SAGE Open Medicine
Volume 12: 1–9

DOI: 10.1177/20503121241260613
journals.sagepub.com/home/smo
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A review of dolutegravir-associated weight gain and secondary metabolic comorbidities

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Abstract

Dolutegravir is an integrase inhibitor and is recommended by the World Health Organization as the preferred first-line and second-line human immunodeficiency virus treatment in all populations. Excessive weight gain associated with dolutegravir-based regimens is an emerging issue; however, the long-term metabolic consequences of this effect have not been fully understood. Growing evidence shows that this leads to a higher incidence of hyperglycemia, hypertension, and metabolic syndrome, along with elevated cardiovascular risk. Dolutegravir-based regimens, also associated with greater adipocyte differentiation and greater expression of markers associated with lipid storage, continue to be a problem among patients living with human immunodeficiency virus. The mechanisms by which certain antiretroviral therapy agents differentially contribute to weight gain remain unknown. Some clinical investigators speculate that dolutegravir could interfere with central nervous system appetite regulation (melanocortin-4 receptor) and insulin signaling, or may have better penetration of adipose tissue where they could exert a direct impact on adipose tissue adipogenesis, fibrosis, and insulin resistance. This review summarizes our current understanding of weight gain and fat changes associated with dolutegravir and its possible secondary metabolic comorbidities.

Keywords

Dolutegravir, integrase inhibitors, weight gain, HIV, metabolic comorbidities

Date received: 15 December 2023; accepted: 23 May 2024

Background

The introduction of highly active antiretroviral therapy has resulted in a reduction in morbidity associated with opportunistic infections as well as a significant decrease in mortality among persons with HIV (PWH).[1] However, metabolic disorders and their associated comorbidities, such as cardiovascular disease (CVD) and diabetes, continue to pose a challenge to our ability to provide effective long-term treatment to this population.[2] Traditional risk factors like smoking and dyslipidemia, as well as HIV-related inflammation and immune activation, are well-known causes of cardiometabolic comorbidities in ART-treated PWH.[3] However, obesity and weight gain after starting ART are becoming increasingly recognized problems in today's HIV treatment paradigm.[4] Weight gain after starting antiretroviral treatment has become a concern in recent years.[5] Although weight gain may be a positive prognostic indicator in PWH who are underweight at the time of ART initiation,[6–8] it may increase the risk of cardiovascular and metabolic diseases in those who are normal or overweight.[6,9]

There is growing evidence that people who take the integrase inhibitor dolutegravir (DTG) are more likely to gain weight after starting treatment.[10] DTG is an antiretroviral drug that belongs to the class of integrase strand transfer inhibitors (INSTIs) and was approved in Canada in October 2013.[11] The World Health Organization (WHO) recommends a DTG-based regimen as first-line ART due to its non-inferiority antiviral efficacy, high genetic barrier to resistance, and lower potential for adverse drug effects.[12] However, several studies have investigated the relationship between DTG use and weight gain in PWH.[13–15] Recent studies, including two randomized trials in Sub-Saharan Africa, have shown that DTG causes significant weight gain in ART-naive patients who are starting DTG for the first time.[10,15,16] In addition,

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switching from a protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)-based regimen to a DTG-based regimen results in weight gain in ART-experienced patients.[14,17] In this review, the current understanding of weight gain and fat changes associated with DTG and its possible secondary metabolic comorbidities is summarized.

Methodology

This narrative review includes studies from research databases such as Scopus, PubMed, PubMed Central (PMC), Web of Science, Google Scholar, and Cochrane Library that were published in or translated into English. The keywords used were "dolutegravir," "weight gain," "metabolic comorbidities," and "dolutegravir-associated weight gain." Randomized controlled trials, retrospective studies, review articles, cohort studies, and observational studies were included. The review considered studies involving adult populations. There was no set time frame for study inclusion, although the author prioritized recently published papers. As this paper reviews studies of various designs, it is limited in its ability to directly compare the study outcomes.

Evidence of weight gain with dolutegravir

Emerging evidence from ART initiation studies suggests that DTG may play a role in weight gain. In Sub-Saharan Africa, two randomized controlled trials compared DTG and efavirenz (EFV) in ART-naïve PWH. The NAMSAL study randomized 613 ART-naïve PWH to either DTG or EFV, both combined with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), and the ADVANCE study randomized 1053 ART-naïve PWH to DTG or EFV at the standard dose of 600 mg, both combined with FTC and TDF, and a third arm of DTG combined with FTC and tenofovir alafenamide (TAF). In both studies, participants randomized to DTG gained more weight than those on EFV.[18,19] In a Brazilian cohort study of 495 participants, investigators observed that those starting ART with DTG had a mean increase in body mass index (BMI) of 1.02 kg/m^2, whereas those who used DTG after the therapeutic change had an increase of 0.56 kg/m^2 over 96 weeks.[20] Likewise, the randomized controlled trials compared DTG/abacavir (ABC)/lamivudine (3TC) and bictegravir (BIC)/FTC/TAF in treatment-naïve patients. At 96 weeks, patients on DTG/ABC/3TC had a mean weight gain of 2.4 kg compared to those on BIC/FTC/TAF (3.6 kg).[21]

