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Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada

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Abstract

The proportion of overweight and obese adults in the United States and Canada has increased over the past decade, but temporal trends in body mass index (BMI) and weight gain on antiretroviral therapy (ART) among HIV-infected adults have not been well characterized. We conducted a cohort study comparing HIV-infected adults in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to United States National Health and Nutrition Examination Survey (NHANES) controls matched by sex, race, and age over the period 1998 to 2010. Multivariable linear regression assessed the relationship between BMI and year of ART initiation, adjusting for sex, race, age, and baseline $CD4^+$ count. Temporal trends in weight on ART were assessed using a generalized least-squares model further adjusted for HIV-1 RNA and first ART regimen class. A total of 14,084 patients from 17 cohorts contributed data; 83% were male, 57% were nonwhite, and the median age was 40 years. Median BMI at ART initiation increased from 23.8 to 24.8 kg/m^2 between 1998 and 2010 in NA-ACCORD, but the percentage of those obese (BMI $\geq$30 kg/m^2) at ART initiation increased from 9% to 18%. After 3 years of ART, 22% of individuals with a normal BMI (18.5–24.9 kg/m^2) at baseline had become overweight (BMI 25.0–29.9 kg/m^2), and 18% of those overweight at baseline had become obese. HIV-infected white women had a higher BMI after 3 years of ART as compared to age-matched white women in NHANES ($p = 0.02$), while no difference in BMI after 3 years of ART was observed for HIV-infected men or non-white women compared to controls. The high prevalence of obesity we observed among ART-exposed HIV-infected adults in North America may contribute to health complications in the future.

Introduction

The proportion of overweight and obese individuals in the general population of the United States and Canada has increased steadily over the past three decades, affecting all race/ethnicity, sex, and age groups to varying degrees.[1,2] Over one-third of adults in the United States are overweight [body mass index (BMI) 25–29.9 kg/m^2] and a similar proportion is obese (BMI $\geq$30 kg/m^2), while in Canada over one-third are overweight and one-quarter are

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obese.[1,3] Prior studies from single HIV cohorts or clinics in the United States have reported overweight and obesity prevalence rates comparable to the national average, and higher among minorities and women (a finding also observed in the general population).[4–7] However, these studies may reflect local dietary and physical activity patterns, and there have been no analyses to date of sex, race/ethnicity, and temporal trends in BMI and weight gain on antiretroviral therapy (ART) in HIV-infected individuals across multiple, geographically disparate cohorts in North America.

In the pre-ART era, prevention of HIV-associated wasting and the promotion of weight gain were viewed as beneficial, but in the era of effective ART, there is evidence that being overweight or obese may increase the risk of several comorbidities accompanying long-term HIV treatment.[8–10] In a recent single-site study at an HIV clinic with a high proportion of obese patients the prevalence of ''multimorbidity'' (i.e., more than one comorbid chronic illness) increased in a stepwise fashion with BMI strata.[8] Studies of the general population show that longitudinal increases in weight are associated with detrimental changes in cardiovascular and metabolic parameters, including blood pressure, dyslipidemia, markers of systemic inflammation, and insulin resistance.[11–14]

Characterizing the intersection of the obesity and HIV epidemics is important for situating nutritional counseling and primary disease prevention in the context of longitudinal HIV clinical care. We hypothesized that the BMI of HIV-infected adults starting ART in the United States and Canada rose over the first decade of the twenty-first century, just as the mean BMI of the general population increased, and that HIV-infected adults in all BMI categories gained weight after treatment initiation. In this analysis, we assessed temporal, sex, and race differences in BMI at the time of ART initiation and weight change on treatment among adults enrolled in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) over the period 1998–2010. Furthermore, we compared the pretreatment and on-ART BMI values of NA-ACCORD patients with National Health and Nutrition Examination Survey (NHANES) participants matched by age, race, and sex over corresponding calendar periods.

Materials and Methods

NA-ACCORD is a multisite collaboration involving 25 cohort studies representing over 100 clinical and research sites for HIV-infected persons in the United States and Canada, and it is one of the regional cohort study groups supported by the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium of the National Institutes of Health.[15] NA-ACCORD collects standardized data on demographic characteristics, antiretroviral medication use, laboratory values, clinical diagnoses, and vital status. Data are transmitted to a centralized core at regular intervals for quality control and harmonization. Institutional review boards at each participating site have reviewed and approved the activities of NA-ACCORD.

