Weight Gain and Incident Diabetes Among HIV-Infected Veterans Initiating Antiretroviral Therapy Compared With Uninfected Individuals

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Background: The health implications of weight gain after antiretroviral therapy (ART) for HIV infection are not well characterized and may differ from weight gain among uninfected individuals. We use data from the Veterans Aging Cohort Study to determine whether weight gain after ART has a similar association with incident type 2 diabetes mellitus (DM) as weight gained among HIV-uninfected (uninfected) individuals.

Methods: We explored associations of weight gain and incident diabetes (A1c ≥ 6.5%), in the Veterans Aging Cohort Study, a national observational study of HIV-infected (HIV+) individuals demographically matched 1:2 to uninfected controls. From 2000 to 2011, weight change was assessed in the year following ART initiation for HIV+ individuals and date of first available body mass index for uninfected individuals. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for baseline body mass index using Cox regression.

Results: HIV+ individuals had lower prevalence of DM at baseline (12% HIV+, 23% uninfected) and lower incident diabetes (5% HIV+, 11% uninfected). The association of weight gain with risk of DM was linear for HIV+ and uninfected but the slope of the association was steeper for HIV+. For each 5 pounds of weight gained, HIV+ had 14% increased risk of DM (HR, 1.14; 95% CI: 1.10 to 1.17) and uninfected individuals had 8% increased risk (HR, 1.08; 95% CI: 1.07 to 1.10) ($P < 0.01$ for interaction).

Conclusions: Weight gained in the first year after ART initiation is associated with greater risk of DM than that among uninfected individuals. HIV+ individuals initiating ART who are not underweight should avoid substantial weight gain.

Key Words: diabetes, HIV, weight gain, obesity, veterans, inflammation

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After initiating antiretroviral therapy (ART), most HIV-infected individuals (HIV+) gain weight, many becoming overweight or obese,[1] and the clinical implications of this weight gain are not well understood. Although weight gain

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of 10–20 pounds after ART initiation is associated with a survival advantage among normal weight individuals,[2] weight gain may exacerbate risk of comorbid disease. Among uninfected individuals, obesity dramatically increases risk of type 2 diabetes mellitus (DM), hypertension, hyperlipidemia, and associated cardiovascular disease,[3] and obesity increases risk for hepatic cirrhosis and several forms of cancer.[4] Furthermore, in uninfected individuals, obesity is associated with inflammation and hypercoagulability.[5] Concentrations of circulating IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) are elevated in obesity and predict incidence of diabetes.[6] Given the increased risk for metabolic syndrome, cardiovascular disease, liver disease, cancer, and the putative harmful role of chronic inflammation among those with HIV,[7,8] minimizing weight gain after ART would seem advisable (except in those who are underweight).[9]

However, weight gain after ART may not be the same as weight gain in middle-aged individuals free of HIV infection. In earlier studies, higher body mass index (BMI) has been associated with slower HIV progression[10] and mild-to-moderate obesity has been associated with better HIV survival compared with nonobese HIV+ individuals.[11] Overweight BMI (in kilograms per square meter) categories are associated with lower declines in CD4 count and greater gains in CD4 count compared with normal BMI.[1] In more recent studies, weight gain after ART is associated with HIV-1 RNA suppression and CD4 count response.[2,12,13]

Complicating the picture further, ART has been found to be associated with incident DM.[14] This finding may be explained by direct effects of medications, particularly the promotion of hyperglycemia through resistance to or decreased production of insulin, an effect primarily observed for protease inhibitors (PIs).[15] Thus, HIV-infected individuals on ART may be at higher risk of developing DM as they age.

The characterization of weight gain and DM incidence among HIV+ initiating ART compared with that observed among uninfected individuals may offer important insight regarding competing effects of HIV-1 RNA suppression, weight gain, and ART toxicity. Using data from the Veterans Aging Cohort Study (VACS), which includes a large sample of HIV+ and demographically and behaviorally similar uninfected individuals, we explore this association.

METHODS

Study Population

The VACS has been described previously.[16] Briefly, VACS is an ongoing observational cohort of HIV+ veterans, matched 1:2 with uninfected veterans by age, sex, race, and site of care, who received medical care at a Department of Veterans Affairs (VA) health care facility. Patients were identified from VA national electronic health records. Clinical information includes *International Classification of Diseases, Ninth Edition diagnosis codes (ICD-9 codes)* from inpatient and outpatient visits, laboratory results, and all medications dispensed from VA pharmacies. Height and weight from clinic visits as of 2000 are available. VACS was approved by the Human Investigation Committee at the Yale School of Medicine and the VA Connecticut Human Subjects Subcommittee.

