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Weight Gain After Antiretroviral Therapy Initiation and Subsequent Risk of Metabolic and Cardiovascular Disease

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Background. Weight gain following initiation of antiretroviral therapy (ART) is common. We assessed the impact of changes in weight in the year following ART initiation with subsequent cardiometabolic disease among AIDS Clinical Trials Group (ACTG) participants.

Methods. Linear regression models were fit to examine the association between change in weight/waist circumference (WC) in weeks 0–48 and change in metabolic parameters in weeks 0–48 and 48–96. Cox proportional hazard models were fit to examine the association between changes in weight/WC in weeks 0–48 and diabetes mellitus (DM), metabolic syndrome, or cardiometabolic and cardiovascular events after week 48.

Results. Participants (N = 2624) were primarily male (81%) and non-White (60%). Mean weight gain from 0–48 weeks was 3.6 kg (SD 7.3); 130 participants developed DM; 360 metabolic syndrome; 424 any cardiometabolic event; 28 any cardiovascular event, over 480 weeks of follow-up. In adjusted models, total cholesterol increased by 0.63 mg/dL (95% confidence interval [CI] [.38, .089]) and LDL by 0.39 mg/dL (0.19, 0.59) per 1 kg increase in weight from weeks 0 to48. Participants who experienced >10% weight gain (vs −5% to 5%) had an increased risk of DM (hazard ratio [HR] 2.01, 95% CI [1.30, 3.08]), metabolic syndrome (HR 2.24, 95% CI [1.55, 2.62]), and cardiometabolic outcomes (HR 1.54, 95% CI [1.22, 1.95]). Participants who lost more than 5% of their baseline weight had a lower risk of incident metabolic syndrome (HR 0.67, 95% CI [0.42, 1.07]). Trends for WC were similar.

Conclusions. Weight and body composition changes in the first year following ART initiation are associated with contemporaneous changes in metabolic parameters and subsequent cardiometabolic disease.

Keywords. HIV; ART initiation; weight gain; metabolic disease; cardiovascular disease.

Weight gain following the initiation of antiretroviral therapy (ART) is common and often attributed to a "return to health" phenomenon, due in part to reversal of the catabolic state associated with viremia and a reduction in systemic inflammation [1–8]. Although any ART may be associated with weight gain, this has become a particular focus with newer regimens, particularly integrase strand transfer inhibitors (INSTIs). Furthermore, as current guidelines recommend ART initiation regardless of CD4$^+$ T-cell count (CD4), and given the growing obesity epidemic in the United States, the mean body mass index (BMI) at the time of ART initiation has increased

considerably over the last 10 years [5]. Weight gain with ART initiation is associated with a mortality benefit in people with human immunodeficiency virus (HIV, PWH) who initiate ART with a BMI in the normal or underweight categories, but this same mortality benefit is not seen in PWH who initiate ART with BMI in the overweight or obese categories [8, 9]. Whether this lack of mortality benefit is due to an increased risk of cardiometabolic diseases is not well understood.

To further investigate this question, we assessed the impact of changes in weight and body composition in the first year following ART initiation with contemporaneous changes in metabolic parameters as well as subsequent development of cardiometabolic and cardiovascular disease. We also investigated the impact of natal sex, race and ethnicity on the associations between weight change and the outcomes of interest.

METHODS

Study Population

Participants from 2 AIDS Clinical Trials Group (ACTG)-sponsored, longitudinal, observational cohorts were included. In

2000, A5001 (ALLRT, ACTG Longitudinal Linked Randomized Trials) [10] began enrolling participants previously enrolled into ACTG randomized trials. A5001 followed participants every 4 months through 2013. In 2013, A5001 follow-up ended and participants 40 years of age or older from treatment-naive parent trials were offered enrollment into A5322 (the HIV Infection, Aging, Immune Function Long-Term Observational Study [HAILO]), which followed participants for 8 years, initially every 6 months (through 2019) and then annually. This analysis included A5001 and A5322 participants who had participated in trials including any of the following antiretrovirals: tenofovir disoproxil fumarate, emtricitabine, lamivudine, abacavir, efavirenz, atazanavir, darunavir, and raltegravir (A5142, A5202, and A5257).

