Chapter

HIV Treatment and Obesity: What's New?

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Abstract

Obesity among people living with human immunodeficiency virus (people living with human immunodeficiency virus (HIV) (PLWH)) is an emerging public health issue. In recent years, new drugs have been approved for the treatment of HIV infection, which have greatly extended the lives of patients, but they may also play a role in rising obesity rates. In addition to HIV-specific factors, traditional risk factors shared with the general population (aging, diet, inactivity, and genetics) are credible culprits for this pandemic. Importantly, the compounded presence of obesity and HIV infection seems to magnify the risk of metabolic disease. To date, several questions remain to be fully elucidated including the mechanisms by which antiretroviral drugs may lead to excessive weight gain, the influence of the interplay with environmental and genetic factors, and the long-term clinical effect of obesity in PLWH. Recently, new drugs for the treatment of obesity and new metabolic surgeries have emerged, shading new hope on obesity management. The aim of this chapter is to take a journey into the world of obesity, showing the most recent evidence in HIV patients.

Keywords: obesity, human immunodeficiency virus (HIV), antiretroviral therapy, anti-obesity treatments, metabolic surgery

1. Introduction

Infection with the human immunodeficiency virus (HIV) was once a debilitating and ultimately fatal condition. With the advent of highly active antiretroviral therapy (HAART), posteriorly renamed combined antiretroviral therapy (cART), the course of the disease has rapidly changed. HIV is now considered a chronic and manageable condition with a significant improvement in life expectancy, meaning that individuals infected with HIV are at risk of the same comorbidities as an aging population without HIV may suffer, including obesity and its related metabolic dysfunction and cardiovascular disorders [1, 2]. Furthermore, people living with HIV (PLWH) face additional problems as HIV itself is an independent risk factor for metabolic and cardiac disorders, and modern cART regimens may promote excessive weight gain in some HIV-infected patients [3].

Obesity is one of the greatest pandemics of the twenty-first century, and since 1980, its prevalence has doubled in more than 70 countries. Over 600 million adults were obese in 2015, with a high body mass index (BMI) accounting for approximately 4 million deaths worldwide and several years of lost lifespan [4, 5].

Obesity is a chronic, complex, heterogeneous, and relapsing disease that remains a global health concern, associated with an increased risk of multiple conditions [6].

In HIV-infected patients, the presence of obesity may potentially increase the risk of morbidity and mortality. Hence, it is crucial to promptly act to prevent and/or treat obesity in PLWH, paying special attention to the potential impact of antiretroviral therapy on weight gain [7].

The treatment of obesity is challenging and frequently requires a multidisciplinary approach including lifestyle modifications, behavioral therapy, pharmacotherapy, and/or bariatric surgery. In recent years, new drugs have been approved (with others underway) that are revolutionizing the way obesity is treated and will be treated in the near future [8].

Much of the knowledge about pharmacological obesity treatment is extrapolated from studies in people without HIV, but a growing body of research has come to light in recent years regarding nonpharmacological and pharmacological treatment and bariatric surgery in HIV-infected patients [9, 10].

The aim of this chapter is to provide an overview of the pathophysiology, impact, and management of obesity in the context of HIV infection, highlighting the most recent advances on the field.

2. Pathophysiology of obesity in people living with HIV

Following the widespread trend of rising obesity rates and thanks to the undisputable success of cART in prolonging the life expectancy of PLWH, obesity in PLWH is also becoming an emerging public health challenge. In recent years, the prevalence of obesity among PLWH in high-income countries has risen and is now estimated to be 12.5–34% [7, 11, 12]; the same trend is found in low-middle-income countries [13, 14].

Obesity is associated with increased adipose tissue, a special connective tissue containing adipocytes and several other types of cells, surrounded by capillary and innervation networks that function together as an integrated unit. In addition to the classical functions attributed to adipose tissue such as lipid storage, thermal activity, and mechanical insulation, this tissue is also now recognized as a multifunctional and metabolically active immune and endocrine organ, directly modulating many processes including energy balance and metabolism [15].

