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HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

Metabolic Consequences of Antiretroviral Therapy

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Abstract

Purpose of Review This review reports on published studies describing metabolic changes associated with antiretroviral therapy (ART) to treat HIV disease including a historical perspective of earlier ART agents, but with the main focus on newer ART agents currently in use.

Recent Findings Studies from different countries around the world have shown that integrase inhibitor (INSTI)-based regimens as well as tenofovir alafenamide (TAF) are associated with weight gain, with women and people of black race at especially high risk. Some studies preliminarily suggest worsened metabolic outcomes associated with this weight gain including adverse effects on glucose homeostasis.

Summary Antiretroviral therapy can affect weight, adipose tissue, glucose, and lipids. As obesity is prevalent and increasing among people with HIV, awareness of risk factors for weight gain, including the ART medications associated with greater weight gain, are needed in order to inform prevention efforts. Further research is needed to better understand the long-term health consequences of INSTI- and TAF-associated weight increases.

Keywords Weight gain · Antiretroviral therapy · Integrase inhibitors · Diabetes · Dyslipidemia · Cholesterol

Introduction

Metabolic consequences of antiretroviral therapy (ART) have evolved markedly over the past three decades with the development of new treatment regimens to control HIV. Early ART medications were instrumental in suppressing viral load and extending life expectancy of people living with HIV (PLWH) [1], but regimens including the earlier nucleoside reverse transcriptase inhibitors (NRTIs), especially stavudine (D4T) and to a lesser extent zidovudine (ZDV) and didanosine (ddI), as well as select PI-based regimens, were found, over time, to cause side effects including lipodystrophy [2–6], unfavorable shifts in lipid levels [7–10], and, in some cases, diabetes [11–14]. While lipodystrophy is less common today with newer ART medications, the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), newer protease inhibitors (PIs) and NRTIs, and, most recently, integrase inhibitors (INSTIs), has been accompanied by a rise in obesity rates among PLWH in recent years [15•, 16]. Today, the World Health Organization and U.S. Department of Health and Human Services recommend an INSTI, in combination with NRTIs, as first-line ART [17, 18]. Integrase inhibitors are efficacious, well-tolerated, and generally safe to be taken with other medications [18]. Dolutegravir (DTG) and bictegravir (BIC) in particular are associated with relatively low levels of ART resistance [18]. However, recent significant weight gain has been observed in association with INSTI-based antiretroviral regimens [19••, 20••]. Tenofovir alafenamide (TAF), the more recently approved formulation of tenofovir, has also been found to have weight-promoting effects [19••, 21••]. Whether INSTIs and TAF play a causal role in weight changes among PLWH and the long-term metabolic consequences of INSTI and TAF use remain to be fully understood and are areas of active investigation.

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Antiretroviral Therapy and Body Composition

Lipodystrophy

Older antiretroviral agents, especially NRTIs and PIs, caused abnormal fat redistribution including loss of subcutaneous fat mass in the face and extremities and gain of adipose tissue in the abdomen, a pattern of fat redistribution known as lipodystrophy [6, 12, 22, 23]. Findings of ART-associated lipodystrophy led to an important prospective study demonstrating that these early antiretrovirals resulted in progressive, selective loss of limb fat after initial "return to health" weight gain, with stavudine being the strongest independent factor associated with rate of limb fat loss [24]. Stavudine use was later found to be a strong risk factor for the development of lipodystrophy in studies in the Asia–Pacific region, Malawi, and the USA [25–27]. These changes in body fat distribution were found to disrupt patients' psychological wellbeing, privacy, and adherence to treatment [28]. In 2009, the WHO recommended avoidance of stavudine because of lipodystrophy and the availability of newer NRTIs without such side effects [29].

Weight Gain

ART regimens approved more recently, particularly those including INSTIs and TAF, have been reported to be associated with weight gain [19••, 20••, 30, 31•, 32•].