Outcomes

Metabolic Parameters

Fasting high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglycerides, and glucose were measured 2–3 times per year during A5001 and annually during A5322.

Clinical Events

Two separate cardiovascular (CV) outcomes were considered: cardiometabolic events and CV events. Cardiometabolic events included hypertension, initiation of antihypertensive medication, hyperlipidemia, initiation of statin or other lipid lowering medication, coronary artery disease, myocardial infarction, stroke, transient ischemic attack, CV surgery, or procedure. CV events included myocardial infarction, CV surgery or procedure, transient ischemic attack, or stroke. Diabetes mellitus (DM) was defined as diagnosis of DM or initiation of antiglycemic medications. Metabolic syndrome was defined as 3 or more of: WC >102 cm for men or >88 cm for women; blood pressure >130/85, diagnosis of or drug treatment for hypertension; fasting triglyceride level ≥150 mg/dL; fasting HDL <40 mg/dL (men) or <50 mg/dL (women); fasting blood glucose ≥100 mg/dL or incident DM.

Exposures and Covariates

Standardized weight was measured every 4 months in A5001 and yearly in A5322, and waist circumference (WC) was measured initially every 4 months, then yearly in A5001, and yearly in A5322.

Medical history and medications were updated every 4 months in A5001 and every 6 months in A5322. CD4 counts were measured 2–3 times per year during A5001 and annually during A5322; Human immunodeficiency virus type 1 (HIV-1) RNA was measured every 6 months at local, certified laboratories. Other covariates considered as potential confounders included: age; natal sex; race/ethnicity; education level; parent study; geographic region; initial ART regimen; pre-ART CD4 count and HIV-1 RNA; BMI; smoking status; hypertension; lipid-lowering medications; and anti-diabetic medications (all measured at baseline). Gender data were not available and thus not included as a covariate.

Statistical Analysis

We fit linear regression models to examine associations between changes in weight/WC from week 0 to week 48 and changes in continuous metabolic parameters from week 0 to week 48 and week 48 to 96.

To examine associations between changes in weight/WC and subsequent clinical events after the first year of ART initiation, we fit Cox proportional hazard models, excluding individuals with prevalent clinical events or those occurring within the first year after treatment initiation. We categorized changes in weight over the first year as <−5%, −5% to 5%, >5% to 10%, and >10%; changes in WC were categorized as ≤3 cm, >3 cm to 7 cm, and >7 cm.

We included a priori covariates known to be strong risk factors in the models for incident events. We included age, sex, history of DM, family history of CVD, and smoking status in the model for cardiometabolic events; in the model for CV events, we also included history of hypertension and history of dyslipidemia. Age, sex, race/ethnicity, baseline BMI, and history of dyslipidemia were included in the model for DM, and age, sex, and race/ethnicity in the model for metabolic syndrome.

We then considered additional potential confounders in each of the above models. Covariates that changed the unadjusted effect estimates (linear regression models) or estimates from the above Cox proportional hazards models by ≥10% were retained in these multivariable models.

We also fit Cox proportional hazard models to examine associations between age, sex, baseline BMI and baseline CD4 cell count on weight gain >10% and treatment emergent obesity as defined by a change from either normal or underweight BMI to a BMI > 25 kg/m^2 at week 48.

To explore multiplicative effect modification by sex, race, and ethnicity on the associations between weight/WC change and clinical events, we added interaction terms between the potential effect modifier and weight change to each multivariable model.

We conducted all statistical analyses using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Study Population

Participants (N = 2624) were primarily male at birth (81%) and non-White (60%) (Table 1). The median (Q1, Q3) follow-up time was 208 (160, 384) weeks after ART initiation.