In addition to ART initiation trials, numerous ART switch trials also show an increase in weight after PWH switches to DTG from alternate ART regimens (NNRTIs, PIs, and non-DTG INSTIs).[13,17,22] In the retrospective observational study, the investigator assessed weight change over 18 months in patients who switched from EFV/TDF/FTC to an INSTI-containing regimen or a PI-containing regimen versus those on EFV/TDF/FTC. Patients who switched to an INSTI-containing regimen gained an average of 2.9 kg compared to 0.9 kg among those who continued on EFV/TDF/FTC, while those who switched to a PI regimen gained 0.7 kg. Among INSTI regimens, those who switched to DTG/ABC/3TC gained the most weight at 18 months.[17] This was supported by another study that assessed 460 virally suppressed adolescents who transitioned to DTG, showing an increased rate of BMI change by 0.8 kg/m^2 per year in the year after DTG started to a rate of 1.2 kg/m^2 per year.[23]

Several subsequent studies have supplemented these preliminary findings. For example, in the retrospective observational study, the investigator reported that a DTG-based regimen was significantly associated with greater weight gain than other INSTI- or PI-based regimens.[13] Likewise, the African Cohort Study (AFRICOS) found a 1.3 kg weight gain and a 0.44 kg/m^2 increase in BMI among participants in the first year after the transition to DTG + 3TC + TDF.[24] A retrospective observational cohort study of HIV patients who have been shifted from EFV/TDF/3TC to DTG/TDF/3TC and those who have been maintained on EFV/TDF/3TC have been on a specified regimen for at least 1 year. Patients on a DTG-based regimen had a mean weight gain of 3.88 ± 2.021 kg in 1 year compared to those on an EFV-based regimen (2.26 ± 2.39 kg).[22]

By contrast, two recent studies of DTG in treatment-naive patients did not report weight change. The SPRING-2 study compared DTG versus raltegravir (RAL), while the FLAMINGO trial compared DTG versus darunavir (both studies also included nucleoside reverse transcriptase inhibitors (NRTIs)).[25,26] Likewise, the SINGLE trial compared DTG/ABC/3TC versus fixed-dose EFV/TDF/FTC in treatment-naïve patients. At 48 weeks, the incidence of weight gain recorded as an adverse event was 6 of 414 subjects on DTG/ABC/3TC versus 3 of 419 subjects on EFV/TDF/FTC.[27]

In general, these studies support more weight gain with DTG (especially when switching from NNRTIs), but the data are inconsistent and many must be interpreted cautiously because they originate from observational cohorts and/or retrospective analyses. Further details on some studies can be found in subsequent sections (Table 1).

Body composition and fat changes with dolutegravir

Dolutegravir causes changes in the structure of fat cells that may promote obesity and insulin resistance, according to studies of cells taken from HIV-positive people and monkeys given the drug.[35] However, it is unclear how INSTIs may affect metabolism and lead to weight gain.[36] A study from France found that DTG has direct effects on adipose tissue, which could lead to weight gain.[35] To see whether INSTIs affect fat cells directly, DTG was given to human adipose stem cells from HIV-negative women in the laboratory

Table 1. Summary of studies assessing dolutegravir-induced weight Gain.

