Weight Gain in People With Treated HIV

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Panel's Recommendations and Key Considerations
• All people with HIV should receive antiretroviral therapy (ART) to reduce morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI).** • Weight gain after ART initiation is common. ART initiation should not be delayed because of concerns for weight gain **(AIII),** and ART should not be interrupted or discontinued because of weight gain **(AIII).** • ART selection, whether for initiation or switch, should be based on optimization of virologic suppression. Specific antiretrovirals should not be selected to prevent or reduce weight gain **(AII),** as available evidence suggests this strategy is ineffective. • Providers should include weight monitoring in conjunction with counseling on strategies for weight control as part of comprehensive care for people with HIV.
Rating of Recommendations: *A = Strong; B = Moderate; C = Weak* ***Rating of Evidence:*** *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Introduction

Weight gain is an increasingly recognized and now expected consequence of antiretroviral therapy (ART) initiation in many people with HIV. Although the mechanisms of weight gain after ART initiation remain unclear, the pathogenesis is complex and multifactorial.[1,2]

Historically, weight gain following ART initiation was thought to be related to a "return to health" phenomenon, given that early in the HIV epidemic, many people suffered from AIDS-wasting syndrome before receiving lifesaving ART. Although "return to health" may explain some weight gain for people with advanced HIV, weight gain occurs regardless of the time between HIV acquisition and ART initiation, including among people who initiate ART shortly after HIV seroconversion.[3-5] Similarly, weight gain with ART initiation occurs with most modern regimens and regardless of baseline body mass index (BMI).[6-9]

People with HIV on ART may experience greater weight gain than the expected age-related changes in people without HIV.[10] The greatest weight gain often occurs within the first 2 years after ART initiation. Notably, pooled data from eight randomized controlled trials suggest that approximately 13% of people with HIV experience excessive (>10%) weight gain within the first year of ART initiation.[11] The average weight gain trajectory frequently slows after 2 years on ART.[10,11] Overall, studies differ on the amount of weight gain seen in people with HIV, depending on the ART regimen and study population.

Weight gain among people with HIV is further complicated by the obesity epidemic in the general population in the United States.[10,12] Importantly, some people with HIV experience a differential weight gain after ART initiation, with increased central fat and/or visceral fat gain, generally termed "lipohypertrophy."[2] Generalized weight gain and obesity can obscure the diagnosis of HIV-associated lipohypertrophy, which can carry additional cardiometabolic risk. Yet, no clear definition or consensus exists to distinguish HIV-associated lipohypertrophy from generalized weight gain following ART or from weight gain unrelated to HIV.

Although weight gain after ART initiation is common, the lack of a clear understanding of its pathogenesis has limited the development of HIV-specific prevention and/or treatment guidance. Thus, what follows is a synopsis of contributors to weight gain in people with HIV and general management considerations, based on available data.

Contributors to Weight Gain

Antiretroviral Therapy

Because weight gain is common with almost all ART regimens, antiretrovirals (ARVs) have been implicated as contributors to weight gain in people with HIV, although data on the mechanisms of ART-induced weight gain are limited. The differential effects observed between ART classes, as well as within-class variability, suggest the possibility of multiple mechanisms by which ARVs contribute to weight gain.

Contemporary Antiretroviral Drugs

Weight gain occurs with nearly all ART regimens, although some are associated with more weight gain than others. For example, the least weight gain occurs with some non-nucleotide reverse transcriptase inhibitor (NNRTI)–based and tenofovir disoproxil fumarate (TDF)–based regimens.[6-9] Weight gain is most pronounced with integrase strand transfer inhibitors (INSTIs), especially bictegravir and dolutegravir, and the nucleotide reverse transcriptase inhibitor (NRTI) tenofovir alafenamide (TAF),[11,13] especially when compared to protease inhibitors (PIs) and older NRTIs.[6,11,13-19] The reasons for differential weight gain among ARVs are unknown. Importantly, differences in weight changes between ART regimens that are described in switch studies may be explained either by a weight-gain effect from exposure to a specific ARV (e.g., INSTI or TAF) and/or the removal of a weight-reduction effect from the ARV(s) that was discontinued (e.g., efavirenz or TDF). Some experts have suggested that medication side effects and/or unknown factors limit weight gain with certain older ARVs, when compared to the newer ARVs that have been linked to greater weight gain. Additional details and specific weight changes associated with individual ARVs can be found in the INSTI and NRTI sections of the guidelines.

