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# Beyond the Numbers: Weight Gain Risk Factors, Implications, and Interventions among Individuals with HIV

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## Abstract

**Background:** Advancements in antiretroviral therapy (ART) have significantly improved life expectancy, leading to an increased prevalence of older adults with HIV. This population may face challenges related to age-related comorbidities in addition to HIV and possibly antiretroviral therapy-related comorbidities. Among those, weight gain has emerged as an increasingly recognized problem raising clinical concern. This narrative review provides an overview of existing data and outlines risk factors, implications, and management strategies including ART switch, lifestyle modifications, and the use of weight-reducing pharmacologic agents.

**Body of evidence:** Recent studies support the concept that weight gain following ART initiation is multifactorial and is associated with demographic-, HIV-, lifestyle-, and ART-related risk factors. Female sex, Black race, individuals presenting with low CD4 T-cell count and elevated HIV-1 viral load appear to be particularly susceptible to this weight gain. The impact of ART, including integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide (TAF), on weight gain is undergoing reassessment as accumulating evidence elucidates weight-suppressive effects of older agents like efavirenz (EFV) and tenofovir disoproxil fumarate (TDF). In reviewing evidence from ART switch studies, concerns have emerged regarding whether ART directly causes weight gain among persons with HIV (PWH), or if the observed weight gain is a consequence of discontinuing older agents that previously mitigated such effects. Management strategies includes careful assessment of ART, striking a balance between efficacy and adverse effect profiles, and the use of weight loss pharmaceuticals as adjuncts to lifestyle modification through diet and exercise.

**Summary:** Weight gain among PWH requires a comprehensive and individualized management approach which considers the unique needs of individuals with HIV. Risk factors for weight gain among PWH have been identified, however, the underlying mechanism remains poorly understood. More studies are needed to understand the pathogenesis of weight gain, individual variability, long-term implications on cardiometabolic factors and other comorbidities, and optimal management strategies.

**Keywords:** HIV, Weight gain, Diet, GLP1-RA, Tenofovir, Integrase inhibitor

## Introduction

Over the past forty years, with effective and tolerable antiretroviral therapy (ART), human immunodeficiency virus (HIV) has transformed into a chronic medical problem. The current treatment paradigm requires persons with HIV (PWH) to remain on ART indefinitely to maintain viral suppression, promote immune reconstitution, and decrease morbidity and mortality from HIV [1]. This has resulted in an aging population with the Centers for Diseases Control (CDC) estimating that nearly 50% of PWH in the United States (US) are aged 50 years and older [2]. As PWH are living longer, chronic medical problem such as cardiovascular disease, liver and kidney disease, osteoporosis, and non-AIDS malignancies increasingly affects them [3-8]. These conditions, although also present in the general population, manifest at higher rates and at chronologically younger ages among PWH [9-11].

Obesity is rising in prevalence globally [12]. Among PWH, the body mass index (BMI) has been observed to be increasing while on ART with an increasing proportion being categorized as overweight or obese at the time of ART initiation [13-17]. Obesity increases the risk of cardiovascular disease, essential hypertension, metabolic syndrome, and type 2 diabetes mellitus [18-21].

Overall, there is a growing concern regarding weight gain and its implications among PWH. Substantial weight gain can lead to obesity, which may contribute to the development of co-morbidities among aging PWH [3-8]. The objective of this review is to summarize our current understanding of weight changes observed among PWH with a focus on management strategies.

## Weight Trajectories among PWH Over Time

Historically, extreme weight loss was an indicator of uncontrolled HIV and related to immune dysfunction from ongoing HIV replication, cellular activation and exhaustion [22-27]. Weight gain after ART initiation was thought to be a sign of "return-to-health" associated with viral suppression, immune reconstitution, and resolution of opportunistic infections [28-31]. Early nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) blunted weight rebound due to adverse effects such as lipodystrophy, lipoatrophy, nausea, and diarrhea [32-34].

In the 2000s, newer antiretroviral (ARV) agents with improved tolerability and reduced mitochondrial toxicity replaced older, established drugs. During this period, a cohort study involving more than 14,000 PWH from North America found that after 3 years of receiving ART, 22% of individuals with a normal BMI at baseline had become overweight and 18% of those overweight at baseline had developed obesity. This finding raised questions about the potential association between ARV agents and weight gain [14,35].