Eligible patients entered VACS between January 1, 1999, and September 30, 2011. Patients who died in the year after cohort entry or had no VA visit were excluded. We defined baseline as date of ART initiation for HIV+ and date of first available BMI for uninfected. To ensure that all patients had a year of history before starting follow-up, the earliest baseline date was January 1, 2000. Eligible HIV+ were ART naive, defined as no record of any previous antiretroviral (ARV) prescription, plus HIV-1 RNA >500 copies per milliliter in the 180 days before ART initiation. ART was defined as the combination of at least 3 ARV drugs. Patients were required to have a BMI value (mass in kg/height^2 in meters) recorded at baseline and at least one value recorded in the subsequent 18 months. HIV+ usually have 3–4 clinic visits per year and uninfected have clinic visits as warranted by their individual conditions. Patients with prevalent diabetes at baseline were excluded. We used a previously validated algorithm[7] based on diagnosis of diabetes, blood glucose levels, and prescription for oral antihyperglycemic agent or insulin; or hemoglobin A1c (A1c) ≥6.5% to identify existing diabetes. This broad definition was used to maximize sensitivity to identify those who already had diabetes. Eligible patients were required to have a recorded blood glucose level to restrict analyses to subjects with VA laboratory data. One pregnant woman was excluded.

Weight Change and BMI

The exposure of interest was weight change over a 1-year period. Weight was obtained at baseline and 1 year later. For HIV+, we used weight closest to but no more than 90 days before ART initiation and first available BMI for uninfected. We used weight closest to the target date of 1 year if a value was available within ±30 days. Otherwise we used simple linear interpolation from 2 weights within ±180 days of the 1-year date to estimate the 1-year weight. We considered weight change as a gain or loss of more than 5 pounds, believing ±5 pounds to be an appropriate threshold for exceeding random variation in weight. Patients were categorized by baseline BMI as underweight (<18.5), normal weight (18.5 to <25), overweight (25 to <30), and obese (≥30).[17]

Outcome

The primary outcome was incident diabetes. Patients were followed up to 5 years until last VA visit on or before September 30, 2012, diagnosis of diabetes, or death, whichever occurred first. We defined incident diabetes as A1c ≥6.5% in accordance with 2010 American Diabetes Association guidelines.[18] This very specific definition unifies severity of disease and date of onset. Accuracy is better than other criteria because A1c is not impacted by fasting status, has less day-to-day variability than blood glucose measurements, and only slightly attenuates the association between HIV and diabetes.[19]

Covariates

Patient characteristics and potential confounders included demographics (age, race, and sex), smoking status (current, former, and never),[20] hepatitis C infection (HCV), and calendar

year at baseline. Race/ethnicity was categorized as white, black, Hispanic, or other/unknown. Demographic data, pharmacy records, and *ICD-9* codes (from VA outpatient and inpatient visits) were from data any time before baseline. Baseline $CD4^+$ cell count per cubic millimeter and HIV-1 RNA copies per milliliter were those closest to but within 180 days before the index date.

Statistical Analyses

We summarized and compared characteristics of HIV+ and uninfected using χ^2 or Wilcoxon rank-sum tests as appropriate. We summarized weight change in the first year by HIV status, overall and stratified by baseline BMI. We then compared rates of incident diabetes associated with weight change (lost > 5, ±5 pounds, >5 to 10, >10 to 15, >15 to 20, >20 to 30, ≥30 pounds), by HIV status, stratified by baseline BMI. To account for potential confounding, we analyzed risk of incident DM as a function of weight change using multivariable Cox models. We first used 7 weight change categories (as above) to check for linearity and thresholds, stratified by HIV status. We then restricted our multivariable regression analysis to those with baseline BMI >18.5 because we found a very low rate of incident diabetes (21 events) and because weight gain is beneficial in underweight HIV+.[21–23] Formal testing for interactions (likelihood ratio test) showed significant interaction between HIV status and weight gain for risk of incident DM. To allow for directly interpretable hazard ratios (HRs) from a single model, we created 2 composite variables, one for weight change in uninfected and one for weight change in HIV+, both scaled per 5-pound change. All analyses were conducted with SAS, version 9.4; *P* values <0.05 were considered significant.

