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Weight Gain and Integrase Inhibitors

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Abstract

Purpose of review—Weight gain and obesity among people living with HIV (PLWH) is a serious problem that occurs often after initiation of antiretroviral therapy but may be worse with integrase strand transfer inhibitors (INSTIs). This paper comprehensively reviews available data and summarizes our current understanding of the topic.

Recent findings—Recent studies support the concept that weight gain and treatment emergent obesity are worse with INSTI-based regimens, particularly dolutegravir. Women and non-whites appear to be the most at risk, and the accompanying nucleoside reverse transcriptase inhibitor may play a role. Lipohypertrophy, an abnormal accumulation of visceral fat and/or ectopic fat depots, continues to be a problem among PLWH, but the role of INSTIs is inconsistent. The pathogenesis of weight gain and changes in body composition in HIV, especially with INSTIs, is poorly understood but may lead to serious co-morbidities, such as cardiovascular disease and diabetes.

Summary—Although INSTI-based regimens are highly efficacious for viral suppression, they appear to cause more weight gain and treatment emergent obesity than non-INSTI-based regimens and may increase the risk of weight-related co-morbidities. More studies are needed to understand the pathogenesis of weight gain with INSTIs in PLWH, in order to prevent this serious complication.

Keywords

weight gain; obesity; visceral adipose tissue; lipohypertrophy; integrase strand transfer inhibitors

Introduction

Combination antiretroviral therapy (ART) has dramatically reduced AIDS-defining morbidity and mortality among people living with HIV (PLWH). However, metabolic disorders and associated co-morbidities like cardiovascular disease and diabetes continue to

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Conflicts of Interest: GAM has served as a consultant for Theratechnologies, Gilead Sciences, Merck, and ViiV/GSK and received grant support to her institution from Bristol-Myers Squibb, Roche, Astellas, GlaxoSmithKline, and Gilead Sciences. ARE has served as an advisor and speaker for Theratechnologies and Gilead Sciences and has received grant support to her institution from Bristol-Myers Squibb, Cubist Pharmaceuticals, and GlaxoSmithKline.

challenge our ability to provide successful long-term treatment to this population. Traditional risk factors such as smoking and dyslipidemia, as well as HIV-related inflammation and immune activation, are well-described causes of cardiometabolic co-morbidities among ART-treated PLWH [1]. However, obesity and weight gain after ART initiation are becoming increasingly recognized problems in our modern HIV treatment paradigm [2, 3■].

Weight gain after ART initiation is a well-known phenomenon among PLWH and can occur with all antiretroviral classes [4, 5■]. Early in the HIV epidemic, weight gain among PLWH, especially among those with a low baseline body mass index (BMI), low CD4 count, and high HIV RNA, was associated with improved survival and immunologic recovery [6, 7] and therefore was considered a “return to health”. However, median BMI and prevalence of baseline obesity among PLWH initiating ART has been steadily increasing [4, 5], and many people gain an excess amount of weight leading to post-treatment obesity [8]. Weight gain in this context increases the risk of associated co-morbidities like diabetes and cardiovascular disease [9, 10].

Notably, there is mounting evidence that the class of antiretrovirals known as integrase strand transfer inhibitors (INSTIs), particularly dolutegravir (DTG), are associated with more weight gain than other classes of antiretrovirals. This review summaries our current understanding of weight gain and fat changes associated with INSTIs with a focus on new data presented over the last 12 months.

Evidence of Differential Weight Gain with Integrase Inhibitors

One early study investigating differences in weight gain with INSTIs vs. other antiretrovirals was the STARTMRK study, where the INSTI, raltegravir (RAL), was associated with similar increases in BMI compared to the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV), after 156 weeks of ART [11]. Similarly, A5260s, a metabolic substudy of 328 participants from the AIDS Clinical Trials Group (ACTG) A5257 study, investigated the protease inhibitors (PIs), atazanavir/ritonavir (ATV/r) or darunavir (DRV)/r) vs. RAL in ART-naïve PLWH. After 96 weeks, BMI increased similarly in all arms by 3.8%−4.7% [12]. However, in a follow-up analysis including the entire A5227 parent study population, investigators looked at people with severe weight gain (defined as ≥10% weight gain over 96 weeks) or severe BMI gain (defined as an increase of ≥1 BMI category). Those who started with at least a normal BMI (≥18.5 kg/m^2) or who started underweight (<18.5 kg/m^2) at baseline but became overweight or higher at follow-up were included. In both models, initiating RAL was associated with more severe weight/BMI gains than either ATV/r or DRV/r [13].

Several subsequent studies have complemented these early data. For example, a Brazilian cohort study of 1794 PLWH who initiated ART showed that clinical obesity was more likely to occur among those who used an INSTI vs. PI or NNRTI [14]. In a U.S.-based observational study of 495 participants, investigators compared changes in weight over 18 months in those who stayed on EFV vs. those who changed to a PI- or INSTI-based

regimen. Those who switched to an INSTI gained significantly more weight (INSTI: +2.9 kg; PI: +0.7 kg; EFV: +0.9 kg) [15].