We assessed the relationships between BMI at ART initiation, and weight change after 1 and 3 years on treatment, among ART-naive adults starting a first antiretroviral regimen (defined as three or more medications) from 1998 to 2010 in NA-ACCORD. Seventeen of the 25 NA-ACCORD cohorts reported longitudinal BMI data, which included clinical sites in 28 states in all regions of the United States, the District of Columbia, and in Quebec, Ontario, and the Maritime Provinces in Canada. Because NA-ACCORD lacks information on pregnancy among female participants, we excluded women with more than a 10% weight change within 6 months of starting ART from the analysis cohort ($n = 1134$).

To be included in the analysis of BMI at ART initiation, NA-ACCORD participants had to have at least one weight value within 180 days before to 30 days after the start date of the first regimen (the value closest to this date was selected); there were no restrictions on when height, used to calculate BMI, was recorded. To be included in the longitudinal analyses of weight change, participants had to have at least one weight measurement more than 30 days after ART initiation, which was available in 96% of those with a baseline weight. Weight at 1 year was the value closest to 12 months of ART but prior to 1.5 years of follow-up, while weight at 3 years was the value closest to 36 months of ART, within a window period between 2.5 and 3.5 years of follow-up. Participants who died or were lost to follow-up prior to 2.5 years of ART were censored for the 3-year analyses. BMI was treated as a continuous variable in the linear models, but, for the purpose of comparing groups, BMI was categorized according to standard convention as underweight ($<18.5\,kg/m^2$), normal ($18.5–24.9\,kg/m^2$), overweight ($25–29.9\,kg/m^2$), obese ($30–40\,kg/m^2$), and morbidly obese ($>40\,kg/m^2$).[16] Baseline $CD4^+$ T cell count was also the closest value to the start date within 180 days before to 30 days after, while plasma HIV-1 RNA was the closest value within 180 days prior to the start of ART.

The relationship between BMI and year of ART initiation was assessed using a linear model adjusted for sex, race (white, nonwhite, and unknown), age, baseline $CD4^+$ T cell count, and cohort. To avoid assuming a linear relationship, continuous covariates were modeled using restricted cubic splines with four knots.[17] We included an interaction term for sex and BMI, and race and BMI, given differences reported in the general population.[1] The estimated BMI at ART initiation between 1998 and 2010, stratified by sex and by race, was extracted from the model and displayed graphically. For comparison, we calculated sex- and race-stratified BMI estimates for the general U.S. population between 1998 and 2010 using NHANES data (reported in 2-year intervals) appropriately weighted according to CDC guidelines to account for the sampling design.[18] The NHANES estimates were then weighted to match the age distribution of NA-ACCORD participants. The mean number of NHANES respondents per 2-year cohort between 1998 and 2010 was 9,815.

To assess whether the average weight gain after starting ART differed according to sex and race, or changed between 1998 and 2010, we modeled time varying weight after ART initiation (up to 3 years of follow-up) using a generalized least-squares model to account for the within-subject correlation induced by repeated measures on a subject. We chose to report the results from the analysis using weight rather than BMI because weight is more commonly used in clinical practice. The model used weight over time on ART as the outcome, adjusting for time of weight measurement since ART initiation, age, sex, race, cohort, year of ART initiation, the initial ART regimen [classified as nonnucleoside reverse

Table 1. Cohort Demographics, Clinical Characteristics, and Weight Gain at 1 and 3 Years of Antiretroviral Therapy, Stratified by Body Mass Index at Antiretroviral Therapy Initiation