Longitudinal Changes in Weight

Overall, mean (SD) weight gain from ART initiation to week 480 was 7.1 kg (10.7) and higher among female participants than male participants (7.3 kg vs 6.4 kg). The mean (SD) weight gain at week 48 was 3.6 kg (7.3) and higher among females than

Table 1. Baseline Demographics

	Total (N = 2624)	A5142 (n = 68)	A5202 (n = 1213)	A5257 (n = 1343)
Age, y, mean (SD)	37.9 (10.4)	36.2 (9.0)	38.6 (9.9)	37.4 (10.9)
Female sex at birth	504 (19.2%)	15 (22.1%)	204 (16.8%)	285 (21.2%)
Race/Ethnicity				
White Non-Hispanic	1038 (39.6%)	27 (39.7%)	519 (42.8%)	492 (36.6%)
Black Non-Hispanic	921 (35.1%)	27 (39.7%)	369 (30.4%)	525 (39.1%)
Hispanic	582 (22.2%)	12 (17.6%)	282 (23.2%)	288 (21.4%)
Other	83 (3.1%)	2 (2.9%)	43 (3.5%)	38 (2.8%)
BMI (kg/m^2, mean)	25.9	25.7	25.5	26.3
BMI category				
Underweight (<18.5 kg/m^2)	86 (3.3%)	2 (2.9%)	49 (4.0%)	35 (2.6%)
Normal weight (18.5–24.9 kg/m^2)	1228 (46.8%)	31 (45.6%)	593 (48.9%)	604 (45.0%)
Overweight (25–29.9 kg/m^2)	854 (32.5%)	25 (36.8%)	394 (32.5%)	435 (32.4%)
Obese (≥30 kg/m^2)	444 (16.9%)	10 (14.7%)	177 (14.6%)	257 (19.1%)
Waist circumference, cm, mean (SD)	90.5 (13.4)	88.5 (15.1)	90.5 (12.1)	90.5 (14.2)
CD4, cells/mm^2, mean	274.5	219.5	234.8	313.1
HIV-1 RNA, log10 copies/mL, mean	4.7	4.7	4.7	4.6
Tobacco use				
Current	586 (22.3%)	8 (11.8%)	80 (6.6%)	498 (37.1%)
Previous	896 (34.1%)	34 (50.0%)	579 (47.7%)	283 (21.1%)
Never	1113 (42.4%)	25 (36.8%)	526 (43.4%)	562 (41.8%)
Hypertension at baseline	572 (21.8%)	5 (7.4%)	231 (19.0%)	336 (25.0%)
Hyperlipidemia at baseline	237 (9.0%)	3 (4.4%)	104 (8.6%)	130 (9.7%)
Diabetes mellitus at baseline	108 (4.1%)	4 (5.9%)	49 (4.0%)	55 (4.1%)
Metabolic syndrome at baseline	730 (27.8%	10 (14.7%)	301 (24.8%)	419 (31.2%)
Lipid-lowering medication use at baseline	129 (4.9%)	2 (2.9%)	54 (4.5%)	73 (5.4%)

Included ART regimens by parent study were as follows—A5142 (emtricitabine/tenofovir disoproxil fumarate/efavirenz), A5202 (abacavir/emtricitabine/efavirenz, emtricitabine/tenofovir disoproxil fumarate/efavirenz, abacavir/emtricitabine/atazanavir/ritonavir, emtricitabine/tenofovir disoproxil fumarate/atazanavir/ritonavir), A5257 (emtricitabine/tenofovir disoproxil fumarate/raltegravir, emtricitabine/tenofovir disoproxil fumarate/atazanavir/ritonavir, emtricitabine/tenofovir disoproxil fumarate/darunavir/ritonavir).

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, CD4+ T-cell count; HIV-1, human immunodeficiency virus type 1; SD, standard deviation.

males (4.2 kg vs 3.5 kg). At week 48, 22% (n = 550) of participants gained >10% of their baseline weight (21% of male participants, 28% of female participants). At week 480, 40% (n = 118) of participants gained >10% of their baseline weight (38% of male participants, 45% of female participants).

