipose tissue involved**	**Fat changes**	**Antiretroviral drugs**
Lipoatrophy	SAT	SAT loss	NRTI (such as AZT or d4T), NNRTI (such as EFV), PI
Lipohypertrophy	VAT	Trunk fat accumulation (buffalo hump) accompanied with mitochondrial dysfunction, dyslipidemia and insulin resistance, increased inflammation, and high risk of CVD	NRTI (such as AZT or d4T), PI

AZT: zidovudine; CVD: cardiovascular disease; d4T: stavudine; EFV: efavirenz; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside analogue reverse transcriptase inhibitor; PI: protease inhibitors; SAT: subcutaneous fat tissue; VAT: visceral fat tissue.

Table II. Weight gain with INsTI and TAF: evidences and studies

Study	**Time frame**	**Participants**	**Antiretroviral therapy evaluated**	**Key findings**
ACTG substudy A5257	96 weeks	328	ATV/r or DRV/r as two arms of PI compared with RAL as INsTI	Gain in central fat and VAT in INsTI arm ($p <$ 0.01).
Bhagwat et al., 2018	96 weeks	1809	ATV/r/TDF/FTC or DRV/r/TDF/FTC, as two arms of PI compared with RAL as INsTI	Increase in WC was greater in the group that received RAL, compared to the group that received DRV/r as PI (p < 0.005). Females experienced greater increases in WC on RAL vs ATV/r than males ($p <$ 0.01).
NEAT022 (NCT02098837)	96 weeks	420	Switching ATV/r or DRV/r) to DTG-regimen	Modest gain weight after switching PI/r (ATV/r or DRV/r) to DTG-regimen at 48 weeks.
NAMSAL ANRS (NCT02777229)	96 weeks	613	EFV/TDF/3TC compared with DTG-regimen	Increase in body weight in INsTI arm with DTG (+5.0 kg) compared with EFV group (+3.0 kg) and incidence of obesity, 12.3 % vs. 5.4 %, respectively.
ADVANCED (NCT031222	96 weeks	1053	DTG/TAF/FTC compared with	Weight gain was observed in the DTG/TAF/FTC group (+7.1 kg ± 7.4). Additional effect of TAF

62)			EFV/TDF/FTC regimen	in terms of weight gain.
Sax et al., 2021 (8 Gilead Sciences-sponsored trials)	96 weeks	5680	DTG, RAL and EVG arms	Weight gain ≥10% basal body weight at 48 week. BIC arm showed a weight gain of +4.24 kg [95 % CI, 3.71-4.78]; DTG arm showed a weight gain of +4.07 kg [95 % CI, 3.51-4.62]; compared with modest weight gain in EVG group +2.72 kg [95 % CI, 2.45-3.0].
NA-ACCORD	5 years	20000	DTG, RAL and EVG arms	RAL- and DTG-ART regimens were associated with higher weight gain (+7.2 and 5.8 kg, respectively).
Coelho et al. 2022	3 years	60000	Any INsTI	INsTI constitutes the main risk factor for development of obesity (adjusted HR, 7.12; $p <$ 0.0001).
Schafer et al. 2019	1 year	110	Switching from TDF to TAF	BMI increase in 0.45 kg/m^2; 95 % CI, 0.14-0.76

ACTG: AIDS Clinical Trials Group; ASCVD: atherosclerotic cardiovascular disease; ATV/r: atazanavir/ritonavir; BMI: body mass index; CI: confidence interval; BIC: bictegravir; DTG: dolutegravir; DRV/r: darunavir/ritonavir; EFV: efavirenz; EVG: elvitegravir; HDL: high density lipoprotein; LDL: low density lipoprotein; NA-ACCORD: North American AIDS Cohort Collaboration on Research and Design;

NCT: ClinicalTrials.gov ID; PI: protease inhibitors; RAL: raltegravir; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine; TAF: tenofovir alafenamide; WC: waist circumference diameter.

Table III. Mechanisms underlying in gain weight in PLWH under INsTI-ART

Fat tissue	Macroscopic alteration observed	Tissue outcome
VAT	Central obesity, fat expansion, or excess of VAT accumulation in intra-abdominal, pericardial, liver, and skeletal muscle depots.	VAT metabolically dysfunctional resulting in VAT fibrosis, hypertrophy, hyperplasia, and deposition of ectopic fat. Insulin resistance in adipocytes, increased risk of diabetes, cardiovascular disease, and neurocognitive impairment.
	Aging adipose tissue phenotype in VAT	Adipocyte hypertrophy leading to hypoxic environment in promoting fibrosis, adipokines disturbances (leptin increase and decrease of adiponectin), changes in adipocyte size and numbers.
SAT	SAT loss	Changes in adipocyte size and numbers, sarcopenic obesity.

SAT: subcutaneous fat tissue; VAT: visceral fat tissue.

Table IV. Anti-obesity drugs as comedications to treat fat disorders in PLWH under INsTI-ART

Anti-obesity drugs	**Names**	**Benefits**
Synthetic growth hormone-releasing hormone	Tesamorelin	Reduction of VAT (abdominal and liver fat accumulation) in PLWH under INsTI-ART, with beneficial effects on body composition and glycemic control. Approved by FDA.
GLP-1R agonist	Semaglutide Liraglutide	Highly effective for decreasing weight (-18.9 %) in PLWH at the expense of minor abdominal visceral adipose tissue (-30.8 %), and abdominal subcutaneous adipose tissue (-11.2 %). In addition, GLP-1R increase insulin secretion after a meal, suppresses appetite and gastric emptying. Approved by FDA.
Dual agonists (GLP-1-GIP or GLP-1R/GCGRA)	Tirzepatide Survodutide	Potent weight lowering efficacy. Only tirzepatide has been approved by FDA in 2023.
Triple agonists (GIP/GLP-1/GCGRA)	Retatrutide	Acts as a triple-agonist targeting three receptors: GIP, GLP-1, and glucagon. In adults with obesity, retatrutide treatment for 48 weeks resulted in substantial reductions in body weight. Currently investigated in phase II clinical trial, in participants with obesity no-HIV. Not approved by FDA.

GIP: glucose-dependent insulinotropic polypeptide; GLP1R: glucagon-like peptide-1 receptor agonists; GCGRA: glucagon receptor agonist; PLWH: people living with HIV; SAT: subcutaneous fat tissue; VAT: visceral fat tissue.