We also conducted several sensitivity analyses. We adjusted for number of blood glucose levels recorded, excluded patients with cancer diagnosis up to 12 months after baseline, HIV+ who did not achieve viral suppression (<500 copies/mL), and those with HCV. We also restricted analysis to those with any A1c before baseline and those with any A1c during follow-up. In further analyses restricted to HIV+, we adjusted for PI use, defined as receipt of at least one PI during the first year of ART because some PIs have been found to be associated with increased risk of metabolic complications including insulin resistance and incident diabetes.[15,24–26] In a separate model, we adjusted for initial regimens containing zidovudine or stavudine, as these 2 drugs have been associated with development of diabetes.[14,27]

RESULTS

Among 23,175 HIV+ entering VACS after January 1, 1999, and under follow-up for at least 1 year, we excluded 2226 who initiated ART before January 1, 2000, and 5310 who had not initiated ART by September 30, 2011. We also excluded those without documented HIV-RNA >500 copies per milliliter who were assumed to have initiated ART before entering VA care and were excluded, leaving 9423 potential patients (Fig. 1). Initial and subsequent BMI was available for 8325 (89%). Among 47,340 uninfected comparators entering the cohort after January 1, 1999, and under follow-up a year after entry, 45,429 had baseline BMI, and subsequent BMI was available for 32,706 (72%).

The prevalence of DM at baseline was 960/8325 (11.5%) among HIV+ and 7490/32,706 (22.9%) among uninfected. Within strata by HIV status, DM was more common in those with HCV infection. Prevalence of DM increased with increasing BMI across all subgroups by HIV and HCV status. Patients with existing DM were excluded from subsequent analyses.

Our final sample, after excluding 751 patients without blood glucose during follow-up, had 7177 HIV+ and 24,621 uninfected at risk of DM. The 31,798 veterans were primarily male, and approximately half were black (Table 1). Compared with uninfected patients, HIV+ were older, less likely to be overweight or obese, and more likely to be current smokers or have HCV infection. Median baseline year was 2006 for HIV+ and 2004 for uninfected individuals, and median length of follow-up was 4.9 and 5.0 years, respectively. About half of patients ended follow-up at 5 years, and 1/3 at last VA visit. HIV+ patients were less likely to develop DM and more likely to die than uninfected patients. Among HIV+, 60% initiated ART with a nonnucleoside reverse transcriptase inhibitor–based regimen, 35% with a PI-based regimen, and 5% with a triple nucleoside reverse transcriptase inhibitor regimen (Table 1). Forty percent of regimens included zidovudine or stavudine.

Weight Change in 1 Year

Weight gain exceeding 5 pounds was common (Table 2). More HIV+ gained weight (48%) than uninfected (31%) and median weight gain was greater in HIV+, 4 pounds [interquartile range (IQR), −4 to 15] compared with 1 pound (IQR, −5 to 10) in uninfected ($P < 0.001$) [among HIV+ not on ART, not included in our primary analysis, median weight gain over 12 months was 0.7 (IQR, −6.4 to 7.8) pounds]. Among HIV+, lower baseline BMI was associated with higher probability of weight gain. Two-thirds of those with baseline BMI <18.5 (underweight) gained weight in the 12 months after ART initiation, as did half of the normal weight and more than 40% of those who were overweight or obese at baseline. At every level of BMI, weight gain was more common and the amount of weight gained was greater in HIV+ compared with uninfected. Among uninfected patients, one-third gained weight across all levels of baseline BMI. Weight loss was more frequent in uninfected (24%) than HIV+ (21%; $P < 0.001$). Among patients who lost weight, 60% of HIV+ and 82% of uninfected were overweight or obese at baseline.