In obesity, dysfunctional adipocytes and resident-immune cells, particularly T cells and macrophages, display distinct biochemical properties with a pro-inflammatory profile and altered secretion of adipokines and lipokines, thereby creating and perpetuating a state of chronic inflammation, which contributes to the development of comorbidities such as insulin resistance and type 2 diabetes mellitus (T2DM), atherosclerosis, and nonalcoholic fatty liver disease (nonalcoholic steatohepatitis NASH) [16]. Among PLWH, a high BMI has also been shown to magnify the risk of metabolic disease and neurocognitive impairment [17–19]. In fact, HIV-infected patients are a particularly high-risk group, as HIV infection per se, even when treated, induces a state of chronic inflammation and immune activation that contributes to the development of metabolic disease [20]. Accordingly, HIV and obesity seem to act synergistically enhancing the risk of T2DM, as demonstrated in a study that included 7177 HIV-positive American veterans in which a 5-pound gain was associated with a 14% increased risk for diabetes in HIV-infected compared with only 8% in the general population [21].

The anatomical distribution of fat also influences its pro-inflammatory properties. Depending on where it is localized, adipose tissue can be classified as subcutaneous,

with peripheral distribution, or visceral adipose tissue, mainly present in the mesentery and omentum. Clinically, visceral adipose tissue may be evaluated by measures such as increased waist circumference or waist-to-hip ratio, as well as elevated intra-abdominal fat area in cross-sectional abdominal imaging. Visceral adipose tissue has distinct physiological and prognostic differences in comparison with subcutaneous fat, being more cellular, vascular, innervated, and containing a higher number of inflammatory and immune cells [22]. In accordance with these features, visceral adipose tissue is strongly associated with increased cardiometabolic risk and carries a greater prediction of mortality than subcutaneous adipose tissue.

In fact, evidence suggests that the quantity of visceral fat may dictate whether an individual has a "metabolically healthy obesity" (obesity without overt metabolic disease) or a metabolically unhealthy obesity (with metabolic syndrome) [15]. This also seems to hold true in PLWH. In a study that included 580 HIV-infected patients, the proportion of "metabolically unhealthy" patients (patients with metabolic syndrome) was higher among patients with excessive weight and central obesity, with those patients presenting a higher cardiovascular risk [23]. This highlights the importance of addressing obesity and its phenotype (visceral adipose tissue vs. subcutaneous adipose tissue) in patients with HIV, when evaluating cardiometabolic risk [23].

Despite many years of research, the etiopathogenesis of obesity remains to be completely elucidated. Although simple in its most basic principle—it results from an energetic imbalance in which the caloric intake exceeds ongoing energy expenditure—growing evidence indicates that obesity pathogenesis involves processes far more complex than the passive accumulation of excess calories [24]. Many elements influence this equation including genetic, behavioral, and environmental factors, the sleep-wake cycle, hormonal changes, intestinal microbiota, stress, endocrine diseases, and drugs [25]. Besides the antiretroviral agents, many other drugs are also associated with weight gain including antidiabetic agents (insulin, meglitinides, sulfonylureas, and thiazolidinediones), neurologic agents (anticonvulsants, lithium), psychiatric agents [selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics, monoamine oxidase inhibitors (MAOIs), and phenothiazines], and other agents (α-adrenergic blockers, antihistamines, β-adrenergic blockers, centrally acting agents, corticosteroids, and hormonal contraceptives) [26].

Sedentary lifestyle, influences of cultural dietary practices, and lack of education or resources regarding proper nutrition are primary drivers for significant weight gain [10]. In addition to quantity, diet quality also determines the obesogenic effects of foods and affects metabolic health through diverse biological pathways [27]. In this regard, increasing attention is being paid to food insecurity and its role in obesity.

3. Food insecurity in PLWH

Food insecurity is defined as having limited or uncertain access to nutritionally adequate and safe foods to maintain a healthy life [28].

Likely a consequence of the socioeconomic challenges that many HIV-infected patients experience, PLWH are disproportionately affected by food insecurity with studies suggesting that up to half of PLWH in urban areas of North America experience food insecurity [29].

Food insecurity is a known risk factor for obesity in both PLWH and HIV-uninfected people [30] and is a major determinant of poor nutrition; PLWH with food insecurity can have a similar caloric intake as people with food security, but of

poorer quality based on nutrient-poor, energy-dense food [31–33]. Very low food security has been associated with more frequent frailty among women, independently of HIV serostatus and has been implicated in worse clinical outcomes in PLWH, the reason why it should be part of the assessment in PLWH and obesity [33].

In conclusion, obesity is an emerging comorbidity in PLWH with important metabolic consequences. Several factors are implicated, many of which are shared with HIV-uninfected patients, such as diet and sedentarism. However, PLWH face the additional burden of obesity-promoting HIV-specific factors, notably the overlapping immune activation arising from chronic HIV infection and exposure to antiretroviral therapy (ART).