Additional concerns related to weight increases and ARVs emerged with the introduction of tenofovir alafenamide (TAF) as PWH switched from TDF to TAF, along with widespread adoption of second-generation integrase strand transfer inhibitors (INSTIs) [35-40].

## Unveiling Weight Gain: Exploring Risk Factors

In 2019, two studies provided the first prospective randomized evidence concerning weight gain associated with ART. The ADVANCE study was an open label, randomized trial that compared DTG and FTC plus either TAF or TDF against EFV/TDF/FTC in ART-naïve individuals. This study showed that there was more weight gain associated with DTG-containing regimens, especially in combination with TAF, compared to the EFV-containing comparator arm [41]. The second was The New Antiretroviral and Monitoring Strategies in HIV-1 Infected Adults in Low-Income Countries (NAMSAL) which was an open-label non-inferiority trial comparing DTG to low-dose EFV, combined with TDF and 3TC. More weight gain was observed among individuals in the DTG group than the EFV group [median weight gain, 5.0 kg vs 3.0 kg (P<0.001); incident obesity, 12.3% vs 5.4% (P=0.004)] [42]. In a meta-analysis of 8 clinical trials of treatment-naïve PWH, demographic-related factors (female sex, black race), HIV-related factors (low CD4-T cell count and higher HIV-1 RNA viral load), and ART composition were linked to weight gain. Specifically, INSTIs were associated with more weight gain compared to non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs) and PIs, while bictegravir (BIC) and DTG were associated with more weight gain compared to elvitegravir/cobicistat (EVG/c). Although these studies added to the understanding of risk factors, the specific mechanisms through which ARV agents contribute to weight gain remained unclear [43,60].

## The Effect of Tenofovir Prodrugs on Weight

Historically, TDF was widely utilized prior to the introduction of TAF and was associated with renal and bone mineral density toxicities. Subsequently, TAF quickly replaced TDF, but concerns emerged regarding its association with weight gain [35,44-50].

TAF and TDF have been utilized among individuals without HIV as pre-exposure prophylaxis (PrEP) allowing for comparison without the confounding effects of HIV and associated weight loss [51]. In FTC and TAF vs FTC and TDF for HIV pre-exposure prophylaxis (DISCOVER), a significant difference in weight change (p <0.001) was observed between TDF/FTC (-0.1kg) and TAF/FTC (+1.1kg) [52]. In a recent switch study, Bosch et al. observed that women who switched from DTG + TAF/FTC to DTG/TDF/3TC had a median 1.6 kg decrease in weight after week 192 (p=0.0125) [35,53].

In HIV Prevent Trials Network (HPTN) 077, there was no significant weight difference between cabotegravir (CAB) and placebo, with rates of 1.48 kg/year and 1.57 kg/year, respectively [54]. Following this, significant differences in weight changes were observed between CAB and the TDF/FTC arm in both HPTN 083 and HPTN 084 trials [55,56]. Taken together, these findings suggest that CAB may have a neutral impact on weight. The observed weight differences between CAB and TDF/FTC in HPTN 083 and HPTN 084 trials may be potentially attributed to the weight-suppressive effects of TDF.

In the pooled analysis of treatment naïve PWH by Sax et al., individuals started on TAF compared to ABC (OR, 1.9 [95% CI, 1.25-2.88]; p=0.003) or TDF (OR, 1.47 [95% CI, 1.14-1.90); p=0.003) had a greater odds of >10% weight gain after initiating ART [43]. Similar results were observed in the ADVANCE trial, where treatment-emergent obesity was associated with DTG and TAF [41].

Collectively, PrEP and HIV treatment studies suggest that

TAF may independently contribute to weight gain and TDF exhibits weight-mitigating effects [52,55-58]. Doravirine for Obese Persons on Integrase Inhibitors and Tenofovir Alafenamide (ACTG 5391 DO-IT) Study is well positioned to further investigate weight gain differences between TDF and TAF [59].