Integrase Inhibitors

Weight gain has been reported among PLWH beginning ART on INSTIs, particularly DTG, beyond that expected in association with viral suppression and a return to health [12]. The recent 96-week ADVANCE trial, enrolling 1053 PLWH, observed greater weight gain among people starting ART on dolutegravir, emtricitabine (FTC), and either TAF or tenofovir disoproxil fumarate (TDF) compared with people starting on efavirenz (EFV), emtricitabine, and TDF [19••]. Differences in weight gain were significant only between the DTG/FTC/TAF and EFV/FTC/TDF groups, suggesting an additive effect of DTG and TAF on weight gain [19••]. A second multicenter trial based in Cameroon observed median weight increases of 5.0 kg versus 3.0 kg among participants who initiated DTG/lamivudine (3TC)/TDF versus EFV/3TC/TDF, respectively [31•]. Beyond DTG, initiation of INSTI RAL and BIC have been associated with greater weight gain compared with initiation of non-INSTIs ART [20••, 30, 33].

Switch studies of virally suppressed PLWH transitioning from non-INSTI to INSTI-based regimens provide further insights into the relationship between INSTIs and body composition. The greater weight gain observed among ART-naïve PLWH who initiated INSTIs has previously been hypothesized to be a signature of a quick and successful "return to health" [12, 19••, 34]. A report from the Women's Interagency HIV Study (WIHS), however, found that 31.9% of women who switched to INSTIs gained at least 5% of their initial body weight compared with 20.5% of women who remained on their original ART regimen [35]. Similarly, body mass increased significantly more over the course of 18 months among 495 virally suppressed men and women in the Vanderbilt Comprehensive Care Clinic who transitioned from EFV/FTC/TDF to INSTIs compared to those who transitioned to PIs or continued on NNRTI-based ART [36]. Together, these findings suggest that mechanisms apart from faster rate of successful virologic suppression may be driving weight increases among people on integrase inhibitors.

INSTIs have not consistently been associated with body mass increases in excess of that reported with other ART classes, particularly PIs [37]. For example, both INSTIs and PIs were associated with a greater likelihood of body mass increases exceeding 10% compared with NNRTIs 2 and 5 years following ART initiation in the NA-ACCORD study [38]. Recent findings from a multi-site analysis in the USA of PLWH starting one of 11 different NNRTI-, PI-, or INSTI-based regimens showed BIC/TAF/FTC and DTG/TAF/FTC to be associated with greatest weight gain in the first 6 months compared to the reference therapy, EFV/TDF/FTC, and DRV/FTC/TDF to be associated with greatest weight gain in extended follow-up compared with other PI-, NNRTI-, and INSTI-based regimens (although BIC/TAF/FTC and DTG/TAF/FTC were not included in extended follow-up analyses) [30]. Further, some studies have observed no change in body mass at all with INSTI use [39, 40]. For example, in a 177 participant, phase 2a trial assessing the INSTI cabotegravir for HIV prevention, weight changes did not differ significantly over 41 weeks between those randomized to cabotegravir vs. placebo [40].

It is not yet understood whether observed relationships between INSTIs and weight gain are driven by a class-effect or by mechanisms unique to individual INSTI medications. A pooled analysis of eight trials found weight to increase over 96 weeks by 4.24 kg and 4.07 kg, respectively, among PLWH on BIC and DTG, significantly larger than the 2.72 kg increase observed among those on elvitegravir (EVG) + cobicistat [20••]. Findings of greater weight gain in association with DTG versus both EVG and RAL have been observed across study populations [15•, 17, 38, 41, 42]. Interestingly, however, in NA-ACCORD, RAL, but not DTG, was associated with greater likelihood of body mass increases

exceeding 10% compared with EVG [38]. Further underscoring the inconsistency of the DTG-weight gain relationship, smaller increases in BMI were observed among women in the WIHS cohort who transitioned to DTG compared with EVG or RAL, and a 378-participant study found that neither DTG nor RAL initiation was associated with a change in annual weight gain [39, 43]. Together, these studies point to the need for further analyses comparing specific INSTI drugs.

Changes in Body Fat Distribution Associated with INSTI Use

Centralized weight gain, especially gain of visceral adipose tissue (VAT), is known to be associated with signatures of metabolic disease and increased risk of future cardiovascular disease in people with and without HIV [44–47]. Several studies have found waist circumference, a measure associated with VAT and commonly used to assess central adiposity, to increase among PLWH on ART, particularly INSTI-based regimens [32•, 48, 49]. For example, men and women who initiated ART on RAL/FTC/TDF experienced a 4.0-cm rise in waist circumference over 96 weeks, significantly greater than the 2.8-cm rise experienced by participants who initiated ART on darunavir/ritonavir (DRV/r)/FTC/TDF [49]. In line with these findings, waist circumference was found to increase significantly more over the course of 2 years among women living with HIV who transitioned to INSTIs versus remained on non-INSTI ART (2.4 cm vs. 0.4 cm on average, respectively) [32•]. Importantly, however, hip circumference also increased more in association with INSTI use, resulting in similar changes in waist-to-hip ratio between women who did versus did not transition to INSTIs (0.011 vs. 0.009, respectively) [32•].