Design	Description of study	Study population	Number of participants	Main findings	References
RCT	A 96-week, open-label, randomized trial of DTG + FTC/TDF or DTG + FTC/TAF vs. EFV/FTC/TDF	ART-naïve	1053	Weight gain at 96 weeks: DTG + FTC/TAF: +8 kg, DTG + FTC/TDF: +5 kg, EFV/FTC/TDF: +2 kg	Venter et al.[19]
RCT	A 48-week, open-label, randomized trial of DTG + 3TC/TDF vs. EFV400+/3TC/TDF	ART-naïve	613	Weight gain at 48 weeks: DTG: +5 kg, EFV: +3 kg	Calmy et al.[18]
RCT	Post hoc analysis of NEAT-022, an open-label, randomized trial evaluating immediate (DTG-I) vs. delayed (DTG-D) switch from PI to DTG in participants ⩾50 years old and Framingham risk score ⩾10%	ART-treated, virologically suppressed	415	From 0 to 48 weeks weight change: DTG-I: +0.82 kg, DTG-D: +0.25 kg, ($p = 0.008$), from 48 to 96 weeks weight change: DTG-I: +0.03 kg, DTG-D: +0.98 kg in ($p = 0.002$)	Waters et al.[28]
RCT	A 96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG + FTC/TAF	ART-naïve	327	Weight gain at 96 weeks: DTG: +3.9 kg, BIC: 3.5 kg	Stellbrink et al.[29]
RCT	A 96-week, randomized, double-blinded, active-controlled, non-inferiority study of BIC/FTC/TAF vs. DTG/ABC/3TC	ART-naïve	631	Weight gain at 96 weeks: DTG: +2.4 kg, BIC: +3.6 kg	Wohl et al.[21]
RCT	A 144-week, randomized, non-inferiority study (double-blind through 96 weeks) of DTG + 3TC vs. DTG + TDF/FTC	ART-naïve	1433	Weight gain at 144 weeks: DTG + 3TC: 3.7 ± 6.8 kg, DTG + TDF/FTC: 2.4 ± 7.6 kg	Cahn et al.[30]
Retrospective study	Retrospective chart review of patients who switched from non-INSTIs (NNRTIs or PIs) to INSTIs; weight gain 1 year after switch	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	Zimmerman et al.[31]
Retrospective study	Retrospective observational cohort study of ART-naïve participants who initiated INSTIs, PIs, or NNRTIs; adjusted average weight gain after 6 and 18 months.	ART-naïve	1152	Weight gain after 6 months: DTG: +2.9 kg, RAL: +3.0 kg, EVG: +0.6 kg, NNRTI: +1.1 kg, PI: +2.6 kg. Weight gain after 18 months: DTG: +6.0 kg, RAL: +3.4 kg, EVG: +0.5 kg, NNRTI: +2.6 kg, PI: +4.1 kg	Bourgi et al.[32]
Observational cohort	An 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	ART-treated, virologically suppressed		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 ($p = 0.37$)	Lake et al.[33]
Retrospective observational cohort	Retrospective observational cohort study from 9 U.S. HIV clinics of patients who were switched to INSTI vs. non-INSTI	ART-treated, virologically suppressed	653	DTG and RAL (but not EVG) were associated with increases in BMI after the switch; greater increases were seen with DTG vs. RAL, DTG vs. EVG, and RAL vs. EVG	Palella et al.[34]
Retrospective observational study	Retrospective observational study of ART-naïve participants who initiated INSTIs, PIs, or NNRTIs; mean adjusted weight gain after 3 and 5 years	ART-naïve	1579	Weight gain after 3 years: DTG: 3.9 kg, DRV: 3.1 kg, EVG: 2.4 kg, RAL: 1.9 kg, LPV: 1.8 kg, ATV: 2.3 kg. Weight gain after 5 years: DTG: 5.3 kg, DRV: 4.1 kg, EVG: 4.6 kg, RAL: 1.9 kg, LPV: 2.1 kg, ATV: 2.3 kg	Ando et al.[14]
Retrospective observational cohort	Retrospective observational cohort study of HIV patients who have been shifted from EFV+/TDF/3TC to DTG+/TDF/3TC and those who have been maintained on EFV+/TDF/3TC have been on a specified regimen for at least 1 year	ART-treated, virologically suppressed	422	Weight gain after 1 year: DTG: 3.88 ± 2.021 kg, EFV: 2.26 ± 2.39 kg	Eifa et al.[22]

ART: antiretroviral therapy; RCT: randomized controlled trial; DTG: dolutegravir; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; EFV: efavirenz; PIs: protease inhibitors; 3TC: lamivudine; HIV: human immunodeficiency virus; BIC: bictegravir; ABC: abacavir; INSTIs: integrase strand transfer inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; ACTG: AIDS clinical trials group; BMI: body mass index; DRV: darunavir; EVG: elvitegravir; RAL: raltegravir; LPV: lopinavir; ATV: atazanavir.

before and during the differentiation process into adipocytes. Dolutegravir was linked to increased production of collagen types linked to adipocyte fibrosis and obesity.[35] As well, INSTI treatment led to elevated levels of collagen, fibronectin, and the myofibroblast marker, that is, smooth muscle α actin (αSMA).[35,37] In adipocytes, DTG upregulates the expression of collagen proteins and induces adipose tissue fibrosis by promoting a profibrotic phenotype in adipose stem cells and adipocytes.[38]

Dolutegravir exposure was associated with greater adipocyte differentiation and greater expression of markers associated with lipid storage.[38] Cells exposed to DTG had higher levels of lipid accumulation, lower levels of leptin and adiponectin, and a lower uptake of glucose compared to control samples in vitro studies.[35,39] Besides, DTG also promotes lipid accumulation when added to already-differentiated mature adipocytes. These results indicate that INSTIs (particularly DTG) enhance adipogenesis and lipogenesis in differentiated adipose stem cells and mature adipocytes.[35] However, another study found that DTG has no significant effect on human adipose cell differentiation.[40] Consequently, further laboratory-based studies may be needed to understand the mechanism of the association between adipose tissue and DTG.

Risk factors for weight gain and fat changes with dolutegravir

Weight gain is more likely in women, black people, and people taking TAF as a DTG companion drug.[5,33,41] However, in AFRICOS, there was also a difference in weight gain between men and women, with women having a greater weight gain 1 year post-DTG + 3TC + TDF switch, but this difference was not significant after the first year.[24] According to some studies, regimens with NNRTI anchors appeared to have greater weight gain than PIs anchors when transitioning to DTG-based regimens[33]; however, there are conflicting data.[42] In AFRICOS, there is no clear evidence of an overall increase in the rate of weight gain following a switch to a DTG-based regimen.[24]