## The Effect of Integrase Inhibitors on Weight

Numerous observational studies, retrospective analyses, and large randomized clinical trials have suggested that INSTIs, particularly DTG and BIC, may be associated with more weight gain compared to other ARVs. Within the INSTI class, previous studies have observed varying patterns of weight gain [41,43,60-67]. An early study exploring differences in weight gain between INSTIs and other ARVs was the STARTMRK study. In this study, raltegravir (RAL) demonstrated comparable increases in BMI to EFV after 156 weeks of ART [67]. In The African Cohort Study (AFRICOS), PWH on DTG-based ART were twice as likely to have a BMI≥ 25 compared to those on non-INSTI based regimens [68]. Prospective data from ADVANCE and NAMSAL studies showed that DTG-based regimens were associated with significant weight gain as early as 4 weeks post-ART initiation. This effect was particularly pronounced when DTG was combined with TAF in the case of ADVANCE and was most prominent among women in both trials [61,69]. Limited data is available for BIC, but observations suggest that weight gain is comparable to DTG. In a head-to-head study comparing DTG/ABC/3TC to BIC/TAF/FTC among ART naïve PWH, median weight gain after 96 weeks was 2.4 kg [interquartile range (IQR) -0.4-5.8] and 3.6 kg (IQR 0.0-8.5), respectively [63]. In a separate study of ART naïve PWH comparing DTG + TAF/FTC with BIC/TAF/FTC, the median change in body weight was 3. 9 kg (IQR 0.8-7.4) and 3.5 kg (0.1-8.2), respectively, after 96 weeks [64]. In the pooled analysis by Sax et al., no notable difference in weight gain was observed between individuals on BIC or DTG, and both exhibited more weight gain than PWH on EVG/c [43,60]. Collectively, these studies suggest that within the INSTI class, DTG and BIC are associated with more weight gain.

There is some evidence that challenges the notion that INSTIs are associated with weight gain. Griesel et al. compared weight changes between cytochrome (CYP) 2B6 metabolizer genotypes in the EFV and DTG arms. EFV is metabolized via CYP2B6. Slow metabolizers have side effects associated with higher drug levels such as lipid and glucose level changes, bone, central nervous system, and hepatic toxicity. Weight gain in CYP2B6 extensive metabolizers on EFV resembles that in the DTG arm, suggesting that reduced weight gain in the CYP2B6 slow or intermediate metabolizers may contribute to higher relative weight gain with DTG compared to EFV [70]. Letendre et al. investigated ART intensification with DTG and maraviroc, DTG and placebo, or dual placebo over 96 weeks in virally suppressed PWH with neurocognitive impairment. A post-hoc analysis evaluated effects of ARV agents on weight gain and BMI and found that the BMI increased over the study period for the entire cohort and weight did not differ between arms at week 96 [71]. Finally, weight gain following ART switch from NNRTI-based regimens to co-formulated TDF, 3TC, and DTG(TLD) among virally suppressed PWH was investigated in the Academic Model Providing Access to Healthcare (AMPATH) cohort. When stratified by NNRTI, those on EFV had a significant increase in the rate of weight gain when switched to TLD (0.57 kg/year to 1.11kg/year; +0.81kg). Individuals who switched from nevirapine to TLD did not have notable changes in the rate of weight gain (0.35kg/year to 0.32 kg/year; -0.05kg). This highlighted the weight-inhibitory effects of EFV but failed to show any direct weight gain with DTG itself [72].

## Implications of Weight Gain

Weight gain associated with ART has been linked with alterations in cardiovascular disease risk factors, including changes in blood pressure, glucose levels, and lipid profiles [53,73]. Observational studies have suggested an association between weight gain and the development of type 2 diabetes mellitus [74-80]. The relationship between obesity and the development of non-AIDS malignancies is an area of active investigation by the Multicenter AIDS Cohort Study Women's Interagency HIV Study Combined Cohort Study (MWCSS) [81]. Limited data is available on the long-term implications of weight gain among PWH.

## Management of Weight Gain Among PWH

Next, we summarize our current understanding of three primary interventions to tackle weight gain among PWH: ART switch, lifestyle interventions, and pharmacologic interventions.