4. The new era of antiretroviral therapy: integrase inhibitors

In the early days of the HIV epidemic and cART, weight gain in PLWH, particularly in those with low CD4 count and high HIV RNA, was attributed to the reversal of the catabolic state of HIV infection and was associated with improved survival and immunologic recovery, and therefore was considered a "return to health" [34]. Back in those days, the major concern regarding fat alterations was lipodystrophy, characterized by subcutaneous fat loss (lipoatrophy) with or without central fat accumulation. Lipodystrophy was a frequent condition among PLWH receiving combination antiretroviral therapy containing older-generation thymidine analog nucleoside reverse transcriptase inhibitors (NRTIs) and early protease inhibitors (PIs) [35]. In the last 20 years, however, the scenario has changed. Greatly thanks to an earlier diagnosis and highly effective newer generation cART, wasting syndrome and lipodystrophy have become much rarer. Instead, weight gain and obesity are becoming the greatest concern as evidence coming from a multitude of studies show that the median BMI and prevalence of baseline obesity among PLWH initiating cART have been steadily increasing, with most of the patients having normal or high BMI [36]. Moreover, following cART initiation many individuals gain an excessive amount of weight, leading to posttreatment obesity. In a study by Tate and colleagues in 2012, 20% of PLWH had moved to a more deleterious BMI category (from normal to overweight/obese or overweight to obese BMI categories) after 24 months on cART, with greater BMI increases observed for those on a boosted protease inhibitor (PI) regimen [37].

In line with these results, the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study that included over 14,000 individuals showed that after 3 years on cART, 22% of individuals with a normal BMI at baseline had become overweight (BMI 25–29.9 kg/m^2) and 18% of those overweight at baseline had become obese (BMI >30 kg/m^2). The weight gain was largest for women and, for White women greater than age-matched population control [36].

The same phenomenon seems to be replicated and aggravated with newer ART regimens as accumulating evidence suggests that therapies including new generation integrase strand transfer inhibitors (INSTIs) cause more weight gain and treatment-emergent obesity than other ART regimens [38–41].

The first INSTI approved by the U.S. Food and Drug Administration (FDA) was raltegravir in 2007, followed by approval of five other drugs: raltegravir, elvitegravir, cabotegravir, dolutegravir, and bictegravir. Since 2017, acknowledging the good tolerability profile and (for the latter two), a substantial genetic barrier to drug resistance, the INSTI integrate the preferred combination of antiretroviral drugs for initial therapy (consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) and an INSTI) [42].

From 2006 to 2019, the Women's Interagency HIV Study enrolled a geographically and racially diverse sample of 1458 women living HIV and on ART. In this relevant sample, the switch from non-INSTI regimens to INSTIs and/or tenofovir alafenamide (TAF) was associated with significant short-term body weight and BMI gains [43]. Additionally, results from five randomized studies support the association between the use of INSTIs and increases in weight (two studies evaluated raltegravir and three evaluated dolutegravir) [44].

The statistically significant increases in body weight and clinical obesity with INSTIs appear to be most pronounced in Black individuals and women, suggesting the presence of vulnerable subgroups. The effect of cART drugs on weight gain is heterogeneous and differences clearly exist among various INSTIs and NRTI backbones; in particular, evidence suggests that tenofovir alafenamide (TAF) potentially enhances the weight gain effect and that the use of tenofovir disoproxil fumarate (TDF) seems to lessen these effects [44]. In what respects INSTIs and dolutegravir appear to have the greatest effect, while elvitegravir may have minimal effect. Evidence on cabotegravir, the newest integrase inhibitor, is limited [45]. Novel treatments such as the next-generation NNRTI doravirine could offer a suitable alternative therapy, with current evidence showing efficacy and limited effect on weight gain [39].

Still, data on this topic are inconsistent, and more randomized studies accounting for diet and lifestyle factors, such as smoking, are needed. It remains unclear whether INSTI-based regimens also contribute to visceral adiposity or intensification of the cardiometabolic risk [46].

The mechanisms driving weight gain following cART remain largely unknown and certainly override the traditional concept of "return to health." Proposed mechanisms include improved tolerability, direct impact on adipogenesis, and gut microbiome disturbance [39, 45]. Alterations in the composition and function of the intestinal microbiome seem to precede weight gain and may promote obesity through increased bowel permeability, increased fermentation and absorption of dietary polysaccharides, and even through modulation of genes regulating lipogenesis and insulin resistance [47].