In contrast, researchers used data from the Surveillance Cohort Long-Term Toxicity Antiretrovirals (SCOLTA) to evaluate 1118 PLWH who had been on the same regimen of ART for ≥1 year (DTG, elvitegravir (EVG), RAL, DRV without INSTI, or the NNRTI, rilpivirine (RPV)) [16]. While adjusting for multiple confounders, they observed significant increases in BMI for all treatment groups except RPV; however, there were no differences between INSTIs and DRV or RPV in adjusted analyses. Likewise, in a recent observational study using the TRIO Health Network, INSTI use was significantly associated with ≥3% weight gain in bivariate analysis but was no longer significant in multivariate analysis [17■]. The only notable variable independently associated with ≥3% weight gain was a history of a neuropsychiatric disorder.

A summary of findings from other studies presented over the last 12 months are shown in Table 1. In general, these studies support more weight gain with INSTIs (especially when switching from NNRTIs), but the data are not consistent and many must be interpreted with caution as they originate from observational cohorts and/or retrospective analyses [5■, 18■■, 19■■, 20■■, 21■, 22■■, 23■■, 24■■, 25–26, 27■, 28–30, 31■, 32■, 33■, 34■]. Further details for some studies can be found in subsequent sections.

Weight Gain Among Individual Integrase Inhibitors

Some of the discrepancy in the above studies may be due to a differential effect of individual INSTIs and/or other factors like differences in the ART regimens prior to switching to an INSTI. For example, in a retrospective observational cohort study by Bourgi, *et al* [31■], among 1152 ART-naïve PLWH who initiated INSTI-based regimens (135 DTG; 153 EVG; 63 RAL), adjusted average weight gain was higher after 6 and 18 months among those who started DTG (2.9 kg and 6.0 kg, respectively) or RAL (3.0 kg and 3.4 kg, respectively) compared to EVG (0.6 kg and 0.5 kg, respectively), but there was no significant difference between adjusted average weight gain between DTG and RAL. Non-nucleoside reverse transcriptase inhibitor-based regimens had an adjusted weight gain of 1.1 kg and 2.6 kg after 6 and 18 months, respectively, which was no different than EVG but was significantly lower than DTG by 18 months. Protease inhibitor-based regimens were associated with a 2.6 kg and 4.1 kg increase after 6 and 18 months, respectively, which was significantly higher than EVG and lower than DTG, but this latter comparison was not statistically significant.

Similarly, in a retrospective analysis of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) data, INSTIs led to a greater change in weight at 5 years after ART initiation compared to NNRTIs and PIs (although the difference with PIs was not statistically significant). However, at 2 years, there was clearly a difference among individual INSTIs: DTG led to a non-significant weight gain compared to RAL, and both led to significantly more weight gain than EVG [32■]. Likewise, a longitudinal observational study of 691 participants on suppressive ART who switched from a PI or NNRTI to an INSTI showed significant annual weight gain after switching to DTG from either a PI or

NNRTI and to EVG after switching from an NNRTI (but not from a PI), but there was no difference with RAL [33■].

Using HIV Outpatient Study (HOPS) data, greater weight gain was also seen among virally-suppressed participants after a switch to DTG- or RAL-based regimens (greatest with DTG), but EVG was not associated with increases in BMI [34■]. Likewise, in Norwood, *et al* [15], people who switched to DTG/abacavir (ABC)/lamivudine (3TC) gained the most weight (5.3 kg) compared to RAL- or EVG-based regimens (2.8 kg), although this difference was not statistically significant. Finally, in a recent analysis of pooled data from 8 phase 3 randomized-controlled trials, participants on DTG gained significantly more weight gain than EVG [5■].

Weight Gain with Dolutegravir

The above studies suggest that weight gain with DTG may be worse than other INSTIs. There should be caution in this interpretation, however, as these studies were mostly observational or retrospective *post-hoc* analyses, and some suffered from limited sample size within subsets and/or potential confounders. Several studies have now evaluated DTG specifically, given its potential differential effect. Two studies observed weight increases of 3–4 kg among those on DTG [35, 36], and a *post hoc* analysis of NEAT-002 showed a significant, albeit small (<1 kg), weight gain after switching from a PI/r to DTG [21■]. The highest risk was seen among those switching from DRV vs. other PIs.

The most compelling data comes from the randomized trials in Cameroun (New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries; NAMSAL) and South Africa (ADVANCE). The NAMSAL study randomized 613 ART-naïve PLWH to either DTG/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) or EFV/FTC/TDF, and the ADVANCE study randomized 1,053 ART-naïve PLWH to EFV/FTC/TDF, DTG+FTC/TDF, or DTG+FTC/tenofovir alafenamide (TAF). In both studies, participants randomized to DTG gained more weight than those on EFV [18■■, 19■■, 20■■]. In the ADVANCE study, DTG+FTC/TAF was independently associated with ≥10% increase in body weight and treatment-emergent obesity.

Weight Gain with the Newest Integrase Inhibitors

Few data exist for the newest FDA-approved INSTI, bictegravir (BIC), but weight gain appears similar to DTG. In a non-inferiority study of DTG/ABC/3TC vs. BIC/FTC/TAF for ART-naïve PLWH, median weight gains after 96 weeks were 2.4 kg and 3.6 kg, respectively [22■■]. And, in a non-inferiority study of DTG+FTC/TAF vs. BIC/FTC/TAF for ART-naïve PLWH, median changes in body weight after 96 weeks were 3.9 kg and 3.5 kg, respectively [23■■]. Finally, in the pooled analysis by Sax, *et al*, there was no significant difference between weight gain for participants on DTG vs. BIC [5■].