### The effect of ARV switch on weight

The ADVANCE trial served as an early indicator of weight changes associated with tenofovir prodrugs. CHARACTERISE was a follow-up to ADVANCE, where participants were transitioned to open-label DTG/TDF/3TC at week 192. Metabolic and weight changes were explored among the 172 individuals (70 in DTG+TAF/FTC arm; 71 in DTG+TDF/FTC arm; 31 in EFV/TDF/FTC arm) who switched to DTG/TDF/3TC. At week 52, women who switched from DTG + TAF/FTC experienced significant weight loss (median: -1.6 kg; p=0.0125) compared to men (median= -0.2kg; p=0.2561) [53]. This study was among the first indicating that transitioning from TAF to TDF was associated with weight loss among women, reaffirming the weight-suppressive impact of TDF.

Next, the TANGO trial was an open-label, multicenter, phase 3 study of virally suppressed PWH on a 3-drug TAF-based regimen to switch to DTG/3TC or continue the current TAF-based regimen. At week 48, individuals who switched to DTG/3TC showed a non-significant increase in weight (+2.2 kg) from baseline showing that switching off of TAF was not associated with weight loss [82].

Amid concerns about weight gain associated with INSTIs and TAF-based regimens, the SOLAR study evaluated weight changes among virally suppressed PWH transitioning to long acting cabotegravir and rilpivirine (CAB/RPV) from BIC/TAF/FTC or maintaining BIC/TAF/FTC. There were comparable changes in weight, BMI, and body composition in both groups observed at month 11 and month 12 [72,83].

Next, the DEFINE study explored weight changes among virally suppressed PWH with >10% weight gain on INSTI + TAF/FTC when switched to DRV/c/TAF/FTC. At week 24, there was no significant difference in percent change in body weight from baseline between participants on DRV/c/TAF/FTC (0.63 [-0.44, 1.70]) and BIC/TAF/FTC (-0.24 [-1.35, 0.87]). This percent change in body weight remained consistent across various subgroups (BMI >30 kg/m$^2$, sex, race) suggesting that a change from BIC to DRV/c did not contribute to significant reductions in weight [84,85].

Finally, weight and body composition changes were investigated among virally suppressed PWH on BIC/TAF/FTC who were either maintained on BIC/TAF/FTC or switched to fixed combination doravirine and islatravir (DOR/ISL). This study highlighted that switching from an INSTI and TAF-based regimen to DOR/ISL did not reduce weight over 48 weeks [86].

**The effect of lifestyle modifications on weight**

Previous studies have observed that most PWH do not meet current diet and physical activity recommendations [87-94]. Studies investigating dietary counseling as a sole intervention for weight loss have not been associated with significant weight loss at 48 months of follow-up [95]. Other studies have suggested that dietary counseling and self-reported dietary improvements may blunt the effects of ART-associated weight gain [96]. An integral component of dietary weight loss programs includes calorie restriction by at least 500 calories/day which has been associated with weight loss among PWH across multiple studies, accompanied by varying improvements in cardiometabolic parameters [97-102].

The benefits of physical activity among PWH on cardiometabolic parameters of blood pressure, lipid profiles, glucose levels, insulin sensitivity have been well established [103-106]. Barriers identified among PWH to meet physical activity and dietary recommendations include older age, low education level, low CD4 count, presence of lipodystrophy, low socioeconomic status, perceptions of decreased weight as health risk, housing instability, and lack of social support [107-110].

In summary, a combination of dietary counseling, at least a 500 calorie/day deficit and physical activity of about 150 minutes/week have been associated with weight loss and improvement in cardiometabolic parameters among PWH.

**The effect of chronic weight management (CWM) pharmaceuticals on weight**

Pharmaceuticals for CWM among PWH who have gained significant weight after ART initiation may provide a valuable adjunct to lifestyle interventions. The Food and Drug Administration (FDA) approved pharmacologic agents for CWM include orlistat, naltrexone-bupropion (NAL-BUP), phentermine-topiramate (PHN-TOP), and glucagon-like peptide 1 receptor agonists (GLP-1 RA) [111].