Furthermore, *in vitro* studies have shown that dolutegravir inhibits the binding of radiolabeled α-melanocyte-stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) [48]. Since MC4R is involved in the regulation of energy homeostasis and food intake, and deficiency in MC4R is associated with monogenic obesity, increased appetite caused by dolutegravir could contribute to the observed changes [49].

5. Treatment of obesity

Many strategies can be effective in inducing weight loss in people with obesity, including low-calorie diets, exercise-based interventions, pharmacological treatments, and surgery, either separately or in combination [50]. Besides the beneficial impact on weight, these interventions also lead to enhanced quality of life in addition to improvement in glycemic and lipid control, particularly for those who lose more than 10% of their baseline weight [50, 51]. However, how weight loss exactly affects adipose tissue physiology and obesity-related systemic inflammation as well as its long-term implications in terms of mortality and life expectancy remain to be fully clarified [52].

In PLWH specifically, obesity treatment remains largely unaddressed and little research has yet tested the efficacy of these weight loss programs and whether the benefits translate to this population.

Understanding the multifactorial nature of obesity is essential for better informing its management [38].

6. Nonpharmacological treatment

When determining the optimal weight-loss strategy for individuals living with HIV (PLWH), several factors should be considered.

Lifestyle interventions are crucial in addressing obesity and typically encompass a combination of dietary modifications, physical activity, and behavioral strategies. Caloric restriction should be contemplated as the primary element in weight-loss interventions. Additionally, aerobic exercise and resistance training are recommended for all individuals [53]. Behavioral interventions also play a pivotal role in obesity management; strategies, such as self-monitoring, goal-setting, stress management, and social support systems, can enhance adherence to lifestyle changes and improve long-term outcomes [54].

The optimal lifestyle approach for weight loss in PLWH has not yet been defined. For example, multiple interventions, such as low-fat, Mediterranean, or micronutrient-supplemented nutrition, combined with behavioral interventions, have shown modest improvements in blood pressure, metabolic parameters, immune activation, and favorable gut microbiota changes [55–59]. However, these studies were mainly designed to target cardiovascular factors and/or lipodystrophy rather than on weight loss and its long-term maintenance.

In general, when studied in those without HIV, the effect of different dietary macronutrient patterns (carbohydrate reduction, fat reduction, and moderate macronutrients) and popular named diet programs on weight loss has found small differences of limited clinical significance [60]. Although a recent meta-analysis showed that most macronutrient diets lead to modest weight reductions and substantial improvements in blood pressure and lipids over 6 months, the effects were not sustained [61]. On the other hand, higher intakes of protein and fiber, as well as lower glycemic load diets, seem to contribute to weight maintenance by increasing satiety [62]. The Mediterranean diet has been shown to improve metabolic parameters, immune activation, regulatory T-cell (Treg) function, and the composition of the gut microbiota in HIV-1-infected individuals. Furthermore, the Mediterranean diet has been associated with increased abundances of *Bifidobacterium* after the intervention, which is linked to a beneficial profile [58]. Data are still lacking regarding the effects of intermittent fasting regimens in PLWH with obesity and directed clinical trials are warranted [63].

When addressing obesity, it is crucial to set a realistic and meaningful weight goal. People can lose weight on any dietary plan as long as a total caloric deficit is achieved. The choice of a dietary approach should be individualized, but typically, a deficit of at least 500 kcal per day can lead to a loss of 0.5–1.0 kg per week. Sustained weight loss of as little as 3–5% of body weight can result in clinically meaningful reductions in specific risk factors associated with cardiovascular disease (CVD) [64]. Moreover, moderate diet-induced weight loss (6–8%) has been shown to improve metabolic function in people with HIV, obesity, and insulin resistance [65].

7. Physical activity and exercise training

Compared to adults without HIV but with other chronic diseases, PLWH generally tend to be less physically active [66], which may contribute to weight gain. Studies

investigating the benefits of combined aerobic and resistance exercise training in PLWH have consistently shown (despite the relatively small sample sizes and short intervention duration) physiological improvements, including lower BMI, waist circumference, improved lipid profile, and enhanced cardiorespiratory fitness [67]. Additionally, exercise has been associated with reduced distress, lower levels of depression, and improved neurocognitive function [68–71].