Rates of Incident Diabetes

During follow-up, 24% of patients developed incident DM; 357 HIV+ in 17,780 person-years (PY) (13/1000 PY) and 2656 uninfected in 126,761 PY (27/1000 PY) ($P < 0.001$). In unadjusted analyses, rates of incident DM were higher with increasing baseline BMI and with increasing weight gain (Fig. 2). Among those with baseline BMI <18.5 incidence of DM per 1000 PY was 12 and 10 for HIV+ and uninfected, respectively, 8 and 11 for BMI 18.5 to <25, 15

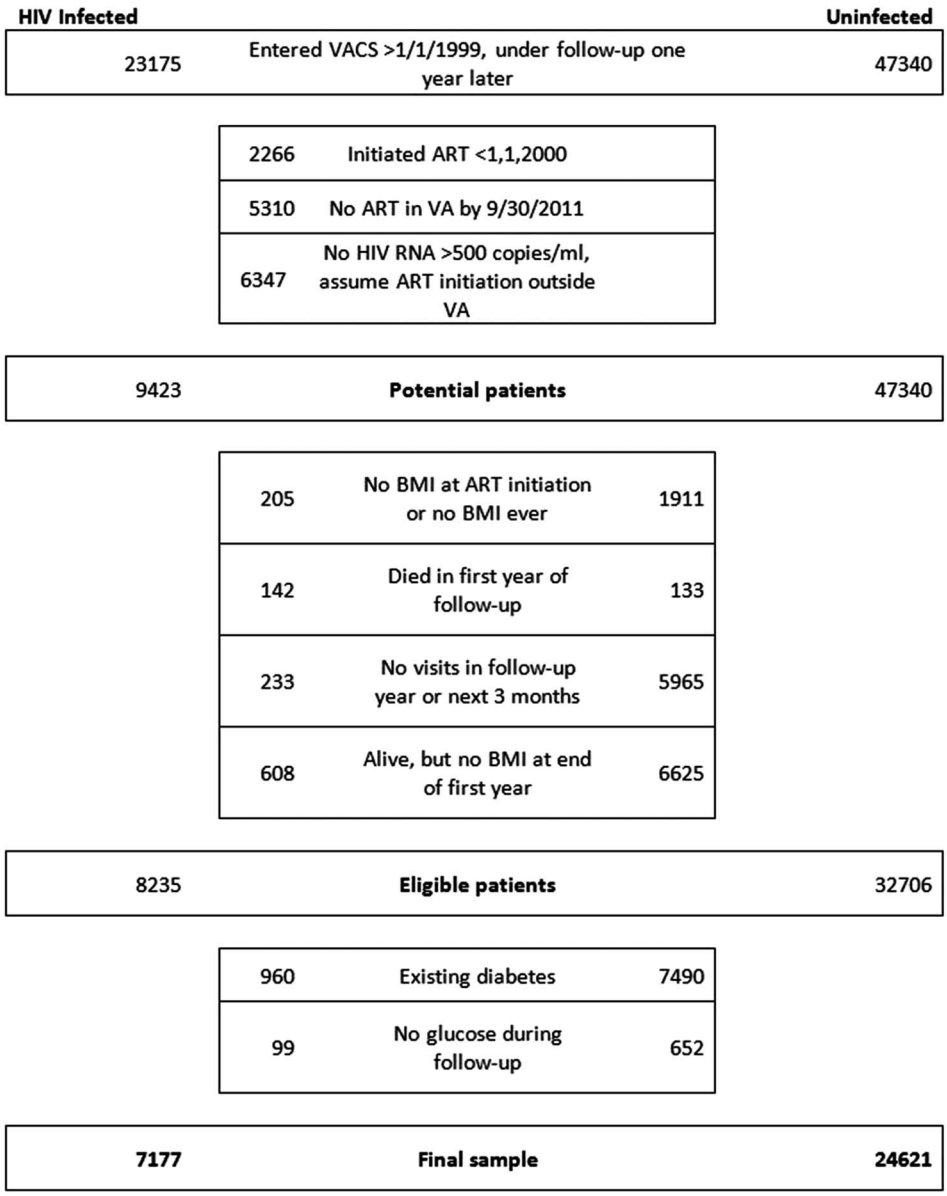


FIGURE 1. Patient flow diagram.

and 20 for BMI 25 to <30, and 26 and 44 for BMI 30 and higher.

There were only 21 incident DM events among those underweight at baseline. HIV+ had lower rates of diabetes than uninfected across all weight change strata, except those with baseline BMI 25 to <30, who gained more than 30 pounds in 1 year. An association between incident diabetes and weight gain was evident in both HIV+ and uninfected across all levels of baseline BMI. An exception to this pattern was seen in those with baseline BMI ≥30 who lost weight; incidence rates were higher than in those without weight change.