	Underweight *<18.5 kg/m²* n = *608*	*Normal* *18.5–24.9 kg/m²* n = *7105*	*Overweight* *25–29.9 kg/m²* n = *4275*	*Obese* *30–40 kg/m²* n = *1793*	*Morbidly obese* *>40 kg/m²* n = *303*	p-*value*	*Overall* n = *14,084*
Cohort at ART initiation							
Female, %	15%	12%	16%	31%	66%	<0.001	17%
Nonwhite race, %	60%	55%	55%	65%	80%	<0.001	57%
Age, median years (IQR)	39 (31, 47)	39 (32, 46)	41 (35, 47)	41 (35, 48)	40 (34, 47)	<0.001	40 (33, 47)
CD4 count, median cells/μl (IQR)	75 (21, 232)	217 (70, 348)	267 (142, 403)	287 (165, 433)	340 (227, 514)	<0.001	241 (94, 377)
Calendar year of ART start, median	2005	2005	2005	2006	2007	<0.001	2005
$\log_{10}$ HIV viral load, median copies/ml (IQR)	5.1 (4.5, 5.7)	4.8 (4.1, 5.4)	4.6 (3.7, 5.1)	4.4 (3.3, 5.0)	4.0 (2.8, 4.7)	<0.001	4.7 (3.9, 5.3)
First ART regimen class						0.002	
PI based	52%	45%	44%	45%	46%		45%
NNRTI based	42%	47%	47%	46%	42%		46%
NRTI only	4%	5%	6%	5%	6%		5%
Other	3%	3%	3%	4%	7%		3%
Cohort at 1 year of ART[a]							
Weight change, kg	5.0 (0.5, 11.3)	1.8 (–0.7, 6.0)	0.5 (–2.1, 4.5)	0.5 (–3.0, 4.5)	0.0 (–5.4, 5.9)	<0.001	1.4 (–1.4, 5.9)
BMI change, kg/m²	1.5 (0.2, 3.7)	0.6 (–0.2, 2.0)	0.2 (–0.7, 1.5)	0.1 (–1.0, 1.6)	0.0 (–2.2, 2.1)	<0.001	0.4 (–0.4, 1.9)
Time from ART initiation to measurement	1.2 (0.6, 1.4)	1.2 (0.7, 1.4)	1.2 (0.7, 1.4)	1.2 (0.6, 1.4)	1.2 (0.7, 1.4)	0.04	1.2 (0.7, 1.4)
Cohort at 3 years of ART[a]							
Weight change, kg	7.7 (2.7, 14.1)	3.6 (0.0, 8.6)	1.8 (–3.2, 6.5)	1.0 (–4.9, 7.7)	0.0 (–6.0, 11.8)	<0.001	1.8 (–1.8, 6.4)
BMI change, kg/m²	2.5 (0.9, 4.7)	1.2 (0.0, 2.8)	0.5 (–1.1, 2.1)	0.3 (–1.6, 2.6)	0.0 (–2.5, 4.5)	<0.001	0.6 (–0.5, 2.1)
Time from ART initiation to measurement	3.3 (3.2, 3.4)	3.3 (3.1, 3.4)	3.3 (3.1, 3.4)	3.3 (3.1, 3.4)	3.3 (3.0, 3.4)	0.03	3.3 (3.1, 3.4)

[a]Median values and interquartile range.

p-value is Kruskal–Wallis test across BMI categories.

ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

transcriptase inhibitor (NNRTI) based, protease inhibitor (PI) based, nucleoside reverse transcriptase inhibitors (NRTI) only, or ''other''], and baseline weight, CD4 count, and $\log_{10}$ viral load. The model also included interaction terms between year of ART initiation and time, between sex and time, and between race and time. To avoid assuming a linear relationship between the continuous covariates and the outcome, weight, CD4 count, viral load, age, and year at ART initiation were modeled using restricted cubic splines with four knots. Participants were censored at the time of a recorded ART discontinuation. Missing baseline viral loads (3%) were singly imputed with the median of the nonmissing values.

Because the criteria for identifying potential pregnancies were imprecise, two sensitivity analyses excluding all women under 35 years of age and under 40 years of age were performed for the time-varying analyses.

Results

Data on 14,084 HIV-infected, ART-naive individuals who started treatment from 1998 through 2010 and had a baseline BMI value recorded were available from 17 cohorts in NA-ACCORD (Table 1). The racial/ethnic distribution was 43% non-Hispanic white, 38% non-Hispanic black, 15% Hispanic, 4% other, and 1% unknown. Higher BMI participants were more likely to be female, nonwhite, have a higher pretreatment $CD4^+$ T cell count, start ART in a later calendar year, and have a lower pretreatment $\log_{10}$ viral load ($p < 0.01$ for all). While the percentage of underweight individuals (BMI $<18.5\,kg/m^2$) starting a PI-based regimen was higher than other BMI categories, the proportion of PI and NNRTI-based first ART regimens was relatively uniform in the normal weight through the morbidly obese categories.

The percentage of NA-ACCORD participants who were overweight at ART initiation was relatively uniform from the period 1998–2000 to 2007–2010 (29% vs. 31%, $p = 0.11$), but the percentage of obese participants increased over this time (11% vs. 17%, $p < 0.001$; Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/aid). The proportion of female and nonwhite participants also increased over time ($p < 0.01$ for both). There was considerable variability in the first ART regimen: PI-based regimens predominated in 1998–2000 and NNRTI-based regimens predominated in 2007–2010.