Cabotegravir (CAB) is a novel, long-acting injectable INSTI in development for HIV prevention and as part of combination ART for HIV treatment. In a recent analysis, investigators looked at weight gain among 177 participants without HIV who received at least one injection or placebo (134 CAB; 43 placebo) [24■■]. Observed weight changes

were approximately 1.0 kg in each study arm over approximately 9.5 months with no significant difference in weight change between arms. These negative data may be due to study limitations, or may reflect a differential effect of CAB compared to other INSTIs, or highlight unique interactions with HIV infection.

Body Composition and Fat Changes with Integrase Inhibitors

Arguably, weight gain and risk of obesity are greater with INSTIs, particularly DTG. However, BMI alone does not provide a fully accurate reflection of adiposity-related risk. In ART-treated PLWH, adipose tissue often preferentially accumulates in the abdominal region and/or in and around visceral organs (like liver and heart) and/or in ectopic fat depots (*e.g.*, dorsocervical pad, intermuscular) and is referred to as lipohypertrophy. This abnormal fat accumulation, especially visceral adiposity and truncal obesity, carries a higher risk of cardiometabolic co-morbidities and mortality [37]. In addition, HIV infection and ART alter adipocyte quality and function and produce changes in lean body mass that affect cardiometabolic risk [38].

To fully assess the implications of weight gain with INSTIs, it is imperative to consider these specific changes in body composition. Several earlier studies investigated RAL vs. non-INSTI regimens. In ACTG 5226s, the subset study of A5227, investigators found no differences in peripheral or central fat (including visceral adipose tissue (VAT)) after 96 weeks between the 2 PIs, ATV/r or DRV/r, vs. RAL. The VAT to total adipose tissue ratio remained unchanged despite a significant increase in BMI in all 3 groups, suggesting that fat gain was generalized and proportionally distributed in the visceral and subcutaneous compartments, even with RAL [12]. However, when analyzing the full ACTG A5257 parent cohort, larger increases in waist circumference with RAL were seen compared to DRV/r but not ATV/r after 48 and 96 weeks of ART [39]. In the PROGRESS study that investigated lopinavir (LPV)/r + FTC/TDF vs. LPV/r + RAL, RAL was associated with increased leg and arm fat but not truncal fat [40]. Likewise, in a convenience sample of 75 participants from the STARTMRK study, similar limb and trunk fat gains were seen after 96 weeks in RAL vs. EFV [41].

There have been several recent studies investigating more modern INSTIs. In Debroy, *et al*, greater trunk and leg fat mass increases were associated with per-year INSTI use, although the effect sizes were small (both +<0.1%) in combined sex mixed-effect models. In sex-stratified models, per-year INSTI use was only significantly associated with increases in trunk and limb fat mass for men (with an effect size similar to that in the combined-sex models) [42■]. In an analysis within the Women's Interagency HIV Study (WIHS), investigators evaluated women from 2006–2017 who switched or added an INSTI vs. those on ART with no INSTI use [27■]. Women with INSTI use had significantly greater average increases of body weight, BMI, and body fat % (+2.1 kg, +0.8 kg/m^2, 1.4%, respectively), as well as greater increases in waist, hip, arm, and thigh circumferences (+2.0, +1.9, +0.6, +1.0 cm, respectively) and waist-to-hip ratio (+0.002). There were no differences in changes by INSTI type (DTG, EVG, or RAL).

Risk Factors for Weight Gain and Fat Changes with Integrase Inhibitors

Not all people initiating ART gain weight. In fact, 30.2% of participants lost weight in a recent analysis of pooled data from 8 phase 3, randomized-controlled trials; however, 17.3% of participants had ≥10% weight gain from baseline [5]. Studies investigating risk factors for weight gain and fat changes specifically with INSTIs demonstrate that women, blacks, and Hispanics are particularly vulnerable [15, 33■, 35, 43–45■], although data are inconsistent [31■, 32■]. Risk factors identified in studies presented over the last 12 months are shown in Table 2. Notably, INSTI use in combination with TAF or ABC is emerging as a significant risk factor (although there are fewer data supporting the latter). In Lake, *et al*, for example, a switch to any INSTI with ABC and a switch to EVG with TAF were both statistically significant, albeit subset sample sizes were limited. In fact, TAF alone appears to be a risk factor [5■, 46]. More research is needed to know if there is an incremental increase in weight when TAF and an INSTIs are used together.

Among women in the NAMSAL study, there were more participants who had ≥10% change in weight from baseline in the DTG+3TC/TDF arm compared to the EFV/3TC/TDF arm, a difference that was not seen among men. On the other hand, men on DTG+3TC/TDF were more likely to develop obesity than men on EFV/3TC/TDF, which was not seen among women. Interestingly, however, there was no difference in overweight or obesity incidence between men and women on DTG after 48 weeks, despite more women experiencing a ≥10% weight gain. Among women in the ADVANCE study, there was a preferential weight gain among those who were on DTG+FTC/TAF vs. DTG+FTC/TDF which was not seen among men [18]. Risk factors associated with weight gain among women in the WIHS study included minority race/ethnicity, CD4 ≥350 cells/mm^3, undetectable HIV RNA, ≥50 years of age, and BMI <30 kg/m^2 [27■].