Independent Risk Factors for Incident Diabetes

In multivariable analysis restricted to those with baseline BMI >18.5, stratified by HIV status, risk of DM increased significantly with weight gain of 10 pounds or more (Fig. 3), for both HIV+ and uninfected. Models were adjusted for age, race, sex, baseline BMI, smoking, calendar year at baseline, and HCV infection. The association seemed to be linear and stronger in HIV+. Based on these results, we used weight gain as a continuous variable, restricted to those with baseline BMI ≥18 and those without weight loss. We found significantly increased risk of DM with increasing age, black or Hispanic race/ethnicity, and being overweight or obese at baseline. Smoking history and later calendar year were associated with increased risk (Table 3). HCV infection was associated with increased risk in HIV+. These findings persisted when adding a continuous BMI term to account for subtle differences by HIV status or stratifying by baseline BMI (see Supplemental Digital Content, http://links.lww.com/QAI/A832, Table 1).

TABLE 1. Baseline Characteristics of 31,798 Veterans at Risk of Incident Diabetes, 2000-2011

	HIV+	HIV−	
	N = 7177	N = 24,621	*P*
Age, yrs, median (IQR)	50 (43–56)	48 (41–54)	<0.001
Male, N (%)	6944 (96.8)	23,813 (96.7)	0.88
Race, N (%)			
White	2592 (36.1)	10,782 (43.8)	<0.001
Black	3764 (52.4)	10,692 (43.4)	
Hispanic	453 (6.3)	1544 (6.3)	
Other/unknown	368 (5.1)	1603 (6.5)	
BMI, kg/m^2, N (%)			
Underweight < 18.5	332 (4.6)	276 (1.1)	<0.001
Normal 18.5 to <25	3557 (49.6)	5378 (21.8)	
Overweight 25 to <30	2322 (32.4)	9464 (38.4)	
Obese ≥ 30	966 (13.5)	9503 (38.6)	
Median (IQR)	25 (22–28)	28 (25–32)	<0.001
Smoking, N (%)			
Never	2006 (28.0)	7534 (30.6)	<0.001
Current	4149 (57.8)	11,854 (48.1)	
Former	843 (11.7)	4456 (18.1)	
Unknown	179 (2.5)	777 (3.2)	
HCV, N (%)	2303 (32.1)	3513 (14.3)	<0.001
Start of follow-up, yr			
2000–2002	1660 (23.1)	8336 (33.9)	<0.001
2003–2005	1805 (25.1)	6610 (26.8)	
2006–2008	1778 (24.8)	5166 (21.0)	
2009–2011	1934 (26.9)	4509 (18.3)	
Median (IQR)	2006 ('03–'09)	2004 ('02–'08)	<0.001
Followed until			
5 yrs	3533 (49.2)	13731 (55.8)	
Last VA visit	2763 (38.5)	7291 (29.6)	<0.001
Incident diabetes	357 (5.0)	2656 (10.8)	
Death	524 (7.3)	943 (3.8)	
Total years, median (IQR)	4.9 (2.6–5.0)	5.0 (3.0–5.0)	<0.001
CD4, cells/mm^3, median (IQR)	218 (85–338)	NA	
HIV-1 RNA, log copies/mL, median (IQR)	4.8 (4.3–5.3)	NA	
ART regimen			
NNRTI	4321 (60.2)		
PI	2503 (34.9)		
Triple nucleoside	353 (4.9)		
AZT or D4T	2886 (40.2)		

NNRTI, nonnucleoside reverse transcriptase inhibitor.

TABLE 2. Weight Change After 1 Yr by Baseline BMI

		HIV+	HIV−
Baseline BMI	Weight Change	N (%)	N (%)
Overall		N = 7177	N = 24,621
	Lost > 5 lbs	1495 (20.8)	5824 (23.7)
	No change +5 lbs	2249 (31.3)	11,062 (44.9)
	Gained > 5 lbs	3433 (47.8)	7735 (31.4)
	Median (IQR)	4.3 (−3.5 to 14.9)	1.0 (−4.9 to 7)
Underweight < 18.5		N = 332	N = 276
	Lost > 5 lbs	25 (7.5)	31 (11.2)
	No change +5 lbs	83 (25.0)	154 (55.8)
	Gained > 5 lbs	224 (67.5)	91 (33.0)
	Median (IQR)	13 (2.8 to 26.3)	2.0 (−2.9 to 7.6)
Normal 18.5 to <25		N = 3557	N = 5378
	Lost > 5 lbs	575 (16.2)	1024 (19.0)
	No change +5 lbs	1160 (32.6)	2576 (47.9)
	Gained > 5 lbs	1822 (51.2)	1778 (33.1)
	Median (IQR)	5.6 (−1.7 to 16.1)	1.7 (−3.5 to 7.3)
Overweight 25 to <30		N = 2322	N = 9464
	Lost > 5 lbs	599 (25.8)	2017 (21.3)
	No change +5 lbs	731 (31.5)	4554 (48.1)
	Gained > 5 lbs	992 (42.7)	2893 (30.6)
	Median (IQR)	3.0 (−5.4 to 12)	1.0 (−4.1 to 7)
Obese ≥ 30		N = 966	N = 9503
	Lost > 5 lbs	296 (30.6)	2752 (29.0)
	No change +5 lbs	275 (28.5)	3778 (39.8)
	Gained > 5 lbs	395 (40.9)	2973 (31.3)
	Median (IQR)	1.7 (−7 to 11.2)	1.0 (−4.1 to 7)