Thus, despite that waist circumference has been found to be a useful indicator of metabolic health, measures of waist circumference do not, alone, provide insight into adipose tissue distribution (central vs. more generalized) nor composition (visceral vs. subcutaneous adipose tissue) [44, 46]. Data collected from DXA and CT scans have helped shed light on changes in body composition in association with INSTI use. In a shift away from the lipodystrophy phenotype associated with thymidine analogues, the ratio of trunk fat-to-limb fat fell over 48 weeks among PLWH switching from D4T to RAL, while total body fat and percent leg fat normalized to BMI rose [50]. In a majority-male cohort of PLWH starting ART with an INSTI (RAL) or PI (atazanavir/ritonavir (ATV/r) or DRV/r), both visceral and subcutaneous adipose tissue increased across treatment groups over 96 weeks, resulting in no overall increase in VAT as a proportion of total adipose tissue [51]. Further emphasizing the more-uniform pattern of INSTI-associated weight gain, not only waist circumference but also hip, arm, and thigh circumference were found to rise significantly more among women who transitioned to INSTIs compared to those who remained on non-INSTI ART in a study from the WIHS cohort [32•]. Together, these findings are suggestive of more generalized and metabolically neutral increases in body fat in association with INSTIs.

Tenofovir Alafenamide

Complicating the clarity of the relationship between INSTIs and weight gain, TAF, a component of two INSTI-based regimens, has also been shown to be associated with weight gain [19••, 21••, 52, 53]. In a cohort of 4375 PLWH, those who transitioned from TDF to TAF were found to gain 1.8 kg over a median of 17.1 months of follow-up, significantly higher compared with the 0.7 kg weight increase observed over a median of 17.5 months of follow-up among those who remained on TDF [21••]. TAF correlated with greater weight increases regardless of whether participants took INSTIs, NNRTIs, or PIs ($p < 0.001$, $p = 0.001$, $p = 0.061$, respectively) in combination [21••]. Similarly, pooled comparison of four NRTIs found that PLWH starting TAF were more likely to experience 10% or higher increases in body mass compared with PLWH starting TDF, ZDV, or abacavir (ABC) [20••]. A separate analysis from the CNICS cohort, however, found comparable 6-month increases in body mass between people starting either DTG/ABC/FTC or DTG/TAF/FTC, stressing the lack of clarity regarding the TAF-weight gain relationship [30].

The extent of TAF-associated weight gain may be dependent on initial BMI [43]. In a 1458-participant analysis from the WIHS cohort, weight and BMI rose among women with baseline BMI below 30 kg/m^2 upon transitioning to INSTI, TAF, or INSTI and TAF together [43]. The effect sizes for both body weight and BMI increases were largest among women who started INSTI and TAF together, underscoring the hypothesis raised by the results of the ADVANCE trial that INSTIs and TAF have additive effects on weight [19••, 43].

Risk Factors for ART-Associated Weight Gain

Several populations and clinical characteristics have been found to be associated with more pronounced weight gain on INSTIs [20••, 31•, 49]. In a pooled analysis of eight Gilead trials, weight gain ≥ 10% of baseline body mass was more common among females (sex defined specifically here as sex at birth), Black individuals, and people with lower body mass, lower CD4 + T cell count, and higher HIV-1 RNA levels at ART initiation, findings that have been replicated across cohorts [20••, 31•, 42, 49]. Interestingly, in the Gilead trials analysis, individuals less than 50 years old were found to gain more weight after starting on ART compared with individuals ≥ 50 years old, while weight

gain was found to be greater among participants ≥ 60 years old in a study enrolling individuals switching from non-INSTI- to INSTI-based ART, specifically [20••, 42].