Potential Mechanisms of Weight Gain and Fat Changes with Integrase Inhibitors

The cause of the differential weight gain with INSTIs is unknown. One proposed explanation has been the rapid reduction in HIV RNA seen with INSTIs, given the correlation between HIV RNA and resting energy expenditure (REE) [47]. Indeed, no study of REE changes in the setting of randomized treatment initiation exists, and, thus, it is possible that people with untreated HIV start with a high REE that corrects differentially with different types of ART. In Bourgi, *et al*, participants starting INSTIs were significantly more likely to achieve virologic suppression early after treatment initiation (at 6 weeks, 3 months, and 6 months). However, by the end of the study follow-up (at 18 months), rates of viral suppression were similar across all ART regimens, despite increased weight gain among INSTIs. Likewise, there was no difference in rates of virologic suppression between DTG and EVG, although there was more weight gain with DTG [31■]. Similarly, in some studies, larger decreases in plasma levels of inflammation and immune activation are more evident with INSTIs compared to other antiretrovirals [48–50■], but biomarker changes do not appear to be correlated with weight gain [48].

Serum levels of biomarkers, however, may not accurately reflect processes occurring at the adipose tissue level and/or within adipocytes. For example, drug concentrations within adipocytes vary among different antiretrovirals, with high concentrations for DTG, EVG, ATV, and EFV and reduced concentrations for NRTIs [51]. Elvitegravir was shown *in vitro* to impair adipogenesis and adipocyte metabolism but to a lesser extent than EFV, and RAL had no effect [52]. This confirms earlier studies showing minimal effect of RAL on adipogenesis [53, 54]. Likewise, a recent study showed that PLWH with a CYPB26 "slow metabolizer" genotype gained more weight after switching from EFV to an INSTI; however, this effect was only seen among white participants (and not blacks) and with EVG and RAL (and not DTG) [55■]. Dolutegravir also inhibits the binding of radio-labeled α-melanocyte-stimulating hormone to the human recombinant melanocortin 4 receptor, which is involved in the regulation of energy homeostasis and food intake [56].

Another potential explanation that was highlighted by the previously mentioned Trio health study is that INSTIs may be associated with an exacerbation of neuropsychiatric disorders and the subsequent use of psychiatric medications known to increase weight in the general population [17■]. In that Trio analysis, the presence of neuropsychiatric disorders was the only factor independently associated with weight gain of ≥3% over 1 year of continual suppressive ART in treatment-experienced individuals. Notably, the conglomeration of studies mentioned above did not collect or mention neuropsychiatric diagnoses or medications in the analyses.

Another possible hypothesis is that the weight gain and subsequent metabolic complications may be due to altered gut integrity, potentially due to changes in the intestinal microbiome. Indeed, in A5260s, we found that pre-treatment levels of intestinal fatty acid binding protein, a marker of gut integrity, was an independent predictor of weight gain and visceral adipose tissue gains for PLWH on ART [57■]. The differential effect of INSTI on gut dysfunction, however, remains unclear.

Clearly, no single process explains the increased weight gain with INSTIs, particularly given the differences among specific INSTIs and patient subgroups. Furthermore, in the NEAT-022 study, decreases in serum adiponectin levels were associated with increases in BMI after switching from a PI to DTG [50■]; however, another study showed improvements in insulin sensitivity despite decreases in serum leptin levels and a trend toward increased waist circumference after switching from a PI to DTG or RAL [58]. These seemingly contradictory study findings add to the mystery regarding the etiology of weight gain associated with INSTIs.

Implications of Weight Gain with Integrase Inhibitors

While prior studies show that weight gain after ART initiation increases the risk of diabetes and cardiovascular disease [9, 10], little is known about whether weight gain with INSTIs has differential effects in terms of co-morbidity risk. A few recent studies have suggested that despite weight gain with INSTIs, there may not be an equal increase in clinically-significant metabolic parameters [30, 59, 60], although data are conflicting [61]. Further research in this area is needed.

Conclusion

There is mounting evidence that INSTI-based regimens cause more weight gain and treatment-emergent obesity than other ART regimens, although there are clearly differences among various INSTIs, NRTI backbones (specifically the TAF component), and patient subsets. Dolutegravir appears to have the greatest effect with perhaps minimal effect with EVG, although data are inconsistent, and more randomized studies accounting for diet and lifestyle factors are needed. The role of the accompanying NRTI backbone is ill-defined, although TAF is emerging as a potential independent contributor of weight gain. Whether INSTI-based regimens also contribute to lipohypertrophy, especially increases in visceral adiposity, or whether they increase the risk of cardiometabolic co-morbidities remains unclear. Additional studies to better delineate these unanswered questions are paramount as we move forward in this modern ART era.