As a principle, PLHW should follow the general guidelines that recommend engaging in 30 min or more of moderate-intensity physical activity most days of the week for weight loss and maintenance, with the goal of achieving a minimum of 150 min per week [64, 67]. Resistance training should also be incorporated into the regimen, preferably performed 2 to 3 times per week [53]. Furthermore, periodization of exercise, which involves manipulating the volume, intensity, and recovery between exercises, has also demonstrated better results than nonperiodized training in PLWH [72] and can be considered.

In conclusion, exercise training is considered safe and beneficial for medically stable adults living with HIV and should be part of the recommendations [68].

8. Metabolic adaptation

Why do people who follow a diet plan not continue to lose weight? And why is weight regain so common? The answer lies in metabolic adaptation.

Metabolic adaptation occurs during weight loss and involves an increase in hunger as a result of elevated levels of the orexigenic hormone ghrelin and decreased levels of anorexigenic hormones. Simultaneously, energy requirements decrease, thereby creating what is known as the "energy gap" [62]. The decrease in total daily energy expenditure that occurs during weight loss results from many contributors such as a decrease in circulating leptin levels, a reduction in resting metabolic rate, a diminished thermic effect of food, and increased energy efficiency during daily activities [62]. Further investigation is required to identify effective strategies for narrowing the energy gap and reducing weight regain. Nevertheless, factors related to long-term weight loss maintenance have been recognized and include increased protein and dietary fiber intake, consuming diets with lower glycemic loads, and high levels of physical activity. Maintaining a high-energy flux state, characterized by a significant daily energy expenditure that matches energy intake, may help mitigate reductions in resting metabolic rate and may facilitate a more precise regulation of energy intake to align with daily energy expenditure [62].

9. Pharmacological treatment of obesity

Limited information is available regarding the safety and effectiveness of weight-loss medications in PLWH since they are often excluded from clinical trials and not adequately reported. However, the efficacy of treatment is likely to be similar to that in the general population, although potential interactions with antiretroviral therapy need to be considered. Notably, there are theoretical and documented drug-drug interactions between anti-obesity pharmacotherapy and antiretroviral therapy [10]. Therefore, healthcare providers must acknowledge the potential hazard of impaired control over HIV viremia when specific weight-loss medications are administered concurrently with antiretroviral therapy [10].

Glucagon-like peptide 1 (GLP-1) receptor agonists have demonstrated promising results in managing obesity in individuals without HIV, and studies investigating their effectiveness in PLWH are currently underway.

Further research is needed to optimize the selection of ART and the combined use of weight loss medications, when indicated [38].

10. Orlistat

Orlistat is the sole anti-obesity drug approved by the FDA and European Medicines Agency (EMA) available both as a prescription medication and an over-the-counter (OTC) product. This accessibility allows widespread public use without close medical supervision [10].

Orlistat induces weight loss by reversibly inhibiting the activity of the enzyme lipase and consequently blocking the hydrolysis of triglycerides into absorbable fatty acids and monoglycerides. Hence, orlistat acts mainly via its local effect, directly reducing the absorption of dietary fat by around 30% [10]. Systemic exposure is minimal as it is primarily metabolized within the gastrointestinal wall and mostly undergoes fecal elimination. While orlistat does not interfere with the activity or elimination of other drugs through conventional mechanisms, it can potentially interact with other medications due to its impact on absorption [10, 73].

The impact of orlistat on weight loss, weight maintenance, cardiovascular disease risk, and glycemic control has undergone thorough investigation among overweight individuals, including those with and without T2DM. In the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, participants who received orlistat, in addition to lifestyle changes, experienced an average weight change of 5.8 kg throughout the study duration, compared to a mean weight change of 3 kg in the lifestyle plus placebo group ($p < 0.001$). Furthermore, orlistat therapy reduced the incidence of T2DM beyond the result obtained with lifestyle changes only, an effect particularly evident in patients with impaired glucose tolerance at baseline [74]. Notably, while clinical trials have not explicitly excluded individuals with HIV infection, there is a lack of data specifically documenting outcomes in this particular population. [10].

Regarding the safety of orlistat use in PLWH, multiple case reports have linked the initiation of this weight-loss agent to loss of HIV viremia control [10].

In general, drugs classified as Class II according to the Biopharmaceutics Drug Disposition Classification System (BDDCS), characterized by extensive metabolism, low water solubility, and high lipid permeability, are prone to significant alterations when-coadministered with orlistat, potentially resulting in unfavorable outcomes [10].