The estimated BMI at ART initiation increased in a roughly linear manner between 1998 and 2010 after adjusting for differences in baseline $CD4^+$ T cell count, age, sex, and race ($p < 0.001$; Table 2). Compared to the reference year 2003, pre-ART average BMI was lower in 1998 ($-0.55\,kg/m^2$; 95% CI: –0.94, –0.17) and higher in 2010 ($0.83\,kg/m^2$; 95% CI: 0.57, 1.10). There were also significant differences in baseline BMI by race and sex. Among men, the BMI of nonwhites was $0.65\,kg/m^2$ higher compared to whites, while among women this difference was $1.19\,kg/m^2$. In addition, older age and a higher pretreatment $CD4^+$ T cell count were associated with a higher BMI.

Median BMI in the matched NHANES participants increased from 25.0 to $26.0\,kg/m^2$ between 1998 and 2010, as compared to an increase from 23.8 to $24.8\,kg/m^2$ in NA-ACCORD over the same period. The estimated BMI increased in all gender and racial groups between 1998 and 2010 in NA-ACCORD, but there was more variability observed in NHANES (Fig. 1). In 1998, the prevalence of obesity in the NA-ACCORD participants was lower than in the matched NHANES participants (9% vs. 22%), but the difference in obesity prevalence between cohorts was less pronounced in 2010 (18% vs. 27%, data not shown).

Of NA-ACCORD participants 13,591 (96%) had a recorded weight value during the 3 years after starting ART. BMI and weight (kg) measurements changed in tandem after treatment initiation because height was treated as a fixed value. Weight gain at 1 and 3 years after ART initiation was significantly greater among those with a lower BMI at the start of treatment (Table 1). In all BMI categories, approximately 80% of the weight gain observed at 3 years could be attributed to the change in the first year of treatment. However, there were marked sex and race differences ($p < 0.001$ for both interaction terms). White and nonwhite men had a

Table 2. Relationship of Body Mass Index and Year of Antiretroviral Therapy Initiation, Adjusted for Age, $CD4^+$ T Cell Count, Sex, and Race in NA-ACCORD

Covariate	*Estimated effect on BMI at ART initiation (kg/m^2)*	*95% confidence interval*	p-*value*
Year of ART initiation			
1998	−0.55	(−0.94, −0.17)	<0.001
2000	−0.41	(−0.57, −0.25)	
2003 (reference)	0		
2005	0.32	(0.16, 0.48)	
2007	0.56	(0.37, 0.76)	
2010	0.83	(0.57, 1.10)	
Age at ART initiation (years)			<0.001
25	−1.55	(−1.81, −1.29)	
30	−0.68	(−0.78, −0.58)	
35 (reference)	0		
40	0.31	(0.21, 0.41)	
45	0.32	(0.11, 0.54)	
CD4 at ART initiation (cells/μl)			
100	−1.68	(−1.89, −1.47)	
200	−0.72	(−0.90, −0.54)	<0.001
350 (reference)	0		
500	0.39	(0.31, 0.47)	
Sex			<0.001
In subjects of white race			
Male	−2.80	(−3.30, −2.29)	
Female (reference)	0		
In subjects of non-white race			
Male	−3.33	(−3.61, −3.06)	
Female (reference)	0		
Race			<0.001
In men			
Nonwhite	0.65	(0.45, 0.84)	
White (reference)	0		
In women			
Nonwhite	1.19	(0.65, 1.73)	
White (reference)	0		