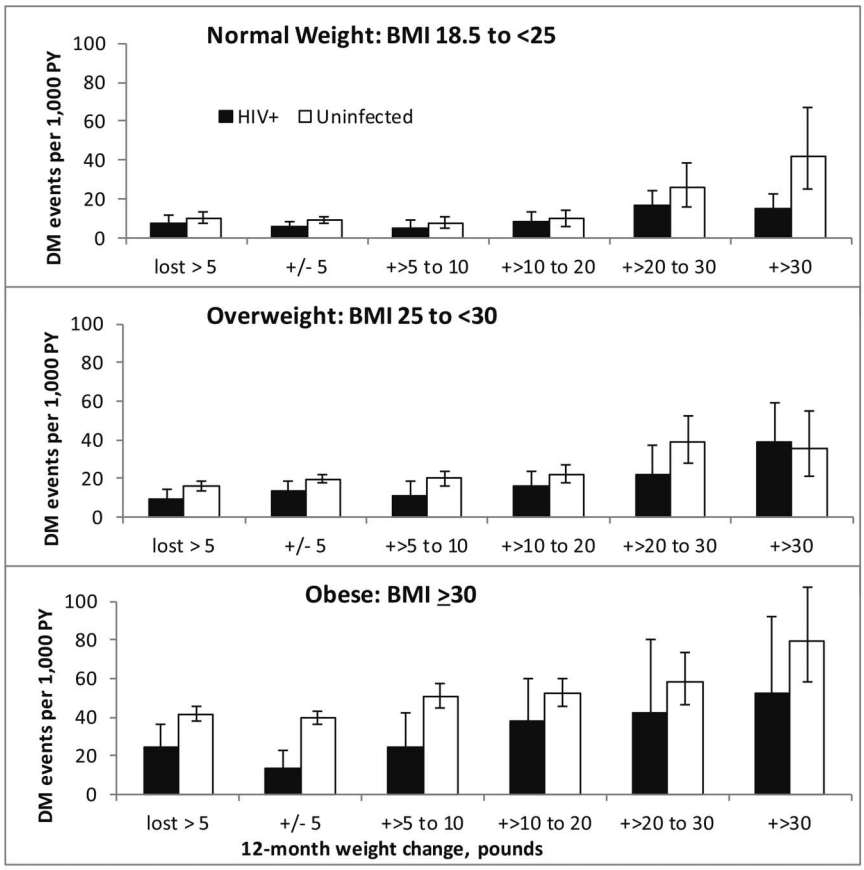
In a final combined model, formal tests of interaction were significant for HIV and weight gain, but not for HIV and smoking, calendar year, or HCV infection. After adjusting for age, race, baseline BMI, smoking history, and calendar year at baseline (Table 3), HCV infection was associated with higher risk of incident DM compared with uninfected individuals [HR, 1.09; 95% confidence interval (CI): 1.00 to 1.18] and HIV infection was associated with lower risk (HR, 0.56; 95% CI: 0.47 to 0.66) However, risk of DM associated with weight gain was greater among HIV+ individuals. Each 5-pound increment was associated with 14% increased risk of incident DM in HIV+ and 8% increased risk in uninfected [HR = 1.14 (95% CI: 1.10 to 1.17) vs. 1.08 (95% CI: 1.07 to 1.10), *P* for interaction <0.01].