Significantly, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INSTIs) are classified as BDDCS Class II drugs, which imply that coadministration with orlistat is likely to result in reduced drug absorption [10]. Furthermore, NRTis, such as zidovudine, abacavir, and TDF, although belonging to different BDDCS classes, are generally acknowledged to possess lipophilic properties [75–77], hence enhancing the probability of potential interferences. Considering the significant risk associated with compromised control of HIV viremia, the absence of efficacy data in HIV patients, and the availability of alternative weight-loss agents suitable for PLWH, orlistat is generally not recommended in all HIV patients currently taking cART. Given the over-the-counter (OTC) availability of orlistat, it is critical that PLWH on cART are properly advised to consult their health-care provider before independently initiating any weight-loss medication [10].

11. Naltrexone-bupropion

Naltrexone-bupropion is a combination regimen that consists of an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion). The use of bupropion in combination with naltrexone is believed to help regulate food intake by leveraging their individual effects on the mesolimbic dopamine circuit and hypothalamus, respectively.

In phase 3 trials, such as Contrave Obesity Research-I (COR-I), Contrave Obesity Research-II (COR-II), Contrave Obesity Research-Intensive Behavior Modification (COR-BMOD), and Contrave Obesity Research-Diabetes study (COR-Diabetes), the administration of naltrexone-bupropion demonstrated significant weight reduction compared to placebo [78–81]. Using a modified intent-to-treat analysis, these trials reported average weight losses of approximately 4.7, 5.9, 4.2, and 3.4 kg, respectively, surpassing the outcomes observed with placebo [82]. However, it is important to note that these trials did not include individuals with HIV [10].

Naltrexone and its major active metabolite, 6-β-naltrexol, undergo minimal metabolism by cytochrome P450 (CYP) enzymes and do not exhibit significant inhibition or induction capabilities. Both the parent compound and metabolite are primarily eliminated through renal excretion, with average elimination half-lives of 4 and 13 h, respectively [83].

In contrast, bupropion undergoes extensive hepatic metabolism via cytochrome P450 2B6 (CYP 2B6) to hydroxybupropion, while non-CYP-mediated pathways contribute to the production of erythrohydrobupropion and threohydrobupropion. Bupropion has an average half-life of 21 h, whereas its metabolites exhibit extended half-life in comparison with the parent compound [10].

Based on the pharmacokinetics of bupropion, multiple drug-drug interactions can be recognized or anticipated. Importantly, antiretroviral agents, such as ritonavir and certain NNRTIs, are known inducers of CYP2B6, which may potentially interfere with bupropion concentration. However, at present, no dose adjustments are recommended based on the current understanding of this interaction.

Still, for healthcare providers considering the initiation of naltrexone-bupropion in PLWH, increased monitoring of bupropion is recommended when coadministration with ritonavir-boosted PIs, efavirenz, nevirapine, or any regimen containing cobicistat is planned. Periodic monitorization should include evaluating the efficacy of weight loss, assessing the occurrence of neuropsychiatric events and suicidal behavior and ideation, and evaluating blood pressure, heart rate, and renal and hepatic function. In the event of negative changes in mood or behavior, irrespective of the HIV status or antiretroviral regimen, it is recommended to promptly initiate a tapering process and discontinue the use of naltrexone-buproprion for all patients [10].

12. Liraglutide

Liraglutide is a GLP-1 receptor analog primarily designed for treating T2DM. It is administered via subcutaneous injection and is highly bound to human serum albumin, with more than 99% binding *in vitro*. Liraglutide promotes weight loss by slowing gastric emptying and inducing early satiety [84, 85].

The efficacy of liraglutide for weight loss in patients without T2DM was evaluated in the Satiety and Clinical Adiposity–Liraglutide Evidence (SCALE) randomized controlled clinical trial. In this study, 3.0 mg of liraglutide in addition to diet and

exercise was associated with a significant reduction in body weight (mean weight change of 8.4 kg compared to a mean weight change of 2.8 kg with placebo, at week 56 of treatment) [86]. However, individuals living with HIV were not eligible for enrollment in this trial. Other studies, primarily conducted to address liraglutide efficacy in treating T2DM although not explicitly excluding PLWH, have not conducted specific subgroup analysis on this patient population [10]. Nevertheless, based on what it is currently known, there is no reason to expect the benefits of liraglutide therapy in PLWH to differ from the general population.