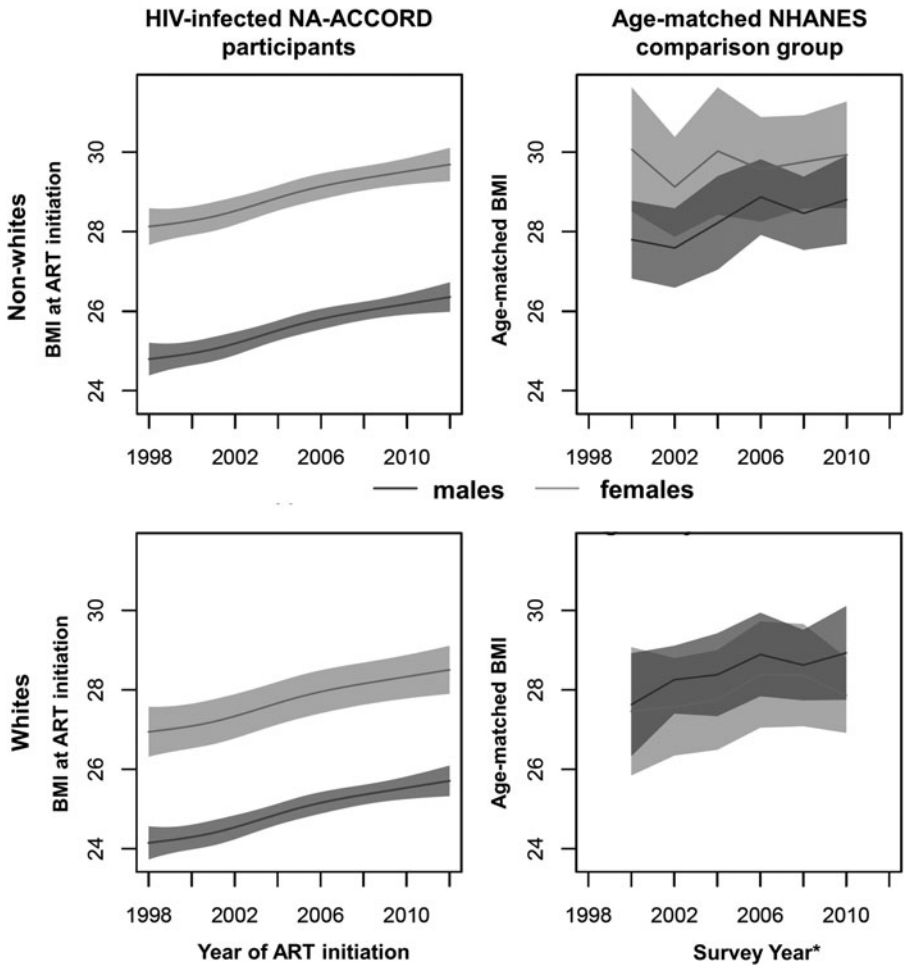

FIG. 1. Estimated mean BMI at ART initiation (and 95% confidence interval) for HIV-infected NA-ACCORD participants and age-matched NHANES participants, stratified by sex and race. NA-ACCORD model adjusted for age, $CD4^+$ T cell count at treatment initiation, and cohort. *NHANES data reported in 2-year intervals and weighted to match the NA-ACCORD cohort according to CDC guidelines. ART, antiretroviral therapy; BMI, body mass index; NHANES, National Health and Nutrition Examination Survey. *Light gray* shading represents females and *dark gray* shading represents males.

sharp early rise in weight while women showed a more uniform rise over 3 years (Fig. 2). A greater weight gain was also associated with a lower pretreatment $CD4^+$ T cell count and higher $\log_{10}$ viral load ($p < 0.001$ for both), and those with an age of approximately 35 years had greater weight gain compared to younger or older individuals ($p < 0.001$, data not shown).

Weight over time since ART initiation stratified by year of ART initiation is shown in Fig. 3. While the presence of multiple interactions between model terms complicates the interpretation of individual variables, we observed a significant, nonlinear relationship between weight change and treatment year ($p < 0.001$). In early cohort years (1998–2002), patients tended to gain weight during the first year, which then reached a plateau or fell in the subsequent two years. In later cohort years the weight gain continued over the full 3 years. Data for those starting ART in 2010 were truncated at 1 year.

After 1 year of ART, 20% of participants with a normal BMI at ART initiation had become overweight, and 15% of those overweight at baseline had become obese (Supplementary Table S2). After 3 years of ART, 22% of participants with a normal BMI at ART initiation had become overweight, and 18% of those overweight at baseline had become obese. A reclassification after 3 years from normal BMI to overweight was most common among white males (23%), while a shift from overweight to obese was most common among nonwhite females (21%). In comparison, relatively few participants moved to the next lower BMI category after 3 years if they were overweight (16%) or obese (13%) at ART initiation.