Differences in Weight Gain by Sex

Women have been found to experience greater ART-associated body composition changes compared with men. For example, women in the ADVANCE trial gained more fat mass and were more likely to develop obesity across treatment regimens [19••]. Sex-associated changes in body mass appear to be especially pronounced among INSTI users, as demonstrated by the results of the NAMSAL trial where DTG-associated weight gain exceeded that of EFV by 2.0 kg in the cohort overall, and by 3.0 kg among women [31•]. A similar sex-specific pattern has been observed in waist circumference changes [49, 54]. Most recently, a 4500-participant analysis from the REPRIEVE trial, which investigated differences in metabolic consequences of INSTIs by natal sex, found that the elevated measures of BMI and waist circumference associated with INSTI versus non-INSTI ART use were more pronounced among women than men [54].

Differences in Weight Gain by Race

Greater INSTI-associated increases in weight and waist circumference have been observed among Black individuals, particularly Black women [42, 49]. For example, Sax et al. found that Black females experienced significantly greater increases in weight after starting ART compared with both black males and females of other races, suggestive of additive effects of gender and race on ART-associated weight gain [20••]. Similarly, women of African origin experienced the largest increases in body weight after transitioning to TAF among a cohort of men and women of African and non-African origin [21••].

Potential Mechanisms

The mechanisms by which antiretroviral agents may promote weight gain are not yet clear. Body weight is known to increase upon ART initiation and higher HIV-1 RNA levels and lower CD4 + T cell counts at baseline have been found to be associated with greater increases in weight and waist circumference [31•, 37, 49, 55]. Inter-regimen differences in weight gain upon ART initiation despite comparable treatment efficacy, however, in combination with weight changes observed in switch studies, suggest that ART-associated factors beyond an initial "return to health" influence body composition [15•]. Sax et al. raise the possibility that their finding of greater weight gain among PLWH taking newer ART may be attributable, at least in part, to the more favorable gastrointestinal side effect profile that's been associated with these regimens [20••]. Lower rates of gastrointestinal and other side effects could result in improved regimen adherence [20••, 56]. In the case of TAF-associated weight gain, TDF may have weight-suppressive effects, making it unclear whether body mass increases observed among PLWH switching from TDF to TAF are driven by initiation of TAF or discontinuation of TDF [57].

Several mechanisms have been proposed to explain INSTI-associated weight gain. Integrase inhibitors may affect appetite [58, 59]. An in vitro study showed that subcutaneous adipocytes exposed to DTG released lower levels of leptin and adiponectin compared with those exposed to DRV [60]. A separate in vitro experiment found a 64% decrease in the interaction between melanocortin-4 receptor (MC4R) and alpha-MSH, an interaction known to lower appetite, in response to DTG exposure [58, 59, 61]. This hypothesis has recently been tested in vitro, however, and the amount of INSTI delivered therapeutically was found to be far less than the concentration needed to reduce the MC4R/alpha-MSH interaction by 50% [59]. A second hypothesis implicates adipocyte dysregulation in INSTI-associated weight gain [34, 62]. In vitro exposure of adipose stem cells to DTG was found to promote a mitochondrial phenotype characteristic of impaired function, to generate greater levels of reactive oxygen species, and to be associated with greater lipid build-up in adipocytes [62]. Similar, although less pronounced, results were observed in response to RAL. In this same study, larger adipocytes were observed in the SAT and VAT of macaques treated versus not treated with DTG. Adipose tissue dysfunction may also help explain the greater INSTI-associated weight gain observed among women. Dolutegravir was found to lower UCP1 mRNA and mitochondrial protein levels and interfere with adipocyte estrogen receptor activity in vitro and to decrease brown adipose tissue UCP1 mRNA levels and thermogenesis in mouse models [63]. However, body weight did not differ among mice treated with DTG versus control mice. Future research is crucial to understand the mechanisms driving INSTI-associated weight gain, as well as the greater weight gain observed among women and Black individuals. Adipose tissue biopsy may be particularly useful for understanding whether adipocyte dysregulation and subsequent inflammation contribute to both weight gain and downstream metabolic consequences.