Sensitivity Analyses

We performed several sensitivity analyses (data not otherwise shown). The associations with weight gain and incident DM were similar when we adjusted for number of blood glucose levels recorded; excluded those with cancer, those with HIV+ not achieving viral suppression, and those with HCV. When we restricted to those with A1c measured before baseline, the number of events declined to 390, but the association with weight gain remained significant and differential. There was some suggestion of increased DM risk with PI use [HR = 1.14 (95% CI: 0.90 to 1.45)] and zidovidine or stavudine containing regimens [HR = 1.30 (95% CI: 0.92 to 1.82)], but these did not reach statistical significance.

DISCUSSION

In VACS, HIV+ had lower prevalence and incidence of DM compared with uninfected individuals. Incidence among HIV+ remained lower compared with uninfected after adjustment for established risk factors including age and BMI. However, incident DM increased substantially with



Baseline BMI	HIV		Lost >5	No change +/- 5	Gained >5 to 10	Gained >10 to 20	Gained >20 to 30	Gained >30
<18.5	+	DM	2	3	1	4	3	2
		N	25	83	32	74	49	69
	-	DM	2	5	1	1	1	1
		N	31	154	40	27	10	14
18.5 to <25	+	DM	16	26	10	23	23	21
		N	575	1160	494	634	342	352
	-	DM	42	102	27	25	23	18
		N	1024	2576	847	600	219	112
25 to <30	+	DM	22	38	13	22	14	22
		N	599	731	313	358	159	162
	-	DM	130	374	116	98	42	20
		N	130	374	116	98	42	20
≥30	+	DM	26	14	12	19	9	12
		N	296	275	130	141	60	64
	-	DM	436	585	269	219	75	44
		N	2752	3778	1370	1106	339	158

FIGURE 2. Rate of incident DM during median follow-up of 5.0 years, by baseline BMI, according to amount of weight gained in 12 months, in HIV+ and uninfected veterans, 2000–2011 (BMI <18.5 not shown due to sparse data).

weight gain of 10 or more pounds in both groups and this increased risk was greater for HIV+ compared with uninfected. For every 5 pounds of weight gained, HIV+ showed greater risk of DM compared with demographically similar uninfected individuals.

Other investigators have reported the association of HIV status and/or baseline BMI with incidence of DM.[7,28–32] Previous work from VACS has documented that HIV+ individuals are at increased risk of weight gain in the first year after initiation of ART compared with demographically matched uninfected comparators and that weight gain after ART confers no survival advantage among overweight or obese individuals.[2] The current study extends these observations to show that weight gain after ART is associated with excess risk of DM compared with weight gain among uninfected individuals.[33]

Weight gain after ART initiation is likely a double-edged sword with respect to inflammation. On one hand, successful suppression of HIV-1 RNA with ART is logically accompanied by a rapid decrease in the metabolic demand associated with HIV infection.[34] If established eating habits remain unchanged, decreased metabolic demand inevitably results in increased weight. Thus, all else equal, weight gain after ART may indicate a strong response to treatment and a decreased inflammatory burden. Evidence supporting this

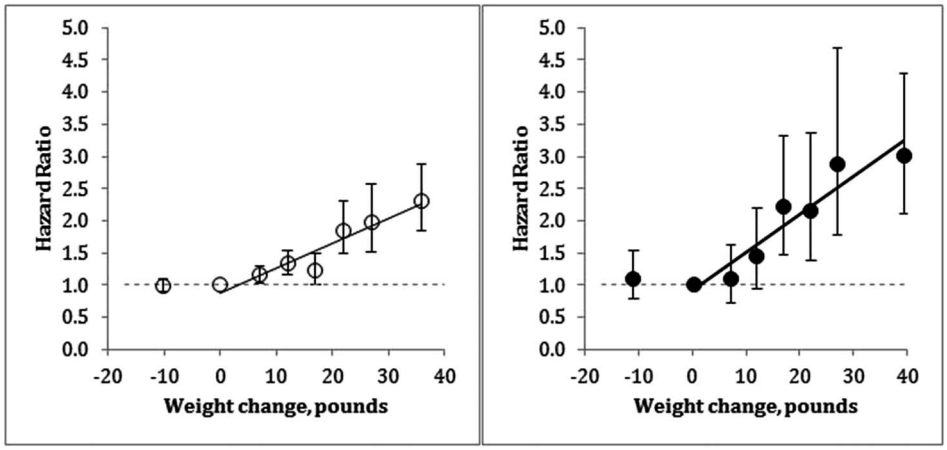


FIGURE 3. Relative risk of diabetes in HIV+ (N = 6845) and uninfected (N = 24,345) veterans, by weight change in a 1-year interval compared with those without weight change, adjusted for age, race, sex, baseline BMI, smoking, HCV infection, and calendar year at baseline (excludes those with baseline BMI <18.5 kg/m^2). Black circles, HIV+; white circles, uninfected.