Liraglutide undergoes rapid clearance by the kidneys through metabolism by endogenous dipeptidyl peptidase IV (DPP-IV) and endopeptidases [87]. As it undergoes a metabolism pathway independent of CYP, the potential for drug-drug interactions is greatly reduced, simplifying its use in individuals receiving cART. Nonetheless, concerns have been raised regarding interactions between liraglutide and antiretroviral agents that necessitate an acidic gastric environment for proper absorption, due to the known inhibitory effect of the natural GLP-1 hormone on gastric secretion. However, an evaluation of individuals at steady state using liraglutide 1.8 mg compared to placebo reported no statistically or clinically significant differences in gastric pH [88]. Liraglutide was also found to have minimal impact on the gastric absorption of concomitant medications from various Biopharmaceutics Drug Disposition Classification System (BDDCS) classes [88].

Overall, liraglutide is regarded as a viable choice for promoting weight loss in PLWH [10].

13. Semaglutide and tirzepatide

Semaglutide, also a GLP-1 receptor agonist, and tirzepatide, a dual GLP-1/gastric inhibitory peptide (GIP) agonist, are both promising options for weight management.

In the STEP 1 trial, individuals treated with semaglutide achieved an average weight loss of almost 15% from baseline (compared to 2.4% with placebo), and nearly 70% of participants experienced more than a 10% reduction in weight (compared to 10% with placebo) [89]. Recent evidence suggests that tirzepatide demonstrates similar or possibly even superior efficacy compared to semaglutide for weight management [90, 91]. Currently, there are two ongoing clinical trials assessing the safety and efficacy of semaglutide in individuals living with HIV (PWH) who also have obesity, with a focus on weight loss achieved through a combination of semaglutide treatment and diet and exercise interventions. These trials aim to evaluate the effectiveness of semaglutide specifically in PWH and its potential impact on weight reduction compared to diet and exercise alone [92], and its effects on ectopic fat, insulin resistance, inflammation markers, and cardiovascular risk [93].

Importantly, despite the lack of substantial data regarding the impact of GLP-1 receptor analogs on weight-loss in PLWH, initial observational studies indicate that treatment of patients with both HIV infection and T2DM using GLP-1 receptor analogs may provide a protective effect against major adverse cardiovascular events such as myocardial infarction and acute heart failure [94].

Regarding weight-loss drugs currently available in Europe, the majority of drugs are generally considered safe for PLWH undergoing cART, except for orlistat. When planning to start pharmacological treatment for obesity, clinicians should contemplate each agent's specific characteristics, counseling points, and monitoring parameters that necessitate assessment when used in conjunction with cART.

In conclusion, obesity in PLWH should be addressed using a similar approach employed to the general population. Healthcare providers should consider incorporating most of the currently approved weight-loss agents as adjuncts to adequate lifestyle modifications [10].

14. New hopes in the treatment of obesity

Several upcoming drugs promise to revolutionize the treatment of obesity by combining different incretin pathways. Retatrutide (LY3437943), a triple agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors, seems of special interest due to the substantial reduction in body weight observed in its Phase 2 trial [95].

Similarly, the coadministration of cagrilintide—a long-acting amylin analogue—and semaglutide (CagriSema), resulted in clinically relevant improvements in glycemic control and significantly greater weight loss versus semaglutide in people with T2DM [96, 97].

Finally, orforglipron, a nonpeptide GLP-1 receptor agonist given as an once-daily oral therapy, has also shown to lead to substantial weight reduction in adults with obesity without T2M [98]. Phase 3 trials are currently underway for all these new promising drugs. Their role in obesity treatment in PLWH remains to be clarified.

15. Bariatric or metabolic surgery

Bariatric surgery is gaining popularity as an effective surgical intervention for addressing severe obesity and metabolic dysregulation in cases where lifestyle modifications are insufficient to attaining weight-related objectives [99]. Bariatric surgery may be a suitable option for patients with a BMI of 40 kg/m^2 or greater, or a BMI of 35 kg/m^2 or greater with one or more severe obesity-related comorbidities [53]. Given the rising prevalence of obesity in PLWH, bariatric surgery is increasingly being used among PLWH [45].

The American Society for Metabolic and Bariatric Surgery recommends laparoscopic approaches, such as Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding, and biliopancreatic diversion/duodenal switch, as preferred methods compared to over open bariatric procedures [99].