Antiretroviral Therapy and Glucose Homeostasis, Insulin Resistance, and Diabetes

Antiretroviral therapies may influence glucose homeostasis directly or via mechanisms mediated by changes in body composition. Early NRTIs were associated with insulin

resistance in PLWH. The WIHS study revealed that longer cumulative exposure to NRTIs was associated with an increased diabetes mellitus incidence compared with no NRTI exposure after adjustment for potentially confounding factors [64]. In addition, cumulative exposure of over 1 year to 3TC was associated with a nearly three-fold increase in the rate of diabetes mellitus incidence after adjustment for covariates [64]. Supporting these findings, data from the MEDICLAS study found treatment with zidovudine/lamivudine for 3 months to decrease glucose disposal by 25%, while an NRTI-sparing regiment did not result in a significant change in glucose disposal [65]. While D4T exposure was not associated with diabetes mellitus incidence in the WIHS study, it was found to be strongly associated with diabetes mellitus incidence in the global D:A:D study even after adjusting for traditional risk factors and lipodystrophy [11, 64]. Consistent with these findings, insulin sensitivity was significantly reduced after one month of exposure to D4T in healthy control subjects without HIV [66]. Like early NRTIs, PIs are also known to cause glucose dysregulation [67]. The clinical effects of PIs on glucose dysregulation have been observed in the 22,884-participant NA-ACCORD study, where the likelihood of diabetes development was found to be 27% higher among people who started ART on PIs versus NNRTIs [68]. Importantly, however, likelihood of diabetes development was found to be similar between INSTIs versus PIs [68]. These results were supported by a second study, where similar increases in HOMA-IR were observed in association with initiation of RAL and protease inhibitors ATV/r and DRV/r [69]. These findings, in combination with increased weight gain and case reports of hyperinsulinemia and acute diabetes mellitus among people initiating INSTIs, have prompted investigations into whether INSTIs worsen insulin resistance and glucose sensitivity.

Integrase Inhibitors

In 2018, McLaughlin et al. reported a case of a patient with known type 2 diabetes and chronic kidney disease stage 4 who developed significant hyperglycemia (949 mg/dl) and elevated hemoglobin A1c (14.9%) 3 weeks after switching from EFV to DTG [70]. The patient's glucose and hemoglobin A1c improved upon switching to ritonavir-boosted atazanavir. However, as hemoglobin A1c is not usually affected significantly by acute fluctuations in glucose, this patient likely had elevated glucose even prior to switching to DTG. Nonetheless, one cannot be certain if DTG could have further worsened this patient's hyperglycemia. An earlier publication reported the case of a 44-year-old Asian-American man who developed hyperglycemia 4 months after starting raltegravir, abacavir, and lamivudine [71]. Ten weeks after discontinuing RAL and 6 weeks after discontinuing insulin glargine, this patient's hemoglobin A1c decreased. It is unclear in the report, however, whether lamivudine was continued or discontinued when the patient subsequently switched off RAL to EFV, leaving the open the possibility that the hyperglycemia was due to 3TC. In a third case report, hyperglycemia and ketoacidosis were identified in three individuals within weeks to months of switching from non-INSTI- to BIC-containing regimens [72]. Together, these three case reports, among others, raise the question of whether INSTIs as a class may increase the risk for diabetes mellitus or hyperglycemia and suggest the need for further research to assess causality [70–74].

Research studies have begun to systematically investigate relationships between INSTIs and hyperglycemia and have found some evidence supporting their association. In the WIHS cohort, HbA1c was found to rise significantly more among women who transitioned to INSTIs, although this relationship only held in stratified analyses among women who gained at least 5% of their initial body weight over the course of follow-up, and no relationship was found between INSTI use and either diabetes or insulin resistance, assessed by HOMA-IR [35]. A 2020 study based in Uganda found that 0.47% of participants who started dolutegravir developed hyperglycemia over 1 year, significant compared to 0.03% of participants who continued on non-INSTI ART [75]. However, 56.3% versus 16.8% of PLWH who did versus did not develop hyperglycemia were taking D4T at the start of the study.

Challenging the hypothesis that INSTIs play a role in glucose dysregulation, no cases of diabetes were reported in the 96-week NAMSAL trial, where participants were randomized to receive 3TC and TDF plus either DTG or EFV [31•]. Interestingly, in NA-ACCORD, participants taking RAL were 42% more likely to develop diabetes compared to people taking NNRTIs, while likelihood of diabetes development did not differ significantly among those taking DTG, EVG, and NNRTIs, raising the possibility of inter-INSTI differences in metabolic effects [68]. However, a 96-week comparison of PLWH starting ART found an increase in glucose levels of 6 mg/dL among those on the NNRTI EFV, significantly larger than the 2 mg/dL increase observed among those on RAL [76]. The effects of INSTIs versus NNRTIs on glucose homeostasis are thus unclear, and may be regimen-dependent. Future longitudinal studies are needed to determine whether integrase inhibitors lead to alterations in glucose homeostasis and whether these effects are class-wide or regimen-specific.