Association Between Baseline CD4 Cell Count and Weight Gain

Baseline CD4 of <200 cells/uL was significantly associated with both weight gain >10% and treatment emergent obesity (hazard ratio [HR] 5.02, 95% confidence interval [CI] [4.23–5.95], $P < .001$ and HR 2.76 95% CI [2.25, 3.39], $P < .001$, respectively).

Association Between Weight Gain and Change in Fasting Metabolic Markers

In multivariable models adjusting for baseline BMI, history of DM, and history of hypertension, for every 1 kg increase in weight from weeks 0 to 48, fasting glucose increased by 0.13 mg/dL (95% CI [.001, .26], $P = .05$). The increase from weeks 48–96 was less pronounced and no longer clinically significant (0.07 mg/dL, 95% CI [−.05, .19], $P = .23$) (see Table 2).

In multivariable models adjusting for parent study, baseline CD4, nadir CD4, HIV-1 RNA, initial ART drug class, baseline BMI and smoking status, for every 1 kg increase in weight from

Table 2. Impact of Weight Gain on Fasting Glucose and Fasting Lipids

	Adjusted Estimate Change (95% CI) per 1 kg Increment In Weight	
	Week 0 to 48	Week 48 to 96
Glucose (mg/dL)	0.13 (.001, .26)	0.07 (−.05, .19)
Total cholesterol (mg/dL)	**0.63 (.38, .89)***	−0.14 (−.33, .05)
HDL (mg/dL)	−0.04 (−.13, .05)	**−0.11 (−.17, −.04)***
LDL (mg/dL)	**0.39 (.19, .59)***	0.06 (−.10, .23)
Triglycerides (mg/dL)	**1.42 (.61, 2.22)***	−0.55 (−1.34, .23)

Models for different metabolic outcomes were adjusted for the following covariates: parent study, baseline CD4, nadir CD4, HIV-1 RNA, initial ARV drug class, BMI, and/or smoking status. The bolded values are those that are statistically significant as noted by the asterisk.

Abbreviations: ARV, antiretroviral; BMI, body mass index; CD4, CD4+ T-cell count; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; HDL, high density lipoprotein; LDL, low density lipoprotein.

*$P \leq .05$.

weeks 0 to 48, total cholesterol increased by 0.63 mg/dL (95% CI [.38, .89], $P = .05$), LDL by 0.39 mg/dL (95% CI [.19, .59], $P < .001$), triglycerides by 1.42 mg/dL (95% CI [.61, 2.22], $P < .001$), whereas HDL decreased by 0.04 mg/dL (95% CI [−.13, .05], $P = .39$). The associations between weight gain from week 0 to 48 and changes in fasting lipids at week 48 to 96 were less pronounced and non-significant except for HDL,

which decreased by 0.11 mg/dL (95% CI [−.17, −.04], $P = .002$) for every 1 kg increase in weight (see Table 2).

There was no evidence of effect modification by sex, race, or ethnicity in the associations between weight gain and change in fasting metabolic markers.

Association Between Weight Change at Week 48 and Incident Diabetes

One hundred three individuals with prevalent DM and 13 with DM that occurred within the first 48 weeks after ART initiation were excluded. Among those without DM prior to week 48, 130 participants developed DM after week 48. After adjusting for age, sex, race/ethnicity, baseline BMI, history of dyslipidemia and smoking status, those who experienced >10% weight gain by week 48 had a significantly higher risk of incident DM than those who experienced a weight change between −5% and 5% (HR 2.01, 95% CI [1.30, 3.08], Table 3).

Male participants who gained >10% weight at week 48 had a 2.5 times higher incidence of DM (HR 2.48, 95% CI [1.55, 3.98]) than those with a weight change between −5% and 5%; this increased risk was not seen among female participants (HR 0.91, 95% CI [.34, 2.45]); interaction $P = .07$.

There was no evidence of effect modification by either race or ethnicity in the association between weight gain and incident DM.