Orlistat decreases fat absorption by up to 30%, contributing to weight loss. Systemic exposure to orlistat is minimal and nearly 100% is excreted in the feces [112]. Orlistat can lead to drug interactions due to its impact on absorption. The efficacy among PWH is unknown as clinical trials have not captured this data. In terms of safety among PWH, multiple case reports have suggested the association of HIV viremia with the initiation of orlistat when combined with EFV/TDF/FTC and atazanavir (ATV), ritonavir, and TDF/FTC. In two of the cases, therapeutic drug monitoring of EFV and atazanavir revealed subtherapeutic levels of EFV and ATV at the time of viremia [113-115].

Naltrexone-bupropion (NAL-BUP) contributes to weight loss by regulating food intake through the mesolimbic dopamine circuit and hypothalamus [116]. NAL-BUP resulted in a mean change in bodyweight of -6.1% compared to -1.3% in the placebo group ($p<0.0001$) [116-120]. In terms of safety, bupropion is metabolized via CYP2B6 and has known interactions with CYP2B6 inducers ritonavir, EFV, and lopinavir. Monitoring for adverse events is recommended and prompt tapering and discontinuation of NAL-BUP is recommended if negative changes in mood or behavior occur [121].

Phentermine-topiramate (PHN-TOP) reduces appetite by stimulating the release of norepinephrine into the CNS and increasing satiety. PHN-TOP has resulted in weight loss of -10.9% from baseline compared to placebo (-1.6%; $p< 0.001$) [122-124]. These studies did not explicitly report PWH participants and additional data on efficacy and drug interactions PWH may encounter is limited.

GLP1-RA promotes weight loss by slowing gastric emptying and encouraging early satiety. Three FDA-approved agents in this class (liraglutide, semaglutide, and tirzepatide) exhibit varying mean changes in body weight by specific agent and dosage when combined with lifestyle intervention of dietary counseling (500 calorie/day deficit) and physical activity (150 minutes/week) [125-127]. Of these, tirzepatide was recently approved and results in a mean percent change in weight of -20.9% compared to placebo (-3.1%; $p<0.001$) [127]. There is one randomized double-blind placebo-controlled study on semaglutide among virally suppressed PWH with lipohypertrophy following ART initiation. The study demonstrated that semaglutide was effective in reducing weight and total fat in central and peripheral deposits. The study raised concerns about potential loss of lean muscle mass and minimal reduction in pericardial and liver fat by computed tomography (CT) scan, possibly reflecting the sensitivity of the imaging modality used [128]. The results of

AIDS Clinical Trials Group (ACTG) 5371 will provide data on changes in liver fat stores associated with semaglutide use by magnetic resonance imaging (MRI) [129]. Additional data is needed to understand the interaction between GLP1-RA, ART, and co-morbidities among PWH.

## Future Scope & Conclusions

There is an urgent need to improve understanding of the physiology, underlying mechanisms, and long-term consequences of weight gain. Exploring preventative measures for weight gain at the start of ART treatment is crucial. First, it is essential to delineate the impact of ART regimens on weight gain and pinpoint contributing agents. This may differ for PWH initiating ART compared to those on established treatment, and it may differ for individuals with established risk factors for weight gain. Those with established obesity versus those at risk for the development of obesity may require unique considerations prior to initiating ART [35].

Next, the role and constraints of lifestyle counseling, calorie deficit diets, exercise strategies, and the optimal utilization of new weight loss pharmaceuticals needs to be investigated in the context of HIV management among individuals for both prevention and treatment of weight gain. Furthermore, the role of these efforts in the prevention of HIV-related, aging-related, and obesity-related complications requires additional investigation.

The intersection of obesity and the development of comorbidities among aging PWH are overlapping concerns. Overall, the causal relationship between ART and weight gain remains unclear. The extent of potential weight gain caused directly by ART, as opposed to the influence of agents that previously mitigated such effects, is an active area of investigation. Management strategies include an individualized approach addressing HIV-, lifestyle-, and ART-related factors while balancing efficacy and adverse effect profiles of ART to prevent problematic weight gain, the development of obesity, and its complications.

## Conflicts of Interest

CM has received fees for advisory board participation for Gilead Sciences and Viiv Healthcare for work unrelated to this submission. YP does not have any conflicts of interest to declare.

## Author Contributions

YP and CM contributed to the manuscript preparation.

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