Potential Mechanisms

The mechanisms driving increases in glucose intolerance in association with earlier ARTs are well-studied. For example, NRTIs have been found to cause mitochondrial

dysfunction [77]. Mitochondrial dysfunction, in turn, has been found to be associated with insulin resistance, potentially via bidirectional mechanisms [78, 79]. Protease inhibitors indinavir, ritonavir, and amprenavir were found to cause 45%, 54%, and 52% declines, respectively, in Glut4 function in *Xenopus laevis* oocytes in vitro, showing a direct pathway by which these three PIs disrupt insulin signaling and glucose uptake [67]. β-cell function was also found to decline among 13 PLWH starting on PI-based regimens (nelfinavir, indinavir/r, saquinavir/r, saquinavir, lopinavir/r), irrespective of previous NRTI use [80]. Other mechanisms are likely also at play.

Several mechanisms have been proposed to explain the effects of INSTIs on glucose homeostasis. Gorwood et al. investigated whether INSTIs disrupt insulin signaling in adipose tissue and found that DTG and RAL treatment were associated with markers of impaired mitochondrial function in adipose stem cells in vitro, as described above [62]. Further, these INSTIs interfered with phosphorylation mechanisms necessary for insulin signaling, as well as with the ability of insulin to promote glucose uptake in adipose stem cells, findings that implicate adipose tissue dysfunction in INSTI-associated glucose intolerance [62]. However, results on the effects of INSTIs on adipose tissue have not been found to be consistent across studies or INSTI regimens, underscoring the need for further translational work to understand the impact of INSTIs on insulin resistance [81, 62]. Interestingly, elevated levels of ROS and mitochondrial DNA, markers suggestive of mitochondrial impairment, have also been observed in CD4 + T cells exposed to INSTIs DTG and EVG, as well as ritonavir, compared with RAL, DRV, RLP, and four NRTIs ex vivo, indicating that select INSTIs and PIs may have widespread adverse effects on cellular metabolism [82]. Separately, Fong et al. proposed that INSTIs, which disrupt interactions between HIV integrase and magnesium ions in cells, also sequester the Mg2 + necessary to maintain insulin function [71].

More generally, impairments in glucose tolerance may be mediated by ART-associated weight gain, as was suggested by the positive correlation observed between fasting glucose levels and weight gain among 972 participants who switched to INSTI-based ART [12, 42]. Lipidomic analyses may also shed light on potential relationships between select lipid species, glucose tolerance, HIV status, and antiretroviral regimen [83]. A recent study of PLWH on and off ART and healthy controls from the Multicenter AIDS Cohort Study (MACS) and WIHS cohorts found that four of the five lipid species that correlated positively with diabetes incidence were elevated among PLWH, particularly those taking PI-based ART [83]. No participants took INSTIs in this analysis and the causal mechanisms have yet to be elucidated.

Antiretroviral Therapy and Lipids

Total and high-density lipoprotein (HDL) cholesterol levels are known to fall in people with acute HIV infection and untreated HIV disease [84]. Triglyceride levels, by contrast, are elevated in people with untreated HIV [84–86]. The response of lipids to antiretroviral therapy has been shown to differ by regimen. Comparisons among NRTIs have found regimens containing TDF to be associated with lower lipid levels than those containing ddI, ZDV, D4T, or ABC, among others [7, 8]. ART (85% PI-based in the MACS cohort included in this analysis) was found to correlate with a rise over 2–3 years in low-density lipoprotein (LDL), HDL, and total cholesterol levels, with HDL cholesterol levels then observed to fall over the following 4–5 years, reaching levels similar to those at baseline [9]. PLWH starting ART on ritonavir have also been found to experience increases in triglyceride levels, but, underscoring the need for regimen-specific studies, this finding was not consistent across PI regimens [10].