Legacy Effects of Older Antiretroviral Drugs

The impact of prior ARV toxicity on an individual's current weight should also be considered. People with HIV who received thymidine analog NRTIs (e.g., zidovudine, stavudine) and older PIs (e.g., indinavir) were at risk for developing lipodystrophy. Lipodystrophy encompasses both lipohypertrophy (i.e., accumulation of visceral adipose tissue [VAT] and subcutaneous adipose tissue accumulation in the dorsocervical region, trunk, and/or breasts) and lipoatrophy (i.e., the loss of subcutaneous adipose tissue predominantly from the face, buttocks, and extremities).[2,20] Lipodystrophy can persist despite stopping the implicated ARV drugs. Particularly in individuals with lipoatrophy, subcutaneous adipose tissue fibrosis can persist and limit normal re-expansion of the fat depot when weight gain (from any cause) occurs, promoting VAT accumulation and its sequelae.[21] Thus, weight gain distribution and consideration of its effects on cardiometabolic risk may need to be contextualized by both prior and current ART exposure.

Individual Risk Factors and Population Differences

Although studies are limited, the following populations and clinical characteristics may contribute to greater ART-associated weight gain: female sex, older age, Black race/African descent, greater HIV disease severity (including lower CD4 T lymphocyte cell count and/or higher HIV-1 RNA),[11] and those who switched from a PI- or NNRTI-based ART regimen to an INSTI-based ART regimen while virologically suppressed.[6,11,22] Data on the influence of weight prior to ART initiation or switch are

conflicting, with some studies showing lower and others higher weight as a risk factor for subsequent ART-associated weight gain.[11,22]

Consequences of Weight Gain

Weight gain in people with HIV undoubtedly contributes to obesity-related comorbidities. In two Advancing Clinical Therapeutics Globally (ACTG) network protocols of longitudinal cohorts of people with HIV, individuals who experienced >10% weight gain within a year of ART initiation had an increased risk of type 2 diabetes mellitus (DM), metabolic syndrome, and cardiometabolic events 48 weeks after ART initiation.[23] Moreover, weight gain in people with HIV may confer a greater risk of cardiometabolic disease compared to people without HIV. The Veterans Aging Cohort Study found that each 5-pound weight gain was associated with a 14% greater risk of DM for people with HIV compared to 8% greater risk in people without HIV.[24] The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) cohort observed an 18% to 20% increased relative risk of cardiovascular disease (CVD) per 1.0 kg/m^2 BMI increase among people with HIV who had a normal weight at ART initiation.[25] In comparison, a cohort of people without HIV from Finland demonstrated a 4% to 5% increase in CVD risk per 1.0 kg/m^2 BMI increase.[26] Thus, even small amounts of weight gain in people with HIV could potentially contribute to increased cardiometabolic risk, and any weight gain >10% from baseline weight has been strongly associated with incident DM, metabolic syndrome, and other cardiometabolic outcomes.[23]

Management of HIV-Associated Weight Gain

General Antiretroviral Therapy Considerations

Data on effective strategies to prevent or reverse ART-associated weight gain remain limited. Although weight gain among people with HIV likely increases risk for multiple cardiometabolic comorbidities and can negatively affect body image and psychosocial functioning, early and sustained ART treatment is critical to optimize short- and long-term clinical outcomes in people with HIV. ART initiation should not be delayed because of concerns for weight gain **(AIII),** and ART should not be interrupted or discontinued because of weight gain **(AIII).** ART selection should be based on optimization of virologic suppression. Specific ARVs should not be selected (for initiation or switch) to prevent or reduce weight gain **(AII),** as available evidence suggests that this strategy is ineffective. Specifically, greater average weight gains associated with INSTI- or TAF-based regimens should not influence decisions on regimen selection, especially in cases when these agents are likely to be the best option for effective virologic suppression, as the reasons for these differential effects on weight among specific ARVs are not clear.