There were more women in the NAMSAL study who had a 10% change in weight from baseline in the DTG + 3TC/TDF arm than in the EFV/3TC/TDF arm, a difference not seen in men. Men on DTG + 3TC/TDF, on the other hand, were more likely than men on EFV/3TC/TDF to develop obesity, which was not observed in women. Surprisingly, there was no difference in overweight or obesity incidence between men and women on DTG after 48 weeks, even though more women gained 10% of their body weight.[18] In the ADVANCE study, women on DTG + FTC/TAF gained more weight than men on DTG + FTC/TDF.[43] Recent studies have shown that TAF is associated with body weight gain.[5,44] Especially, the combination of TAF and INSTIs has been reported to be associated with an increase in body weight both in treatment-naïve patients[5] and treatment-experienced patients.[45] As for TAF use, the pathophysiology of weight gain is not elucidated at this time but may include, among persons switching from a TDF-based regimen, the absence of weight gain suppression exerted by TDF use, involving much higher plasma levels of tenofovir.[46] The mechanism by which TDF suppresses weight gain is by suppression of appetite or weight gain with potential mitochondrial toxicity.[47]

Following ART initiation, both lean and fat mass increased, and a lower CD4+ T-cell count, a higher baseline HIV-1 RNA, and older age were associated with treatment-emergent obesity.[41] HIV patients with long-term viral suppression gained significantly more weight after switching from daily, fixed-dose EFV/TDF/FTC to an INSTI-containing regimen compared to those who remained on EFV/TDF/FTC. Those who switched to the DTG/ABC/3TC regimen gained the most weight.[17] A baseline CD4 cell count of <200 cells/mm^3 and a lack of ART were associated with a greater weight change from baseline.[48] Indeed, HIV infection itself and virus activity may also play a role in weight changes. ART-naïve patients and those with the lowest CD4 T-cell counts were at higher risk of weight gain, supporting the hypothesis that weight gain might be explained, at least in part, as a "return to health" phenomenon, the result of successfully suppressing viral replication, controlling inflammation, and normalizing resting energy expenditure.[49]

Potential mechanisms of weight gain and fat changes with dolutegravir

The mechanism of weight gain attributable to DTG is unknown, but some mechanisms have been postulated. One possible explanation is the rapid drop in viral load seen with DTG-based regimens and the correlation of virologic suppression with lower energy expenditure.[50] A long-term viral infection depletes fat stores. Body fat stores are replenished when people recover from a severe infection.[51] Another possible mechanistic explanation is possible differences in the effects of ART regimens on systems that regulate energy homeostasis and food intake, as well as insulin resistance. For example, DTG has been shown in vitro to inhibit the activity of the melanocortin-4 receptor (MC4R). Melanocortin-4 receptor is involved in human energy homeostasis, and MC4R-knockout mice are severely obese when both alleles are nonfunctional and moderately obese when only one allele is compromised.[52] In the general population, women have higher circulating leptin levels,[53] subcutaneous adipose tissue leptin mRNA expression,[54] subcutaneous adipose tissue metabolic rates,[55] and more hypothalamic-to-subcutaneous adipose tissue neuronal connections than men,[56] and leptin stimulates the production of pro-opiomelanocortin peptides (POMCs), which reduce food intake and body weight through the MC4R receptor.[57,58] Furthermore, leptin receptor expression on POMC neurons may be required for fat

distribution modulation in women but not in men.[59] Early implications of DTG weight gain: animal and human studies of MC4R/POMC deficiency suggest that pharmacologic MC4R agonism induces weight loss and that people with POMC deficiency benefit more than people with MCR4 deficiency.[60] Data from PWH are contradictory[61,62] in their reporting of sex differences in leptin insufficiency or resistance or do not report sex-stratified results, but it is reasonable to speculate that women may have a differential or more exacerbated response to DTG-induced MC4R functional insufficiency. This is also a proposed mechanism for the weight gain associated with antipsychotics and merits further study with DTG.[63] Clearly, there is no single process that explains DTG-associated weight gain.

The most influential study negating that DTG is causative in weight gain came from the ADVANCE clinical trial.[64] Previous research has shown that EFV is metabolized through the cytochrome P450 2B6 enzyme (CYP2B6) pathways and that slow metabolizers exhibit significant side effects closely associated with elevated drug levels, such as metabolic changes, central nervous system symptoms, and hepatic injury.[65,66] Afterward, researchers found that slow metabolizers of EFV who switched to INSTI-containing regimens gained the most weight.[67] Griesel et al.[64] showed that medium and fast metabolizers of EFV had the same weight trajectory as the DTG arm once the slow metabolizers were removed from the analysis, and a subsequent study found that increasing EFV levels in the cohort was associated with greater weight loss.[67]