Integrase Inhibitors

Integrase inhibitors have been found to have a relatively small impact on lipid levels. A head-to-head comparison of efavirenz/tenofovir/emtricitabine vs. raltegravir/tenofovir/emtricitabine found that total, HDL, and LDL cholesterol levels rose by 38, 10, and 21 mg/dL, respectively, among those on EFV, significant compared with the 10, 3, and 7 mg/dL increases observed among those on RAL [76]. Further, those on EFV experienced increases in triglyceride levels of 40 mg/dL, significant compared with the 4 mg/dL declines in those on RAL [76]. An analysis from the WIHS cohort found that total, LDL, and HDL cholesterol levels fell more among women on ART who transitioned to INSTIs compared with women who did not, but this inter-group comparison was only significant for HDL cholesterol [35]. Data from three trials of PLWH initiating cabotegravir + rilpivirine, a regimen approved by the FDA in early 2021, found that lipid levels did not shift significantly during 48 weeks of follow-up [87]. A similar absence of lipid changes was observed over 144 weeks among PLWH initiating ART on BIC/FTC/TAF or DTG/FTC/TAF [88]. Importantly, this overall consistency of lipid levels was found to correspond to a relatively stable, and even comparatively beneficial total cholesterol-to-HDL ratio, suggestive of minimal lipid-associated cardiovascular risk among PLWH on INSTIs [89, 90].

The increased weight gain observed among PLWH on INSTIs, however, raises the question of whether integrase inhibitors may adversely impact lipid levels via changes in body composition. In a combined analysis of ACTG A5001

and A5322, weight gain among participants who transitioned to INSTIs was negatively correlated with changes in HDL cholesterol and positively correlated with changes in LDL cholesterol, total cholesterol, and triglyceride levels [42]. Similarly, weight gain of 10% or greater was associated with a rise in triglyceride and cholesterol concentrations among participants in the NAMSAL trial [31•]. Recent data from the REPRIEVE trial, by contrast, showed that INSTIs were not associated with increased LDL or total cholesterol levels, nor with increased risk of metabolic syndrome, despite that INSTI users in this cohort were found to have higher BMI and waist circumference [54].

Tenofovir Alafenamide

Increases in lipid levels including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides have been observed among PLWH switching from TDF- to TAF-based regimens [21••, 52]. These findings were supported by a recent meta-analysis of 10 studies enrolling people living with HIV or chronic hepatitis B, where total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were found to rise by 13.97 mg/dL, 2.25 mg/dL, 8.68 mg/dL, and 14.22 mg/dL more, respectively, among people starting on or switching to TAF versus TDF [91]. It is unknown, however, whether these observed increases are due to initiation of TAF or termination of TDF, a medication known to reduce total and LDL cholesterol levels [92]. Further, concurrent increases in both HDL and total cholesterol have resulted in minimal shifts in total cholesterol-to-HDL ratio [91]. In vitro and clinical studies are needed to understand the mechanisms behind TAF-associated lipid changes, and whether these lipid changes confer, in the long run, any increased cardiovascular risk.

Potential Mechanisms

The mechanisms driving increases in cholesterol and decreases in triglyceride levels in untreated HIV infection are not fully understood, but pathways mediated by acute inflammation may play a role [93, 94]. For example, triglyceride levels, specifically, have been found to increase with increasing IFN-α levels in HIV/AIDS [85]. HIV-associated inflammation may lower HDL cholesterol levels via several pathways, such as by interfering with cholesterol efflux, as was suggested by an in vitro study showing lower ABCA1 mRNA and protein levels in macrophages exposed to LPS [94, 95]. Thus, changes in lipid levels with ART initiation may be due, in part, to a reversal of the mechanisms causing their original rise or fall, such as a reduction in systemic inflammation. Declines in HDL cholesterol levels in acute HIV may also be mediated by *Nef*, an HIV viral protein, which has been shown to lower protein levels of the ABCA1 transporter and induce an irregular accumulation of ABCA1 on the plasma membrane, leading to a decline in cholesterol efflux from macrophages [96].

Increases in cholesterol and triglyceride levels beyond that expected by a "return to health," however, may be mediated by ART class- or regimen-specific pathways. PIs may induce hyperlipidemia via a range of mechanisms. Ritonavir administration, for example, was found to increase concentrations of circulating triglycerides, very-low-density lipoprotein, LDL, and HDL cholesterol in mice, as well as increase SREBP-1 and SREBP-2 protein levels in the nucleus of liver cells, a likely explanation for the ritonavir-associated rise in mRNA levels of fatty acid synthase, HMG-CoA synthase, and HMD-CoA reductase [97]. PI-associated increases in triglyceride levels may also be driven by elevated visceral fat accumulation and corresponding increases in free fatty acids [51, 98–100]. Efavirenz, known to have a relatively strong association with dyslipidemia among NNRTIs, has been found to increase cholesterol and triglyceride levels in the liver, as well as cholesterol levels in plasma, possibly by acting directly on the pregnane X receptor (PXR) [101]. EFV was also shown to increase mRNA levels of proteins associated with hepatic steatosis and cardiovascular disease via a PXR-dependent mechanism [101]. Future longitudinal research should monitor whether INSTI-associated weight gain is associated with metabolically unhealthy shifts in lipid levels.