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31. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis. 18 5 2019 Epub ahead of print.■ This retrospective observational cohort study showed that adjusted weight gain after ART initiation with an INSTI was similar between DTG and RAL but greater than EVG. Weight gain with an NNRTI was no different than EVG at 6 or 18 months but was less than DTG at 18 months, and weight gain with a PI was greater than EVG but but not significantly different than DTG. Investigators were unable to correlate rates of virologic suppression with differences in weight gain among INSTIs.
32. Bourgi K, Jenkins C, Rebeiro P, et al. Greater weight gain among treatment-naïve persons starting integrase inhbitors. Abstract 670. Conference on Retroviruses and Opportunistic Infections March 4–7, 2019 Seattle, Washington, USA.■In a retrospective analysis of NA-ACCORD, after 2 years of ART, DTG led to a non-significant weight gain compared to RAL, and both led to significantly more weight gain than EVG. At 5 years, INSTIs combined led to significantly more weight gain compared to NNRTIs and a non-significant increase in weight compared to PIs.
33. Lake J, Wu K, Erlandson K, et al. Risk factors for excess weight gain following switch to integrase inhbitor-based ART. Abstract 669. Conference on Retroviruses and Opportunistic Infections March 4–7, 2019 Seattle, Washington, USA.■ Investigators showed a significant annual weight gain after switching to DTG from either a PI or NNRTI and to EVG after switching from an NNRTI (but not a PI), but there was no difference in weight after switching to RAL. Increases were particularly significant for women, blacks and people ≥60 years old. Notably, a switch to any INSTI with ABC and a switch to EVG with TAF was statistically significant, albeit subset sample sizes were limited.
34. Palella F, Rayeed N, Li J, et al. Weight gain among virally suppressed persons who switch to INSTI-based ART, the HIV Outpatient Study. Abstract 674. Conference on Retroviruses and Opportunistic Infections March 4–7, 2019 Seattle, Washington, USA.■Weight gain was seen after switching to a DTG- or RAL-based regimen (greatest with DTG) but not with EVG.
35. Menard A, Meddeb L, Tissot-Dupont H, et al. Dolutegravir and weight gain: An unexpected bothering side effect? AIDS. 2017;31(10):1499–500. [PubMed: 28574967]

36. Sculier D, Doco-Lecompte T, Yerly S, et al. Stable HIV-1 reservoirs on dolutegravir maintenance monotherapy: The MONODO study. HIV Med. 2018;19(8):572–7.
37. Scherzer R, Heymsfield SB, Lee D, et al. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. AIDS. 2011;25(11):1405–14. [PubMed: 21572308]
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39. Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis. 2015;60(12):1842–51. [PubMed: 25767256]
40. Reynes J, Trinh R, Pulido F, et al. Lopinavir/ritonavir combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. AIDS Res Hum Retroviruses. 2013;29(2):256–65. [PubMed: 22730929]
41. Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr. 2010;55(1):39–48. [PubMed: 20404738]
42. Debroy P, Sim M, Erlandson KM, et al. Progressive increases in fat mass occur in adults living with HIV on antiretroviral therapy, but patterns differ by sex and anatomic depot. J Antimicrob Chemother. 2019;74(4):1028–34. [PubMed: 30668716] ■This study showed that greater increases in trunk and leg fat mass were associated with per-year INSTI use, but effect sizes were small. In sex-stratified models, per-year INSTI use was only associated with increased trunk and leg fat mass among men (again with small effect sizes).
43. Bhagwat P, Ofotokun I, McComsey GA, 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. [PubMed: 30465010]
44. Bedimo R, Adams-Huet B, Xilong L, et al. Integrase inhibitor-based HAART is associated with greater BMI gains in blacks, Hispanics, and women. Abstract 538. ID Week. 2018 San Francisco, CA, USA.
45. Bedimo R, Xilong L, Adams-Huet B, et al. Differential BMI changes following PI- and INSTI-based ART initiation by sex and race. Abstract 675. Conference on Retroviruses and Opportunistic Infections March 4–7, 2019 Seattle, Washington, USA.■Investigators observed a differential effect of individual INSTIs on BMI changes by sex and race. EVG appeared to be associated with greater BMI gains overall, an effect that did not vary by sex or race/ethnicity. DTG and RAL were associated with greater BMI gains in women, and DTG was associated with greater gains in blacks & Hispanics.
46. Schafer J, Sassa K, O'Connor J, et al. BMI and ASCVD risk score changes in virologically suppressed patients with HIV switching for TDF to TAF containing ART. Abstract 979. IDWeek 2019 Oct 2–6, 2019 Washington D.C., USA.
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50. Martinez E, Assoumou L, Moyle G, et al. 48-week changes in biomarkers in subjects with high cardiovascular risk switching from ritonavir-boosted protease inhibitors to dolutegravir: The NEAT-022 study. Abstract O113. HIV Drug Therapy October 28–31, 2018 Glasgow, UK.■ In an analysis of the NEAT-022 study, participants who switched to DTG vs. those who remained on a PI had significant decreases in sCD14 and adiponectin after 48 weeks. % change in adiponectin was inversely correlated with % change in BMI.
51. Couturier J, Winchester LC, Suliburk JW, et al. Adipocytes impair efficacy of antiretroviral therapy. Antiviral Res. 2018;154:140–8. [PubMed: 29630975] ■These in vitro experiments show that INSTIs penetrate adipocytes, but NRTIs have limited penetration.