Lastly, we compared the BMI after 3 years of ART in the subset of NA-ACCORD participants who started treatment in 2006 or 2007 (i.e., we used the mean BMI of these individuals in 2009 or 2010) against the mean BMI of NHANES participants in the 2009–2010 survey period matched for age and stratified by sex and race. The NHANES participants in our comparison group were not followed longitudinally and therefore a BMI value after 3 years was not available for those evaluated in 2006 or 2007; as a surrogate we used the BMI of age-matched participants in the 2009–2010 cohort. After 3 years of ART, the mean BMI of HIV-infected white men, nonwhite men, and nonwhite women was not significantly different from age-matched peers in the 2009–2010 NHANES data ($p > 0.05$ for all). However, while HIV-infected white women appeared to gain the least weight on treatment, the mean BMI of HIV-infected white women after 3 years of ART (30.8 kg/m^2) still exceeded the mean BMI of age-matched NHANES participants (27.9 kg/m^2, $p = 0.02$).

Two sensitivity analyses excluding all women under 35 years of age and under 40 years of age were performed with the goal of reducing confounding due to unrecorded pregnancies (pregnancy status is not included in NA-ACCORD). The results for both were similar to the primary analysis for

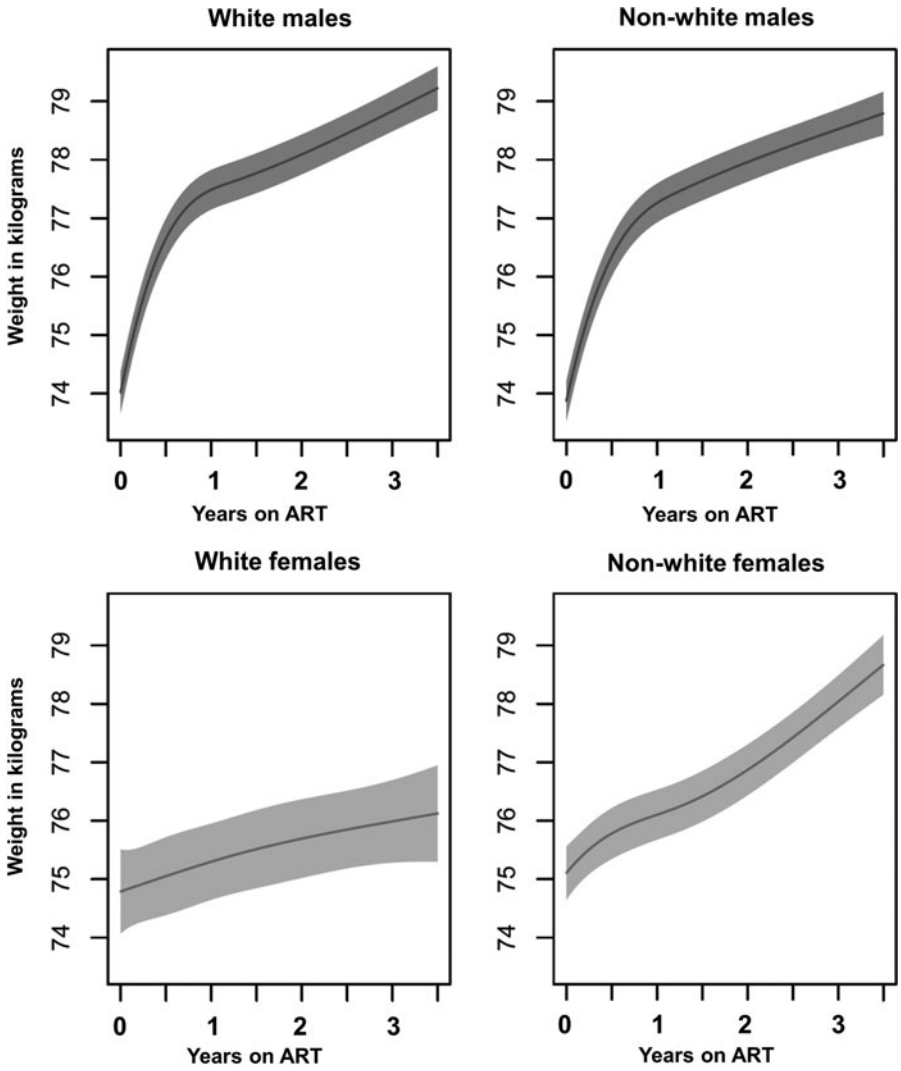

FIG. 2. Predicted mean weight (and 95% confidence intervals) over 3 years after ART initiation, stratified by sex and race in NA-ACCORD, 1998–2010. Model adjusted for age, initial antiretroviral regimen, year of treatment initiation, cohort, and baseline weight, $CD4^+$ T cell count, and $\log_{10}$ HIV RNA.