Metabolic comorbidities of dolutegravir-induced weight gain

Weight gain soon after beginning treatment reduces the risk of death in people who were previously underweight. This is an illustration of the "return to health" effect.[6,7] Prior research, however, indicates that weight gain following ART initiation increases the risk of diabetes and CVD.[6,9] For example, a cohort study report showed that a 1 kg/m^2 increase in BMI after initiating ART could have a 12% increased risk of developing diabetes and an 18%–20% increased risk of developing CVD, regardless of the pre-ART BMI,[6] but little is known about whether weight gain with DTG has different effects in terms of comorbidity risk. Several recent studies have suggested that, despite weight gain from DTG, there may not be an equal increase in clinically significant metabolic parameters,[68,69] although the data are conflicting.[70–72] The prevalence of metabolic syndrome was estimated to be around 10 cases per 1000 person-years.[48] A higher prevalence of metabolic syndrome in PWH than in the general population has previously been reported,[73] with an estimated incidence in developed countries ranging between 8 and 14 cases per 100 person-years.[74–76] The ACTG A5001 and A5322 trials found that weight gain was associated with lower high-density lipoprotein (HDL) levels and higher levels of low-density lipoprotein (LDL), total cholesterol (TC), triglyceride (TG) levels, and fasting blood glucose (FBG) among PWH on an INSTIs-based regimen.[33] However, in the SCOLTA prospective cohort study, blood levels of TC, TC/TG, and FBG did not differ between weight gainers and non-gainers, indicating that the metabolic impact of weight gain was minimal.[48]

The impact of DTG on insulin sensitivity is still subject to debate. Some researchers have not observed any impact of DTG on the homeostatic model assessment of insulin resistance or glycemia.[25,77] Nonetheless, other researchers have found that DTG promoted insulin resistance and lowered circulating adiponectin levels.[71,78] Adiponectin expression was low in the subcutaneous adipose tissue of DTG-treated macaques.[35] In addition, despite DTG's proadipogenic effect in vitro, the drug can impair adipocyte function, resulting in insulin resistance and low leptin and adiponectin secretion.[40] Furthermore, long-term exposure to DTG blunts insulin-stimulated glucose transport and induces insulin resistance in adipocyte-differentiated adipose stem cells (ASCs).[35] In addition, DTG increased reactive oxygen species production and induced mitochondrial dysfunction characterized by increased mitochondrial mass and decreased membrane potential in proliferating ASCs and, to a lesser extent, in adipocytes.[35] Surprisingly, increased levels of oxidative stress have been linked to insulin resistance in vitro and in obese individuals.[79,80]

Fibrosis is a major feature of adipose tissue dysfunction, and it has been linked to metabolic disorders.[35,81] Excess visceral fat is linked to several cardiometabolic risk factors, including high blood pressure, LDL, insulin, and glucose resistance, as well as a decrease in HDL.[82] A large study of over 49,000 people who were followed for 5 years after starting treatment discovered that those who had normal body weight when they started treatment had a higher risk of CVD the more weight they gained after starting treatment.[6] Obesity is associated with adipose tissue expansion, which can result from either adipocyte hypertrophy or hyperplasia.[81] Obesity plays a role in the development of non-alcoholic fatty liver disease (NAFLD).[83] Bischoff et al.[84] showed that the use of INSTIs increases the occurrence of hepatic steatosis and the progression to non-alcoholic steatohepatitis (NASH) in the context of increased body weight. Non-alcoholic fatty liver disease is a risk factor for liver cancer and promotes the development of diabetes and CVD.[85] In general, the impact of DTG on adipose tissue and its possible secondary metabolic comorbidities are described in Figure 1.

This work represents a narrative review. As a result, it has a limited scope and does not provide a comprehensive review of the subject matter. The authors did not systematically review the literature, and there were no direct comparisons between studies. Therefore, the material included and the conclusions drawn are subjective, non-comprehensive, and subject to the bias of the author.

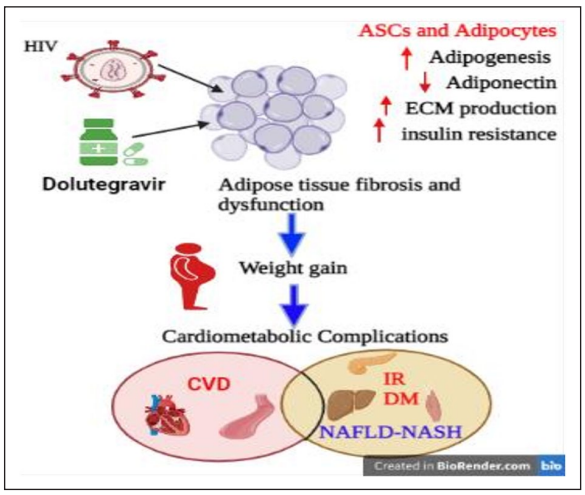

Figure 1. Impact of dolutegravir on adipose tissue and its possible metabolic comorbidities.
CVD: cardiovascular disease; IR: insulin resistance; DM: diabetes mellitus; NAFLD: non-alcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; ECM: extracellular matrix; ASCs: adipose-derived stromal/stem cells.

Conclusion and future perspectives

There is mounting evidence that DTG-based regimens cause more weight gain and treatment-emergent obesity than other ART regimens, although data are inconsistent, and more randomized studies accounting for diet and lifestyle factors are needed. It is unclear whether DTG-based regimens cause lipid accumulation or increase the risk of cardiometabolic co-morbidities. Therefore, further studies are needed to confirm these findings in larger, multicenter cohorts and investigate the effects on cardiometabolic disease risk factors. There remains much to be learned, both about the mechanisms of DTG-associated weight gain and its health impacts. Future studies are needed to provide more definitive answers to these questions.