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55. Leonard M, Bourgi K, Koethe J, et al. Pharmacogenetics of weight gain after switch from efavirenz to integrase inhibitors. Abstract 472. Conference on Retroviruses and Opportunistic Infections March 4–7, 2019 Seattle, Washington, USA.■ PLWH with a CYPB26 “slow metabolizer” genotype gained more weight after switching from EFV to an INSTI; however, this effect was only seen among white participants (and not blacks) and with EVG and RAL (and not DTG).

56. Committee for Medicinal Products for Human Use (CHMP). European medicines agency. Assessment report. Dolutegravir (Tivicay). November 21, 2013 Accessed: September 27, 2019 Available from: www.ema.europa.eu/documents/assessment-report/tivicay-epar-public-assessment-report_en.pdf.

57. El Kamari V, Moser C, Hileman CO, et al. Lower pretreatment gut integrity is independently associated with fat gain on antiretroviral therapy. Clin Infect Dis. 2019;68(8):1394–401. [PubMed: 30137242] ■ In the ACTG metabolic substudy, A5260s, pre-treatment levels of intestinal fatty acid binding protein, a marker of gut integrity, was an independent predictor of weight gain and visceral adipose tissue gains for PLWH on ART.

58. Calza L, Colangeli V, Borderi M, et al. Improvement in insulin sensitivity and serum leptin concentration after the switch from a ritonavir-boosted PI to raltegravir or dolutegravir in non-diabetic HIV-infected patients. J Antimicrob Chemother. 2019;74(3):731–8. [PubMed: 30541118] ■ This study showed improvements in insulin sensitivity despite decreases in serum leptin levels and a trend toward increased waist circumference after switching from a PI to DTG or RAL.

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60. Hsu R, Brunet L, Fusco J, et al. Risk of type-2 diabetes mellitus after antiretroviral therapy initiation in individuals living with HIV in the United States. Abstract 341. IDWeek 2019 Oct 2–6, 2019 Washington D.C., USA.

61. Rebeiro P, Jenkins C, Bian A, et al. The effect of initiating INSTI-based vs. NNRTI-based antiretroviral therapy on progression to diabetes among north american persons in HIV care. Abstract lb9. IDWeek 2019 Oct 2–6, 2019 Washington D.C., USA.

KEY POINTS

- Weight gain is common after antiretroviral therapy but appears to be greater with INSTIs.
- Dolutegravir seems to have the greatest effect, although data are inconsistent, and the role of the NRTI backbone (especially the TAF component) is poorly-defined.
- Whether INSTIs contribute more than other antiretrovirals to the development of lipohypertrophy (especially increases in visceral adiposity) or increase the risk of co-morbidities is unclear.
- Women and non-whites appear to be most at risk for excess weight gain with INSTIs.
- The etiology of differential weight gain with INSTs is unknown and more data are needed.

Table 1.

Summary of Studies Investigating Weight Gain with Integrase Inhibitors Presented Over the Last 12 Months

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings		
Randomized-Controlled Trials							
ADVANCE Trial [18, 19]	96-week, randomized, open-label trial of DTG + FTC/TDF or FTC/TAF vs. EFV/FTC/TDF	South Africa	ART-naïve	1,053	Weight gain at 96 weeks: DTG+FTC/TAF: +8 kg DTG+FTC/TDF: +5 kg EFV/FTC/TDF: +2 kg	Treatment-emergent obesity at 96 weeks (% of participants): DTG+FTC/TAF: 19% DTG+FTC/TDF: 8% EFV/FTC/TDF: 4%	P<0.001 between arms; P<0.01 for DTG+FTC/TAF vs. other arms
NAMSAL Trial [18, 20]	48-week, randomized, open-label trial of DTG+3TC/TDF vs. EFV_{400}/3TC/TDF	Cameroon	ART-naïve	613	Weight gain at 48 weeks: DTG: +5 kg EFV: +3 kg	Treatment-emergent obesity at 48 weeks (% of participants): DTG: 12% EFV: 5%	P<0.001 between arms for weight gain; P=0.004 for emergent obesity
Sax, et al [5]	Pooled data from 8 phase 3, randomized-controlled trials	Multiple countries	ART-naïve	5,680	96-week LS mean weight gain: INSTI: +3.24 kg NNRTI: +1.93 kg PI: +1.72 kg (P<0.001 INSTI vs. PI and NNRTI)		96-week LS mean weight gain: DTG: +4.07 kg BIC: +4.24 kg EVG: +2.72 kg (P<0.001 DTG and BIC vs. EVG)
NEAT-022 [21]	Post-hoc analysis of NEAT-022, an open-label, randomized trials evaluating immediate (DTG-I) vs. delayed (DTG-D) switch from PI to DTG in participants ≥50 years old and Framingham risk score ≥10%	Multiple sites in Europe	ART-treated, virologically-suppressed	415	0–48-week weight change: DTG-I: +0.82 kg DTG-D: +0.25 kg (P=0.008)		48–96-week weight gain: DTG-I: +0.03 kg DTG-D: +0.98 kg (P=0.002)
Wohl, et al [22]	96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG/ABC/3TC	Multiple countries	ART-naïve	631	Weight gain at 96 weeks: DTG: +2.4 kg BIC: +3.6 kg		
Stellbrink, et al [23]	96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG +FTC/TAF	Multiple countries	ART-naïve	327	Weight gain at 96 weeks: DTG: +3.9 kg BIC: 3.5 kg		
HPTN 077 [24]	Post-hoc analysis of HPTN 077, a phase 2a study investigating CAB vs. placebo randomized 3:1 for HIV prevention; participants given ≥1 injection and with paired	U.S.	HIV-uninfected	177	Weight gain at 96 weeks: CAB: +1.1 kg Placebo: +1.0 kg (P=0.66)		