Sustainable Lifestyle Modifications and Behavioral Weight Loss Programs

Lifestyle modification remains the starting point and gold standard weight management intervention. As in the general population, people with HIV should be educated on long-term healthy eating habits and encouraged to exercise regularly. Some individuals may benefit further from consultation with a licensed dietitian, nutritionist, and/or formal behavioral weight loss program, where available. Of note, few studies have evaluated behavioral weight loss programs specifically in people with HIV, although available data suggest they achieve outcomes similar to those seen in the general population.[27-29] Referral to an obesity medicine specialist and/or bariatric surgery center should be considered for select individuals.

Pharmacotherapy Targeting Adipose Tissue and/or Weight in People With HIV

Currently, there is not enough population-specific evidence for the Panel to recommend weight loss pharmacotherapy for people with HIV beyond what is recommended for the general population. Several therapeutic trials have been conducted targeting abnormal adipose tissue accumulation in people with HIV; some of the medications tested in these trials also cause weight loss, as discussed below.

Tesamorelin, a synthetic growth hormone–releasing hormone analog, is the only U.S. Food and Drug Administration–approved therapy to treat excessive abdominal fat in people with HIV. The efficacy and safety of tesamorelin were largely established by two large Phase 3 trials conducted in people with HIV with central obesity. Tesamorelin 2 mg given as a daily subcutaneous injection was associated with a 13.1% reduction in VAT from baseline over 26 weeks, representing a 15.4% relative reduction compared to placebo. Through 52 weeks, the reduction from baseline reached 17.5%, demonstrating that most VAT loss occurred during the first 6 months of treatment.[30] Although the participants enrolled in the initial trials were primarily treated with the older NNRTIs and PIs used at the time, another small randomized controlled trial demonstrated similar results among people with HIV taking INSTI-based regimens.[31] The use of tesamorelin, however, is limited by modest response rates (two-thirds of the participants with clinically significant VAT reduction), the need for weekly reconstitution, daily subcutaneous injections, and reversal of effects with drug discontinuation.

Glucagon-like peptide-1 (GLP-1) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (RAs) have gained considerable popularity in the general population due to the significant weight loss effects along with reduced risk for multiple CVD outcomes. However, few studies exist among people with HIV. The only randomized controlled trial to date in HIV was conducted in 108 participants with HIV-associated lipohypertrophy and overweight or obese BMI who received subcutaneous semaglutide 1.0 mg or placebo weekly over 24 weeks (plus an 8-week titration phase). People with DM were excluded from study entry. Semaglutide treatment resulted in an estimated weight loss of 10.4%, with significant reductions in total body fat and abdominal total and VAT.[32] In ACTG A5371, a 24-week, open-label, single-arm study of semaglutide 1.0 mg weekly for the treatment of metabolic dysfunction–associated steatotic liver disease in people with HIV who did not have DM, significant improvements in liver fat and other cardiometabolic parameters occurred that strongly correlated with weight loss (average of 8.1%).[33]

Although the few studies conducted in people with HIV showed an adverse event profile similar to the general population, the 1.0-mg dose used is lower than the maximum currently approved 2.0- and 2.4-mg doses for DM and obesity in the general population, respectively. Thus, the safety and side effect profile of GLP-1 and GLP-1/GIP RAs at higher doses or longer duration in people with HIV are currently unknown. Until more data become available, the Panel on Antiretroviral Guidelines for Adults and Adolescents advises prescribing GLP-1 and GLP-1/GIP RAs among people with HIV based on current general population indications and prescribing information.

Other weight loss drugs are available with and without a prescription in the United States and should similarly be used in accordance with general population recommendations. It is important to recognize the potential for known or possible drug–drug interactions with ARV drugs when considering the use of such therapeutic agents. For example, some case reports link orlistat, which promotes weight loss by reversibly inhibiting lipase and reducing dietary fat absorption, to loss of virologic suppression due to decreased ARV drug absorption.[34,35] In another example, the use of naltrexone-bupropion requires increased drug monitoring when coadministered with certain ARVs that may affect expected pharmacokinetic parameters.[36] Thus, it is critical to evaluate for any drug–drug interactions or possible adverse effects that may preferentially affect people with HIV on ARVs.

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