Association Between Weight Change at Week 48 and Incident Metabolic Syndrome

Seven hundred seven individuals with prevalent metabolic syndrome and 375 who developed metabolic syndrome within the first 48 weeks after ART initiation were excluded. Among those without metabolic syndrome prior to week 48, 360 participants developed metabolic syndrome after week 48. Those who lost more than 5% of their baseline weight had a lower risk of developing metabolic syndrome (HR 0.60, 95% CI [.37, .98]) whereas those who experienced >5%–10% weight gain and >10% weight gain had a 50% and 2-fold higher risk of developing metabolic syndrome (HR 1.56, 95% CI [1.19, 2.05] and HR 2.02, 95% CI [1.55, 2.62], respectively) than those who experienced a weight change between −5% and 5% (Table 3).

By race, the association between a weight increase of >5%–10% (vs −5% to 5%) and incident metabolic syndrome was apparent only among those of White race (HR 2.18, 95% CI [1.51, 3.16]) but not Black race (HR 1.08, 95% [CI .61, 1.95]) or other race (HR 1.14, 95% CI [.64, 2.03]); interaction $P = .06$ for contrast between White versus other race). There was no evidence of effect modification by sex or ethnicity in the association between weight gain and metabolic syndrome.

Association Between Weight Change at Week 48 and Incident Cardiometabolic Events

Cardiometabolic events included hypertension, initiation of antihypertensive medication, initiation of statin or other lipid lowering medication, hyperlipidemia, myocardial infarction, transient ischemic attack, CV surgery or procedure, or stroke (Supplementary Table 1). Six hundred ninety-nine individuals with cardiometabolic events that occurred before ART initiation and 235 with cardiometabolic events that occurred within the first 48 weeks after ART initiation were excluded. 424 participants had a cardiometabolic event after week 48. After adjusting for age, history of DM, family history of CV disease, smoking status, and BMI, we found that those who experienced >10% weight gain had a significantly higher risk of experiencing a cardiometabolic event (HR 1.54, 95% CI [1.22, 1.95]) as compared to those with a weight change of −5% to 5% (Table 4). There was no significant association for those who lost more than 5% or those who gained between 5% and 10% of their baseline weight.

By race, the increased risk of incident cardiometabolic events was seen among White and Black participants who gained >10% weight (vs −5% to 5% weight change) at week 48 but not among participants of other races (HR 1.71 95% CI [1.20, 2.44] for White participants, interaction $P = .15$ (White vs other race); HR 2.02 95% CI [1.32, 3.12] for Black participants, interaction $P = .07$ (Black vs other race); HR 1.13 95% [CI .72, 1.78] for other participants). When evaluated by ethnicity, only non-Hispanic participants who gained >10% weight at week 48 (vs −5% to 5% weight change) had

Table 3. Adjusted Cox Proportional Hazard Models of Weight Change at Week 48 and Incident Metabolic Events

	HR (95% CI)	
Degree Weight Change at Week 48	Diabetes Mellitus (n = 130)	Metabolic Syndrome (n = 360)
<−5%	0.63 (.27, 1.47)	**0.60 (.37, .98)**
>5% to 10%	1.46 (.92, 2.29)	**1.56 (1.19, 2.05)**
>10%	**2.01 (1.30, 3.08)**	**2.02 (1.55, 2.62)**

Reference level = −5% to 5%. In addition to variables included a priori model for diabetes mellitus included smoking status, and model for metabolic syndrome included BMI. The bolded values are those that are statistically significant.

Abbreviations: BMI, body mass index; CI, confidence interval.

Table 4. Adjusted Cox Proportional Hazard Models of Weight Change at Week 48 and Incident Cardiometabolic and CV Events

	HR (95% CI)	
Degree Weight Change at Week 48	Cardiometabolic Event (n = 424)	CV Event (n = 28)
<−5%	0.67 (.42, 1.07)	0.97 (.22, 4.31)
>5% to 10%	1.09 (.84, 1.41)	0.26 (.06, 1.15)
>10%	**1.54 (1.22, 1.95)**	0.60 (.22, 1.67)

Cardiometabolic event: HTN, initiation of anti-HTNsive medication, hyperlipidemia, MI, TIA, CV surgery or procedure, or CVA. CV event: MI, CV surgery or procedure, TIA or CVA. Reference level = −5% to 5%. In addition to variables included a priori model for cardiometabolic events included BMI, and model for CV events included CD4 and HIV-1 RNA. The bolded values are those that are statistically significant.