Curr Opin Infect Dis. Author manuscript; available in PMC 2021 February 01.

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings
	week 0 and week 41 data included				
Observational Cohort Data and Retrospective Studies					
TRIO Health Network [17]	Retrospective analysis of observational cohort data obtained from electronic health records and prescription data of patients who switched to an INSTI	U.S.	ART-treated, virologically-suppressed	3,468	INSTI use was significantly associated with ≥3% weight gain in bivariate analysis but was no longer significant in multivariate analysis
U.S. Military HIV NHS [25]	Observational cohort data from U.S. male military personnel; changes in BMI over 2 years after ART initiation with PIs, NNRTIs, or INSTIs	U.S.	Virologically-suppressed	496	BMI increases higher for INSTIs (and PIs) compared to NNRTIs when baseline BMI ≥25 kg/m^2; no difference in BMI increases among ART classes if baseline BMI <25 kg/m^2 or if not stratified by baseline BMI
Khan, et al [26]	Retrospective chart review of patients initiating INSTI-based regimen	India	ART-naïve and treated	331	Average weight gain at 3 months: +3.69 kg; 19.5% of patients gained >4 kg
WIHS [27]	Observational cohort data of women who switched to or added an INSTI vs. women who stayed on non-INSTI; changes in weight/BMI/body composition 6–12 mo. before and 6–18 mo. after switch/ addition of INSTI vs. stayed on non-INSTI	U.S.	ART-treated	1,118	+2.4 kg weight gain with INSTIs vs. +0.2 kg with non-INSTIs (P<0.0001); 22% of patients with ≥7% weight gain with INSTI vs. 14% with non-INSTI (P<0.0001); +1.7% body fat increase with INSTI vs. 0.3% with non-INSTI (P<0.001); greater increases in waist, hip, arm, and thigh circumference (but not waist-to-hip ratio) with INSTI; no differences among individual INSTIs
Bernstein, et al [28]	Retrospective chart review of patients who switched from PIs or NNRTIs to INSTIs vs. stayed on NNRTIs; changes in weight ~18 mo. before and after switch	U.S.	ART-treated, virologically-suppressed	260	More weight gain after switch to INSTIs vs. staying on NNRTIs (+2.73 kg vs. +0.45 kg; P=0.004); weight gain pre—switch greater than post-switch for patients on INSTIs (−0.32 kg vs. +2.68 kg; P=0.0001); no difference in weight gain among different INSTI regimens
OPERA Cohort [29]	Observational cohort data obtained from electronic health records; changes in BMI after switch to DTG, EVG, RAL, RPV, or DRV/r	U.S.	ART-treated, virologically-suppressed	10,653	Small absolute increases in BMI with all agents (statistically significant for DTG, EVG, RPV); adjusted BMI increases statistically less with EVG, RAL, and DRV/r vs. DTG at 6 months, but only DRV/r vs. DTG significant at 12 and 24 months
Zimmerman, et al [30]	Retrospective chart review of patients who switched from non-INSTIs to INSTIs; weight gain 1 year after switch	U.S.	ART-treated, virologically-suppressed	90	More weight gain after switch to INSTIs (+2.2 kg; P<0.001); 26% of patients gained ≥4.5 kg; weight gain greater when switching from NNRTIs (+2.7 kg) vs. PIs (+1.8 kg) but was not statistically significant; weight gain was greater with EVG (+2.7 kg) vs. DTG (+1.8 kg) but was not statistically significant
Bourgi, et al [31]	Retrospective observational cohort study of ART-naïve participants who initiated INSTIs, PIs, or NNRTIs;	U.S.	ART-naïve	1,152	Weight gain after 6 mo.: DTG: +2.9 kg RAL: +3.0 kg EVG: +0.6 kg NNRTI: +1.1 kg	Weight gain after 18 mo.: DTG: +6.0 kg RAL: +3.4 kg EVG: +0.5 kg NNRTI: +2.6 kg	P<0.05 for DTG, RAL, and PIs vs. EVG at both time points; P<0.05 for DTG vs. NNRTIs at 18 mo.