There is limited literature available on the efficacy of bariatric surgery in HIV-infected individuals and no large-scale or randomized clinical trials have been conducted in this patient population. However, existing literature suggest that patients with HIV are likely to share the same benefits in terms of weight loss and resolution of obesity-associated comorbidities to those without HIV. Also, data concerning HIV-related outcomes and pharmacokinetics of cART following bariatric surgery remain scarce and, as a result, there are no specific guidelines for managing HIV-infected individuals after bariatric surgery.

Understandably, factors specific to these patients, such as viral load, CD4 cell counts, absorption of antiretroviral therapy, and other medications, are important outcomes to consider [9].

Patients who undergo bariatric surgery experience significant anatomical and physiological alterations, including changes in gastric volume, acidity, gastrointestinal emptying time, enterohepatic circulation, and delayed entry of bile acids [45].

Additionally, they will have to undertake a specific diet plan, may receive instructions to crush oral medications, and may be prescribed postoperative acid-suppressing agents and vitamin supplements. These alterations can affect different aspects of antiretroviral absorption and pharmacokinetics. Some antiretrovirals with specific characteristics, such as requiring an acidic environment, administration with fatty meals, longer intestinal exposure, and enterohepatic recirculation for absorption, may be more impacted by bariatric surgery interventions [45]. Additionally, certain antiretrovirals can interact with polyvalent cations in supplements or drugs that inhibit gastric acid.

In this context, healthcare providers need to carefully evaluate the patient's antiretroviral medications taking into consideration factors such as the absorption site of the antiretrovirals, their compatibility with being crushed, the need for administration with food, and any contraindications or drug interactions with acid-suppressing agents or supplements [99].

Predicting pharmacokinetics based solely on drug characteristics has proven to be challenging, underscoring the importance of pharmacokinetic studies in this specific population [45]. Still, dolutegravir, darunavir, and most NRTIs seem appropriate drug options postbariatric surgery [45] and despite these concerns regarding drug absorption after bariatric surgery, so far, there is no evidence suggesting a significant impact on markers of HIV disease progression, such as CD4 count and viral load, for both sleeve gastrectomy and Roux-en-Y gastric bypass [9, 100, 101].

Finally, recent research has demonstrated that bariatric surgery induces an immediate and enduring modification of the gut microbiota, which is independent of the surgical procedure itself [102]. It has been suggested that changes in the gut microbiome can influence the pharmacokinetics of certain antiretrovirals, such as abacavir and dolutegravir [103]. Gut microbiota alterations can lead to increased levels of s-glucuronidase enzymes in the gut environment, potently increasing the regeneration of active forms of these drugs and resulting in higher exposure concentrations [104]. However, it is important to interpret these data with caution, as the gut microbiome is influenced by multiple interfering factors such as diet, antibiotic use, and demographic parameters, possibly introducing different biases.

In conclusion, bariatric surgery is a viable option for selected patients with obesity, considering its success in driving weight loss without significantly interfering with cART-induced viral suppression. Nevertheless, the potential impact of perioperative changes in diet, supplements, and medications on antiretroviral regimens must always be carefully considered and close surveillance should be maintained [99].

16. Conclusions

Obesity in individuals with HIV is an emergent and complex issue with various contributing factors, many of which are still not fully understood. While research on weight gain and obesity in people living with HIV has increased in recent years, much of the knowledge is based on studies conducted in individuals without HIV.

The increasing rates of obesity among PLWH are most likely multifactorial, resulting from the compounded effect of exposure to the obesogenic environment we currently live in and its associated traditional risk factors (e.g., inactivity, diet, and genetics) and HIV-specific factors including HIV-associated systemic inflammation/immune dysregulation and direct cART effects, most particularly with the use of integrase strand transfer inhibitors.

Importantly, weight gain in PLWH confers a greater risk of metabolic disease compared with HIV-negative individuals, highlighting the need to properly prevent and/or manage obesity in this population.

To improve the care of the growing population of people aging with HIV, it is crucial to better understand the mechanisms and clinical implications of cART-mediated weight gain and obesity.

Prospective clinical trials and further research are needed to optimize ART selection, explore the use of weight loss medications, and determine the efficacy and safety of metabolic surgeries. A multidisciplinary approach involving a team of surgeons, endocrinologists, nutritionists, psychologists, HIV providers, and clinical pharmacists is necessary to effectively prevent and treat obesity in people living with HIV.

The coordination and collaboration of interdisciplinary healthcare professionals are essential to ensure optimal outcomes for this unique patient population.

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