Abbreviations: BMI, body mass index; CD4, CD4+ T-cell count; CI, confidence interval; CV, cardiovascular; CVA, cerebrovascular accident; HIV-1, human immunodeficiency virus type 1; ICVHR, hazard ratio; HTN, hypertension; MI, myocardial infarction; TIA, transient ischemic attack.

a higher risk of incident cardiometabolic events (HR 1.85 95% CI [1.41, 2.42]; interaction $P = .05$).

Association Between Weight Change at Week 48 and Incident CV Events

Thirty-two individuals with prevalent CV events and 1 with a CV event that occurred within the first 48 weeks after ART initiation were excluded. Twenty-eight incident CV events occurred after week 48. After adjusting for age, history of DM, hypertension, or dyslipidemia at baseline, family history of cardiovascular disease, smoking status, baseline CD4 count, and HIV-1 RNA, weight change was not associated with incident CV events.

Association Between Waist Circumference Change at Week 48 and Metabolic and Clinical Outcomes

Similar associations were observed for an increase in waist circumference of >7 cm versus ≤3 cm and all metabolic and clinical outcomes (data not shown).

Table 5. Adjusted Cox Proportional Hazard Models of Weight Change at Week 48 and Subsequent Clinical Events Among Participants With >10% Weight Gain

Clinical Event	HR (95% CI)
Diabetes mellitus (n = 130)	**2.01 (1.30, 3.08)**
Metabolic syndrome (n = 360)	**2.02 (1.55, 2.62)**
Cardiometabolic event (n = 424)	**1.54 (1.22, 1.95)**
CV Event (n = 28)	0.60 (.22, 1.67)

Cardiometabolic event: HTN, initiation of anti-HTNsive medication, hyperlipidemia, MI, TIA, CV surgery or procedure, or CVA. CV event: MI, CV surgery or procedure, TIA or CVA. The bolded values are those that are statistically significant.

Abbreviations: CI, confidence interval; CV, cardiovascular; CVA, cardiovascular accident; ICVHR, hazard ratio; HTN, hypertension; MI, myocardial infarction; TIA, transient ischemic attack.

DISCUSSION

Leveraging the robust data in these cohorts with nearly 10 years of follow-up, we observed an average 3.6 kg weight increase during the first 48 weeks following ART initiation and an average total of 7.1 kg over the 480 weeks of study follow-up. By week 480, 40% of participants had gained >10% of their baseline weight. Interestingly, this is in line with weight trends in the general US population as noted in a recent cross-sectional study where 36% of adults in the United States gained 10% or more of their baseline body weight over 10 years [11].

Not surprisingly, the initial weight gain was associated with small but statistically significant increases in fasting glucose and fasting lipids (total cholesterol, LDL, and triglycerides). Furthermore, we found an increased risk of incident DM, metabolic syndrome, and cardiometabolic events in association with the initial weight gain after ART initiation. Those who experienced >10% weight gain during weeks 0 to 48 had a nearly 2-fold increased risk of incident DM, >2-fold risk of incident metabolic syndrome, and a 50% higher risk of an incident cardiometabolic event (Table 5 and Figure 1). Furthermore, those who lost more than 5% of their baseline weight had a 40% lower risk of incident metabolic syndrome.

Although we did not have a matched cohort of people without HIV to draw comparisons, studies from the general population have also noted associations between weight gains of >5% and an increased risk of metabolic syndrome, DM and CV disease, among others [12–14].