BMI at ART initiation, weight gain after ART initiation among both white and nonwhite women, and weight gain according to year of treatment initiation.

Discussion

For much of the past decade, U.S. and Canadian HIV-infected individuals in NA-ACCORD had lower BMI at the time of ART initiation compared to the general U.S. population of similar age, sex, and race. However, weight gain in the first 3 years after starting ART resulted in NA-ACCORD participants ''catching up'' to the average BMI of similarly aged members of the general population, and exceeding the general population in the case of HIV-infected white females. Further clinical studies are needed to understand how the overlapping metabolic, cardiovascular, and inflammatory derangements observed more frequently in both excess adiposity and treated HIV interact in a single individual. The pattern of short-term weight gain and increased obesity prevalence after ART initiation we observed in NA-ACCORD may have profound consequences for the future burden of cardiometabolic diseases and other noncommunicable diseases (NCDs) in the HIV-infected population.

Our findings of a high prevalence of overweight/obesity and weight gain on ART are similar to reports from prior single-clinic or smaller HIV cohort studies.[4,5,19,20] An analysis of the U.S. Military HIV Natural History Cohort between 1985 and 2004 found that 37% of participants were overweight at the time of HIV diagnosis and 9% were obese.[4] These rates were not constant, however, as the proportion of overweight doubled when comparing the period 1985–1990 to 1996–2004, and the proportion of obese was 4-fold higher. In a point-prevalence study of HIV-infected adults in Philadelphia, obesity was most common in African American women (30%) and non-African American women (23%) compared to men (13% versus 8%, respectively).[5] Similar studies have also found higher obesity rates among HIV-infected individuals of African origin as compared to whites, and women as compared to men, in the United States and in Europe.[21,22]

Two recent studies report substantial weight gain after ART initiation, particularly among nonwhite and uninsured individuals. In South Texas, an area with a large uninsured and Hispanic population, 38% of patients were overweight and 22% were obese at ART initiation.[7] Overweight/obesity was more common among nonwhites irrespective of insurance status, and modeling based on BMI change per year

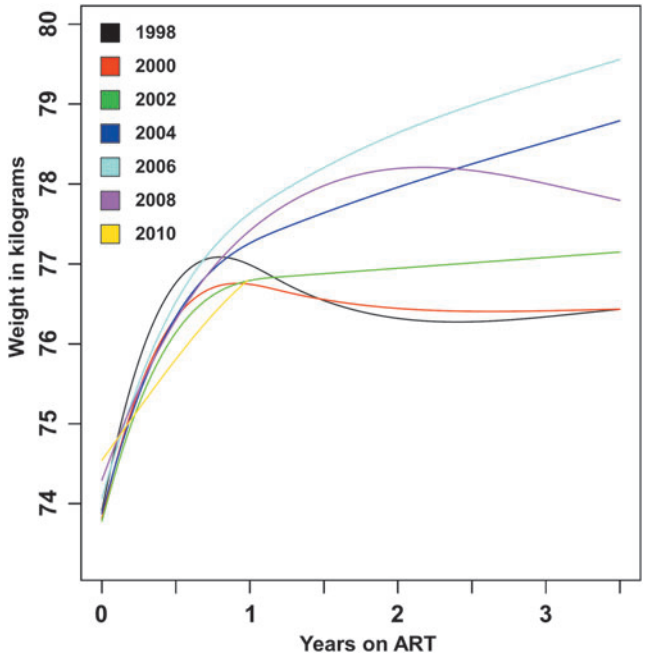

FIG. 3. Estimated mean weight over the initial 3 years following ART initiation, stratified by year of treatment initiation in NA-ACCORD, 1998–2010. Model adjusted for age, sex, race, initial antiretroviral regimen, cohort, and baseline weight, $CD4^+$ T cell count, and $\log_{10}$ HIV RNA. Participants starting ART in 2010 were truncated at 1 year of follow-up.

projected 30% of overweight patients would become obese within 4 years of treatment. Similarly, an analysis of patients starting ART in Alabama found that approximately 20% of normal-weight patients became overweight after 2 years of ART, and 20% of the overweight became obese.[6] Similar trends were seen at 12 months in a North Carolina cohort.[23]