Acknowledgements

Not applicable.

Author contributions

Mohammed Jemal is involved in the conceptualization of this review, prepared manuscript draft and writing-up, manuscript approval and validation, manuscript editing, language editing, and design, as this author is the sole author of this manuscript, involved in all aspects of this paper.

Data sharing statement

Supporting data are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Not applicable.

Informed consent

Not applicable.

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References

1. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA* 2012; 308(4): 387–402.
2. Nansseu JRN and Bigna JJR. Antiretroviral therapy related adverse effects: can sub-Saharan Africa cope with the new "test and treat" policy of the World Health Organization? *Infect Dis Poverty* 2017; 6(1): 24.
3. Lake JE and Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis* 2013; 13(11): 964–975.
4. Godfrey C, Bremer A, Alba D, et al. Obesity and fat metabolism in human immunodeficiency virus-infected individuals: immunopathogenic mechanisms and clinical implications. *J Infect Dis* 2019; 220(3): 420–431.
5. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis* 2020; 71(6): 1379–1389.
6. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med* 2016; 17(4): 255–268.
7. Yuh B, Tate J, Butt AA, et al. Weight change after antiretroviral therapy and mortality. *Clin Infect Dis* 2015; 60(12): 1852–1859.
8. Sharma A, Hoover DR, Shi Q, et al. Relationship between body mass index and mortality in HIV-infected HAART users in the Women's Interagency HIV Study. *PLoS One* 2015; 10(12): e0143740.
9. Herrin M, Tate JP, Akgün KM, et al. Weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared with uninfected individuals. *J Acquir Immune Defic Syndr* 2016; 73(2): 228–236.
10. Pérez SE, Chow SP, Kania A, et al. Weighing in on the role of Integrase Strand Transfer Inhibitors (INSTIs) on weight gain: fact or fiction? *Curr Infect Dis Rep* 2020; 22(7): 19.
11. Dow DE and Bartlett JA. Dolutegravir, the second-generation of Integrase Strand Transfer Inhibitors (INSTIs) for the treatment of HIV. *Infect Dis Ther* 2014; 3(2): 83–102.
12. WHO. *WHO recommends dolutegravir as preferred HIV treatment option in all populations*. Mexico City, 2019.
13. Ando N, Nishijima T, Mizushima D, et al. Long-term weight gain after initiating combination antiretroviral therapy in

treatment-naïve Asian people living with human immunodeficiency virus. *Int J Infect Dis* 2021; 110: 21–28.
14. Tse J, Prajapati G, Zhao X, et al. Weight gain following switch to integrase inhibitors from non-nucleoside reverse transcriptase or protease inhibitors in people living with HIV in the United States: analyses of electronic medical records and prescription claims. *Curr Med Res Opin* 2023; 39(9): 1237–1246.
15. NAMSAL ANRS 12313 Study Group. Kouanfack C, Mpoudi-Etame M, et al. Dolutegravir-based or low-dose efavirenz–based regimen for the treatment of HIV-1. *N Engl J Med* 2019; 381(9): 816–826.
16. McCann K, Moorhouse M and Sokhela S. The ADVANCE clinical trial: changes from baseline to week 96 in DXA-assessed body composition in TAF/FTC+DTG compared to TDF/FTC+DTG2019: and TDF/FTC/EFV. In: *17th European AIDS conference*, Basel, Switzerland, 6–9 November 2019.
17. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr* 2017; 76(5): 527–531.
18. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV* 2020; 7(10): e677–e687.
19. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomized, phase 3, non-inferiority trial. *Lancet HIV* 2020; 7(10): e666–e676.
20. de Souza CR, Ceccato MGB, dos Santos SF, et al. Alterações no índice de massa corporal: coorte em indivíduos em uso de dolutegravir. *Res Soc Develop* 2021; 10(16): e65101623189.
21. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; 6(6): e355–e363.
22. Eifa BA and Ketema W. Could a dolutegravir-based antiretroviral therapy lead to clinical obesity? A retrospective cohort study conducted at Hawassa University Comprehensive Specialized Hospital in Hawassa, Sidama, Ethiopia. *AIDS Res Treat* 2022; 2022: 2965325.
23. Thivalapill N, Simelane T, Mthethwa N, et al. Transition to dolutegravir is associated with an increase in the rate of body mass index change in a cohort of virally suppressed adolescents. *Clin Infect Dis* 2020; 73(3): e580–e586.
24. Esber AL, Chang D, Iroezindu M, et al. Weight gain during the dolutegravir transition in the African Cohort Study. *J Int AIDS Soc* 2022; 25(4): e25899.
25. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet (London, England)* 2013; 381(9868): 735–743.
26. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet (London, England)* 2014; 383(9936): 2222–2231.
27. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; 369(19): 1807–1818.
28. Waters L, Assoumou L, Rusconi S, et al. Switch to dolutegravir from a boosted protease inhibitor associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial. *J Int AIDS Soc* 2018; 21: 77.
29. Stellbrink H-J, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; 6(6): e364–e372.
30. Cahn P, Sierra Madero J, Arribas JR, et al. Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy—naive adults with HIV-1 infection. *AIDS* 2022; 36(1):39–48.
31. Zimmerman M, DeSimone J and Schafer JJ. 332 Exploring the prevalence and characteristics of weight gain and other metabolic changes in patients with HIV infection switching to integrase inhibitor containing ART. *Open Forum Infect Dis* 2019; 6(Suppl 2): S176–S177.
32. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis* 2020; 70(7): 1267–1274.
33. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor–based antiretroviral therapy. *Clin Infect Dis* 2020; 71(9): e471–e477.
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. In: *Poster presented at conference on Retroviruses and Opportunistic Infections (CROI)*, Seattle, WA, USA, 19–22 February 2019.
35. Gorwood J, Bourgeois C, Pourcher V, et al. The integrase inhibitors dolutegravir and raltegravir exert proadipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis* 2020; 71: e549–e560.
36. Eckard AR and McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis* 2020; 33(1): 10–19.
37. Mia MM and Bank RA. The pro-fibrotic properties of transforming growth factor on human fibroblasts are counteracted by caffeic acid by inhibiting myofibroblast formation and collagen synthesis. *Cell Tissue Res* 2016; 363(3): 775–789.
38. Bosch B. DTG and weight gain, 2020. https://sahivsoc.org/Files/Bosch%20-%2019%20Nov%202020.pdf (2020, accessed 17 september 2023).
39. Pickering RT, Asundi A and Lin N. In vitro model to assess antiretroviral therapy on adipocyte biology. In: *Conference on Retroviruses and Opportunistic Infections (CROI), 2021(CROI Abstract 514)*, Boston, MA, USA, 6–10 March 2021.
40. Domingo P, Quesada-López T, Villarroya J, et al. Differential effects of dolutegravir, bictegravir and raltegravir in adipokines and inflammation markers on human adipocytes. *Life Sci* 2022; 308: 120948.
41. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med* 2019; 381(9): 803–815.