Study	Description of Study	Location	Study Population	# of Subjects	Main Findings		
	adjusted average weight gain after 6 and 18 mo.				PI: +2.6 kg	PI: +4.1 kg	
NA-ACCORD [32]	Observational cohort study from 17 NA-ACCORD sites; changes in weight after 2 and 5 years with INSTI, PIs, or NNRTIs; changes in weight after 2 years with DTG, RAL, or EVG	U.S.	ART-naïve	24,001	Weight gain after 2 years: INSTI: +4.9 kg PI: +4.4 kg NNRTI: +3.3 kg	Weight gain after 5 years: INSTI: +6.0 kg PI: +5.1 kg NNRTI: +4.3 kg	Weight gain after 2 years: DTG: +6.0 kg RAL: +4.9 kg EVG: +3.8 kg
Lake, et al [33]	Observational cohort study of participants previously enrolled in ACTG protocols A5001 and A5322; annual rate of weight change 2 years before and 2 years after switch to INSTI	U.S.	ART-treated, virologically-suppressed	691	Difference in weight gain pre-/post-switch: DTG: +1.0 kg/year (P=0.0009) EVG: +0.5 kg/year (P=0.11) RAL: −0.2 kg/year (P=0.37)		
HOPS [34]	Retrospective observational cohort study from 9 U.S. HIV clinics of patients who were switched to INSTI vs. non-INSTI	U.S.	ART-treated, virologically-suppressed	653	DTG and RAL (but not EVG) were associated with increases in BMI after switch; greater increases were seen with DTG vs. RAL, DTG vs. EVG, and RAL vs. EVG		

DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; EFV, efavirenz; ART, antiretroviral therapy; NAMSAL, New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries; LS, least squares; INSTI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; BIC, bictegravir; EVG, elvitegravir; ABC, abacavir; HPTN, HIV Prevention Trials Network; CAB, cabotegravir; NHS, National History Study; BMI, body mass index; WIHS, Women's Interagency HIV Study; RAL, raltegravir; RPV, rilpivirine; DRV, darunavir; r, ritonavir; NA-ACCORD, North American-AIDS Cohort Collaboration on Research and Design; ACTG, AIDS Clinical Trials Group; HOPS, HIV Outpatient Study

Table 2.

Significant Risk Factors Associated with Weight Gain from Integrase Inhibitor Use Identified in Studies Presented Over the Last 12 Months

Study	Description of Study	Risk Factors	
ADVANCE Trial [18, 19]	96-week, randomized, open-label trial of DTG + FTC/TDF or FTC/TAF vs. EFV/FTC/TDF in 1,053 ART-naïve participants from South Africa	Weight gain: • Females • DTG in combination with TAF	Treatment-emergent obesity: • Lower CD4 count • Higher HIV RNA levels • Older age • DTG in combination with TAF
NAMSAL Trial [18, 20]	48-week, randomized, open-label trial of DTG+3TC/TDF vs. EFV_{400}/3TC/TDF in 613 ART-naïve participants from Cameroon	Weight gain: • Females (total weight gain/weight gain ≥10%) • Low baseline BMI (total weight gain/weight gain ≥10%)	Treatment-emergent obesity: • Higher risk in males on DTG vs. EFV, but no difference between men and women on DTG
NEAT-022 [21]	Post-hoc analysis of NEAT-022, an open-label, randomized trials evaluating immediate (DTG-I) vs. delayed (DTG-D) switch from PI to DTG in ART-treated, virologically-suppressed participants in Europe ≥50 years old and Framingham risk score ≥10%	• Framingham risk score >15% • High blood pressure • Switch from darunavir (vs. other PIs)	
U.S. Military HIV NHS [25]	Observational cohort data from 496 virologically-suppressed U.S. male military personnel; changes in BMI over 2 years after ART initiation with PIs, NNRTIs, or INSTIs	• Blacks with baseline BMI ≥25 kg/m^2 • Increased time from HIV diagnosis to ART initiation when baseline ≥25 kg/m^2	
Khan, et al [26]	Retrospective chart review of 331 ART-naïve and treated patients from India initiating INSTI-based regimen	• Opportunistic infections	
WIHS [27]	U.S. observational cohort data of 1,118 ART-treated women who switched to or added an INSTI vs. women who stayed on non-INSTI; changes in weight/BMI/body composition 6–12 mo. before and 6–18 mo. after switch/addition of INSTI vs. stayed on non-INSTI	• Minority race/ethnicity • CD4 count ≥350 cells/mm^3 • Undetectable HIV RNA • Age ≥50 years • BMI <30 kg/m^2	
Bernstein, et al [28]	Retrospective chart review of 260 ART-treated, virologically-suppressed patients in U.S. who switched from PIs or NNRTIs to INSTIs vs. stayed on NNRTIs; changes in weight ~18 mo. before and after switch	• Lower weight or BMI at time of switch • Younger age	
Lake, et al [33]	U.S. observational cohort study of 691 ART-treated, virologically-suppressed participants previously enrolled in ACTG protocols A5001 and A5322; annual rate of weight change 2 years before and 2 years after switch to INSTI	• Women • Blacks • Age ≥60 years • INSTI in combination with ABC (subset sample sizes limited, however) • EVG in combination with TAF (subset sample sizes limited, however)	

DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; EFV, efavirenz; ART, antiretroviral therapy; NAMSAL, New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-income countries; BMI, body mass index; NHS, National History Study; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase inhibitors; ACTG, AIDS Clinical Trials Group; ABC, abacavir; EVG, elvitegravir

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