The causes underlying the progressive rise in body weight among the HIV-infected population are likely a complex mix of interrelated and shifting lifestyle trends in society at large, HIV provider and patient conceptions of health and priorities for care, changes in guidelines for initiating ART, and the introduction of new ART agents, among other factors. While recent data show a stabilization in U.S. obesity prevalence rates outside of the Southeast, this plateau comes at the end of a progressive three-decade climb in the proportion of overweight and obese persons in North America.[1] The epidemic of obesity in the United States and Canada appears to result more from large increases in average daily caloric intake rather than large reductions in physical activity.[24–27] It is reasonable to assume that HIV patients are similarly affected by factors driving obesity in the general population, particularly as earlier treatment and effective ART preempt the cachexia common in advanced untreated disease.[28,29]

Determining an optimal weight for HIV-infected patients is difficult due to a lack of data on how cardiovascular and metabolic disease risk factors interact in comorbid HIV and obesity. In a large Southeastern cohort there was a stepwise increase in the prevalence of ''multimorbidity,'' or the presence of multiple comorbidities involving different organ systems or physiologic pathways, among ART-treated patients in progressively higher BMI categories.[8] Overweight and obese HIV-infected individuals also demonstrate progressively higher levels of several circulating inflammatory cytokines associated with the development of diabetes, cardiovascular disease, and all-cause mortality.[30–34] Increasing BMI is associated with greater dyslipidemia and incident diabetes diagnoses in HIV patients, and abdominal obesity has been linked to accelerated neurocognitive decline.[9,10,35]

The risk of incident comorbid illnesses in HIV-infected adults may not rise in a linear fashion as adiposity increases. In a retrospective cohort study of 1,089 patients over the period 1998–2010 at a large academic HIV clinic in the Southeast, a BMI of 30 kg/m^2 was associated with a lower risk of the combined endpoint of an incident cardiovascular, hepatic, renal, or oncologic disease diagnosis compared to a BMI of 25 kg/m^2, but this protective effect was attenuated at a BMI of 35 kg/m^2.[36] The association persisted after adjusting for differences in statin and antihypertensive treatment, and self-reported tobacco, alcohol, and drug use. The nonlinear relationship between BMI and incident disease diagnoses may be due in part to differences in patient risk behaviors; an analysis of the Women's Interagency HIV Study found that individuals with higher BMI were less likely to be current smokers, or engage in moderate to heavy alcohol intake, injection drug use, or cocaine use.[37,38] Further clinical research is needed to understand how HIV infection and antiretroviral agents affect the already complex interactions of adipose tissue, innate and cellular immune function, metabolism, and cardiovascular health before our current preventive care and disease management practices, formulated largely based on evidence from uninfected populations, can be effectively applied to HIV-infected individuals on long-term ART.[39,40]

A substantial number of NA-ACCORD cohorts do not include longitudinal BMI data and could not be included in our analysis, which may have reduced the power and the geographic representation. Our analysis was also limited by a lack of pregnancy data on female participants. By excluding women with more than a 10% weight change within 6 months of ART initiation, we may have underestimated weight gain on treatment. While our comparator NHANES population was weighted to the age distribution of the NA-ACCORD participants (and matched by sex and race), there may have been geographic, socioeconomic, or other unrecognized confounders between the two groups; the most obvious would be the lack of Canadians in NHANES. The NA-ACCORD cohort also may not be fully reflective of the HIV epidemic in North America, particularly in regard to patients in remote rural areas or smaller, private infectious diseases or general medicine practices. The NA-ACCORD dataset does not include information on income, education, employment status, or dietary composition and total intake, which may have affected body composition at treatment initiation and weight gain on ART. Our analysis did not account for viral load measurements on ART, and we could not assess changes in weight according to virologic suppression status. Our analysis ended in 2010, which precluded an assessment of whether the obesity epidemic may have finally crested in both the HIV-infected and uninfected populations.[1] Lastly, BMI and weight are imprecise measures of body composition, and variability in lean versus fat mass partitioning was likely present.

An enduring image of the pre-ART era was the severely wasted AIDS patient, and early in the epidemic weight gain was viewed as beneficial in HIV-infected individuals. In

North America, we found that the BMI at ART initiation among HIV-infected adults increased between 1998 and 2010, as has weight gain. Among providers and patients, a relic of this earlier period may be the sense that a ''healthy'' (i.e., higher) weight remains desirable, though this view needs to be balanced against the potential health risks of excess adiposity. While further research is needed to understand the metabolic and cardiovascular consequences of comorbid HIV and obesity, the management of weight-related health conditions will be a priority and challenge for the care of contemporary HIV-infected individuals.

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Author Disclosure Statement

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