42. Burns JE, Stirrup OT, Dunn D, et al. No overall change in the rate of weight gain after switching to an integrase-inhibitor in virologically suppressed adults with HIV. *AIDS* 2020; 34(1): 109–114.
43. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. *Lancet HIV* 2020; 7(10): e677–e687.
44. Hill A, Venter W, Delaporte E, et al. Progressive rises in weight and clinical obesity for TAF/FTC/DTG and TDF/FTC/DTG versus TDF/FTC/EFV: ADVANCE and NAMSAL trials. *J Int AIDS Soc* 2019; 2019: 22.
45. Surial B, Mugglin C, Calmy A, et al. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: a cohort study. *Ann Intern Med* 2021; 174(6): 758–767.
46. Shah S, Pilkington V and Hill A. Is tenofovir disoproxil fumarate associated with weight loss? *AIDS* 2021; 35(Suppl 2): S189–S195.
47. Wood BR and Huhn GD. Excess weight gain with integrase inhibitors and tenofovir alafenamide: what is the mechanism and does it matter? *Open Forum Infect Dis* 2021; 8(12): ofab542.
48. Taramasso L, Bonfanti P, Ricci E, et al. Factors associated with weight gain in people treated with dolutegravir. *Open Forum Infect Dis* 2020; 7: ofaa195.
49. Tate T, Willig AL, Willig JH, et al. HIV infection and obesity: where did all the wasting go? *Antiviral Ther* 2012; 17(7): 1281–1289.
50. Bourgi K, Jenkins CA, Rebeiro PF, et al. Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada. *J Int AIDS Soc* 2020; 23(4): e25484.
51. Kumar S and Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol* 2018; 9: 705.
52. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* 1997; 88(1): 131–141.
53. Saad MF, Damani S, Gingerich RL, et al. Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab* 1997; 82(2): 579–584.
54. Montague CT, Prins JB, Sanders L, et al. Depot- and sex-specific differences in human leptin mRNA expression: implications for the control of regional fat distribution. *Diabetes* 1997; 46(3): 342–347.
55. Nookaew I, Svensson PA, Jacobson P, et al. Adipose tissue resting energy expenditure and expression of genes involved in mitochondrial function are higher in women than in men. *J Clin Endocrinol Metab* 2013; 98(2): E370–E378.
56. Adler ES, Hollis JH, Clarke IJ, et al. Neurochemical characterization and sexual dimorphism of projections from the brain to abdominal and subcutaneous white adipose tissue in the rat. *J Neurosci* 2012; 32(45): 15913–15921.
57. Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci* 2005; 8(5): 571–578.
58. Gautron L, Elmquist JK and Williams KW. Neural control of energy balance: translating circuits to therapies. *Cell* 2015; 161(1): 133–145.
59. Shi H, Strader AD, Sorrell JE, et al. Sexually different actions of leptin in proopiomelanocortin neurons to regulate glucose homeostasis. *Am J Physiol Endocrinol Metab* 2008; 294(3): E630–E639.
60. Collet TH, Dubern B, Mokrosinski J, et al. Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. *Mol Metab* 2017; 6(10): 1321–1329.
61. Tiliscan C, Aramă V, Mihăilescu R, et al. Leptin expression in HIV-infected patients during antiretroviral therapy. *Germs* 2015; 5(3): 92–98.
62. Onyemelukwe G, Ogoina D and Bakari A. Serum leptin levels in antiretroviral therapy naive HIV-1 infected patients in Zaria, Nigeria. *Int J Endocrinol Metab* 2009; 7(3): e94623.
63. Bares SH. *Is modern antiretroviral therapy causing weight gain?* Oxford, UK: Oxford University Press, 2020, pp. 1390–1392.
64. Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 genotype and weight gain differences between dolutegravir and efavirenz. *Clin Infect Dis* 2021; 73(11): e3902–e3909.
65. Leger P, Chirwa S, Turner M, et al. Pharmacogenetics of efavirenz discontinuation for reported central nervous system symptoms appears to differ by race. *Pharmacogen Genom* 2016; 26(10): 473–480.
66. Desta Z, Saussele T, Ward B, et al. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. *Pharmacogenomics* 2007; 8(6): 547–558.
67. Leonard MA, Cindi Z, Bradford Y, et al. Efavirenz pharmacogenetics and weight gain following switch to integrase inhibitor-containing regimens. *Clin Infect Dis* 2021; 73(7): e2153–e2163.
68. Hsu R, Brunet L, Fusco JS, et al. 341. Risk of type 2 diabetes mellitus after antiretroviral therapy initiation in individuals living with HIV in the United States. *Open Forum Infect Dis* 2019; 6(Supplement_2): S181–S182.
69. 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): 731–738.
70. Rebeiro PF, Rebeiro PF, Jenkins C, et al. LB9. The effect of initiating integrase inhibitor-based vs. Non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy on progression to diabetes among North American persons in HIV care. *Open Forum Infect Dis* 2019; 6(Suppl 2): S996–S997.
71. McLaughlin M, Walsh S and Galvin S. Dolutegravir-induced hyperglycaemia in a patient living with HIV. *J Antimicrob Chemother* 2017; 73(1): 258–260.
72. Odenyo JA. *Prevalence of dolutegravir associated hyperglycemia and its covariates among persons living with HIV on Treatment at Kenyatta National Hospital*. Nairobi: University of Nairobi, 2020.
73. Bonfanti P, Giannattasio C, Ricci E, et al. HIV and metabolic syndrome: a comparison with the general population. *J Acquir Immune Defic Syndr* 2007; 45(4): 426–431.