Our analysis is unique in that it is the first to include long-term follow-up of data published from persons originally
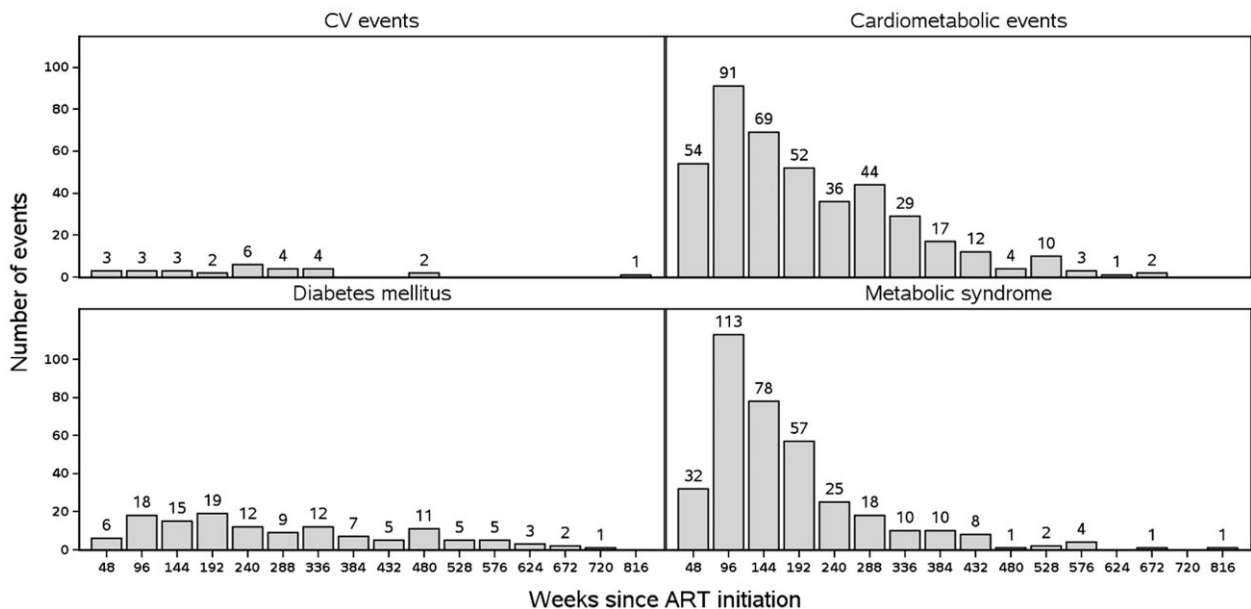

Figure 1. Clinical events by weeks since ART initiation. Abbreviations: ART, antiretroviral therapy; CV, cardiovascular.

enrolled in ART initiation trials and followed at least annually since the conclusion of their trial. The detailed participant characterization allowed for evaluation of comorbidities, concomitant medications, and relevant sociodemographic factors since the initiation of ART.

An important strength of our study is the assessment the impact of sex, race, and ethnicity on the associations between weight change and the outcomes of interest. This evaluation is of particular interest given certain demographic groups are disproportionately affected by ART-related weight gain [15–17] and cardiometabolic disorders [18–22]. We found evidence of sex differences in the association between weight gain and incident DM such that male participants who experienced >10% weight gain at week 48 had a 2.5 times higher incidence of DM, whereas female participants who experienced >10% weight gain did not have an increased risk of incident DM. This finding is notable when considered alongside the results of a recent cross-sectional analysis in which HIV was determined to confer an increase in the odds of DM among women but not men [23]. In this study, Birabhaharan and colleagues found the prevalence of obesity was higher in women with HIV than in men with HIV, but that women were more likely to have DM after controlling for obesity. It is possible that mechanisms *other* than weight gain (eg, enhanced inflammation and immune activation) may be implicated in the excess risk of DM among women with HIV.

We also found associations between weight gain, race/ethnicity, and incident cardiometabolic outcomes. The association between a weight increase of >5% to 10% (vs −5% to 5%) and incident metabolic syndrome was only apparent among those of White race, whereas we found a stronger association between a weight increase of >10% (vs −5% to 5%) and incident cardiometabolic events among those of Black race and those not of Hispanic/ Latino ethnicity. Although the significance of these differences is unclear, these data highlight the importance of continued analyses of race and ethnicity as additional unmeasured sociodemographic factors may contribute to excess cardiometabolic risk.