Therapeutic Strategies

Both lifestyle- and medication-based strategies may help improve metabolic health outcomes among PLWH. Dietary interventions focused on limiting caloric intake and increasing physical activity have been shown to promote weight loss among PLWH [102]. The benefits of lifestyle interventions may also extend beyond weight loss. In a randomized controlled trial enrolling 34 PLWH, weekly counseling focused primarily on dietary habits was found to result in significant declines in waist circumference, systolic blood pressure, hemoglobin A1c, and lipodystrophy score, concurrent with a rise in physical activity levels [103]. Similarly, dietary intervention was found to limit increases in total cholesterol, LDL cholesterol, and triglyceride levels over the course of one year among 83 PLWH initiating ART [104].

Future randomized trials will be important to assess the efficacy of lifestyle interventions for counteracting, and potentially preventing, INSTI- and TAF-associated weight gain. Further research studies are also needed and are under way to assess effects of switching off INSTIs and TAF on weight and metabolic parameters. The AIDS Clinical Trials Group recently launched a 48-week, open-label, randomized

study to assess whether switching from the INSTI bictegravir (BIC), dolutegravir (DTG), or raltegravir (RAL) with TAF/FTC or TAF/3TC to a new ART regimen containing the NNRTI doravirine will affect weight [105]. Half of the participants who switch to doravirine will also switch from TAF to TDF, allowing for comparison of the relative effects of these two NRTIs on weight.

In addition to lifestyle modification, lipid and blood glucose levels may also be managed with medications. In a randomized controlled trial of 806 PLWH, visceral adipose tissue, triglyceride levels, and the total cholesterol-to-HDL ratio were found to fall over 26 weeks among those receiving tesamorelin, significant compared with the increases observed among those receiving placebo [106]. Further, VAT and triglyceride levels continued to be reduced compared with baseline among those receiving tesamorelin over 52 weeks [106]. Cholesterol levels may also be managed by following the IDSA primary care guidelines, which suggest that dyslipidemia be monitored for by measuring cholesterol levels pre- and post-ART initiation and treated by following the National Lipid Association Part 2 and 2018 Multispecialty Blood Cholesterol Guidelines [107]. Similarly, the IDSA guidelines recommend measurement of HbA1c and blood glucose levels before ART initiation and suggest that diabetes be identified among PLWH on ART via measurement of plasma glucose [107]. Metformin is suggested as a first-line medication-based therapy for management of diabetes [107, 108]. Of clinical relevance, metformin AUC and Cmax were found to rise in response to concurrent dolutegravir treatment, thus, the current recommendation is for the dose of metformin not to exceed 1000 mg total per day for individuals taking DTG concurrently [109, 110]. Glucagon-like peptide-1 (GLP-1) receptor agonists may also be helpful for the management of diabetes and also for weight loss [108].

Conclusions

ART dramatically improves survival and is essential for PLWH. Side effects of antiretroviral agents affecting metabolic health, including the effects of exposure to older agents in causing dyslipidemia, glucose dysregulation, and lipodystrophy as well as the effects of newer INSTI-based regimens on weight, are important for clinicians to be aware of for monitoring and prevention efforts. Current INSTI-based regimens are very efficacious in controlling HIV but can lead to weight gain, which is problematic as obesity is rising among PLWH. The long-term health consequences of INSTI- and TAF-associated weight gain are still unclear and are under investigation. Lifestyle optimization to prevent adverse metabolic effects associated with ART should be emphasized for every patient. Future research into other potential therapeutic strategies to mitigate detrimental metabolic effects of ART are needed.

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Declarations

Conflict of Interest Janet Lo has previously served as a consultant for Viiv Healthcare and on medical affairs advisory boards for Gilead Sciences. She is also a Co-Principal Investigator on an investigator-initiated research grant funded by Viiv Healthcare.
Caroline Diggins and Samuel Russo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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