74. Palacios R, Santos J, González M, et al. Incidence and prevalence of the metabolic syndrome in a cohort of naive HIV-infected patients: prospective analysis at 48 weeks of highly active antiretroviral therapy. *Int J STD AIDS* 2007; 18(3): 184–187.
75. Freitas P, Carvalho D, Souto S, et al. Impact of lipodystrophy on the prevalence and components of metabolic syndrome in HIV-infected patients. *BMC Infect Dis* 2011; 11: 246.
76. Jacobson DL, Tang AM, Spiegelman D, et al. Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). *J Acquir Immune Defic Syndr* 2006; 43(4): 458–466.
77. Lo J, Oyee J, Crawford M, et al. Dolutegravir and insulin resistance. In: *Conference on Retroviruses and Opportunistic Infections*, Denver, Colorado, 3–6 March 2019.
78. Hailu W, Tesfaye T and Tadesse A. Hyperglycemia after dolutegravir-based antiretroviral therapy. *Int Med Case Rep J* 2021; 14: 503–507.
79. Okuno Y, Fukuhara A, Hashimoto E, et al. Oxidative stress inhibits healthy adipose expansion through suppression of SREBF1-mediated lipogenic pathway. *Diabetes* 2018; 67(6): 1113–1127.
80. Matsuda M and Shimomura I. Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. *Obes Res Clin Pract* 2013; 7(5): e330–e341.
81. Ngono Ayissi K, Gorwood J, Le Pelletier L, et al. Inhibition of adipose tissue beiging by HIV integrase inhibitors, dolutegravir and bictegravir, is associated with adipocyte hypertrophy, hypoxia, elevated fibrosis, and insulin resistance in simian adipose tissue and human adipocytes. *Cells* 2022; 11(11): 1841.
82. Elffers TW, de Mutsert R, Lamb HJ, et al. Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women. *PLoS One* 2017; 12(9): e0185403.
83. Soti S, Corey KE, Lake JE, et al. NAFLD and HIV: do sex, race, and ethnicity explain HIV-related risk? *Curr HIV/AIDS Rep* 2018; 15(3): 212–222.
84. Bischoff J, Gu W, Schwarze-Zander C, et al. Stratifying the risk of NAFLD in patients with HIV under combination antiretroviral therapy (cART). *EClinicalMedicine* 2021; 40: 101116.
85. Tana C, Ballestri S, Ricci F, et al. Cardiovascular risk in non-alcoholic fatty liver disease: mechanisms and therapeutic implications. *Int J Environ Res Public Health* 2019; 16(17): 3104.