The available published data regarding weight gain and cardiometabolic disease following ART initiation do not diminish the unique contribution of our data. For example, a pooled analysis by Sax and colleagues did not find a clinically significant metabolic impact of weight gain as measured by fasting glucose and investigator reported adverse effects (AEs) [17]. However, this analysis was limited by a short duration of follow-up, a relatively small number of reported adverse effects, and the inability to account for some potential confounders such as tobacco use.

Similar to other published studies, we found that the short-term weight gain that occurred following ART initiation was associated with an increased risk of DM, metabolic syndrome, and cardiometabolic disease. Herrin and colleagues explored associations of weight gain and incident DM in the Veterans Aging Cohort Study (VACS), a national observational study of PWH

demographically matched to controls without HIV, and found that weight gain in the first year after ART initiation was associated with a significantly greater risk of DM among PWH than among controls [24]. Although the VACS study did not include female participants, McComsey and colleagues found an association between weight gain and incident DM in a retrospective analysis of Black and Hispanic females with HIV; those who experienced >5% weight/BMI gain within 6 months after ART initiation were more than 2 times more likely to be diagnosed with DM than PWH who experienced <5% weight/BMI gain (HR 2.19; $P = .044$) [25]. Our study found that >10% weight gain was associated with excess DM risk in male participants only, but sample size may have limited statistical comparisons. In contrast to our study, McComsey and colleagues did not find an association between weight/BMI gain and other cardiometabolic outcomes, but it is possible that that was due to the relatively short-term follow-up time of 2 years.

As noted in other studies, we found that baseline or pre-ART BMI impacted some but not all outcomes. Achhra and colleagues evaluated the impact of the short-term weight gain following ART initiation on the subsequent risk of DM and CV disease in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study and found that the weight gain was associated with baseline BMI for the outcome of incident CV disease but not incident DM [1]. Our analysis confirmed these findings in that baseline BMI and BMI category impacted the risk of incident cardiometabolic disease but not DM.

Unique to our analysis was the finding those who *lost* more than 5% of their baseline weight had a 40% lower risk of incident metabolic syndrome. This is highly relevant to clinical care as providers do not typically counsel patients to lose weight at the time of HIV diagnosis/ART initiation but may now be empowered to do so given the potential long-term benefit.

Our analysis has several limitations. First, because this is an observational study, we cannot exclude the potential for unmeasured confounding including important factors such as diet and physical activity. However, we adjusted for numerous known risk factors in our analyses. Second, we did not have sufficient observations to account for subsequent ART switches, including exposure to integrase strand transfer inhibitor (INSTI)-based ART, following the initial randomized controlled trials. This is of interest given recent data from the RESPOND cohort found that INSTI initiation was associated with early onset and excess incidence of CV disease [26]. Of note, although the aforementioned analysis examined possible mediator effects including time-updated BMI in exploratory analyses, the analysis was not restricted to the population experiencing INSTI-related weight gain. Finally, our results for the outcome of CV events are limited by the small number of incident events (N = 28) in the cohort.

In summary, ours is the first analysis to our knowledge of long-term cardiometabolic complications following short-term weight changes that occur after ART initiation that also

includes analysis to evaluate the impact of sex and race/ethnicity on these outcomes. These data confirm the negative impact of short-term weight gain as evidenced by significant increases in the risks of incident DM, metabolic syndrome, and CV events as well as the positive impact of short-term weight loss on incident metabolic syndrome. The data also highlight important sex differences in the impact of weight gain on incident DM, which illustrates the importance of investigating mechanisms other than weight gain when studying the excess risk of DM in women with HIV. Additional research is needed to determine whether weight control interventions at the time of ART initiation may help to minimize the risk of subsequent cardiometabolic disease.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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