assumption includes the observation that weight gain after ART is highly correlated with HIV-1 RNA suppression and CD4 count recovery, independent of weight status at ART initiation.[2,13] Consistent with this hypothesis, median weight gain over 12 months among HIV+ not on ART was much less (0.7; IQR, −6.4 to 7.8 pounds—data not otherwise shown). However, among middle-aged and older uninfected individuals, weight gain contributes to inflammatory burden and risk of incident DM.[35,36] Because chronic inflammation may be more pronounced among HIV+ than uninfected individuals even after ART,[37] excess risk of diabetes associated with weight gain among HIV+ supports the contention that DM is a disease of inflammation.[35,36]

An alternative explanation for our findings is the possibility that ART, rather than HIV itself, interacts with risk of incident DM associated with weight gain. No consistent picture has emerged for a drug class effect.[7,14,38–40] Potential drug interactions, lengths of exposure, and likely weight change confound the ability to isolate individual drug effects. Our study, which was focused on comparing risk of diabetes by HIV status, is not well suited to characterizing treatment effects. Future work is needed to explore this question.

Our findings concerning DM prevalence and incidence among HIV+ are consistent with previous studies. Incidence rates of diabetes among HIV+ in our study, 13 per 1000 PY in HIV+, are higher than those reported by D:A:D (2.9/1000 PY)[28] but similar to rates reported by the French Hospital Database on HIV (11.7/1000 PY).[32] The Multicenter AIDS Cohort Study reported even higher rates (47/1000 PY).[39] These differences are likely explained by differences in age and the proportion of

TABLE 3. Multivariable Cox Model for Risk of Incident DM in 5375 HIV+ Veterans and 18,552 Uninfected Veterans, Based on 2315 Events (278 HIV+, 2037 Uninfected) During a Median of 5.0 Years of Follow-up (Excludes Those With Baseline BMI <18.5 and Those Who Lost Weight During Follow-up)

	HIV+			Uninfected			Overall		
Predictor Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, per 5 yrs	1.16	1.09 to 1.23	<0.001	1.16	1.13 to 1.19	<0.001	1.16	1.14 to 1.18	<0.001
Race									
White	Ref			Ref			Ref		
Black	1.69	1.30 to 2.20	<0.001	1.56	1.42 to 1.72	<0.001	1.57	1.44 to 1.72	<0.001
Hispanic	1.67	1.03 to 2.71	0.04	1.86	1.58 to 2.19	<0.001	1.84	1.57 to 2.14	<0.001
Baseline BMI, kg/m^2									
Normal, 18.5–24.9	Ref			Ref			Ref		
Overweight, 25–29.9	2.11	1.61 to 2.77	<0.001	2.08	1.77 to 2.45	<0.001	2.05	1.79 to 2.35	<0.001
Obese > 30	3.40	2.48 to 4.65	<0.001	4.57	3.92 to 5.32	<0.001	4.39	3.85 to 5.01	<0.001
Smoking									
Ever vs. never	0.99	0.76 to 1.28	0.930	1.14	1.04 to 1.26	0.006	1.12	1.03 to 1.23	0.011
Calendar yr	1.02	0.98 to 1.06	0.33	1.03	1.02 to 1.05	<0.001	1.03	1.02 to 1.04	<0.001
HCV infected vs. not	1.33	1.04 to 1.71	0.02	1.04	0.91 to 1.18	0.61	1.09	0.97 to 1.22	0.13
HIV infected vs. not							0.56	0.47 to 0.66	<0.001
Weight gain, per 5 pounds									
HIV+	1.13	1.10 to 1.17	<0.001				1.14	1.10 to 1.17	<0.001
Uninfected				1.08	1.07 to 1.10	<0.001	1.08	1.07 to 1.10	<0.001

Interaction of weight change and HIV $P < 0.01$.

overweight and obese individuals in the sample. VACS had a median age at the time of this analysis of 50 years compared with a mean age of 36 years in D:A:D. Our HIV+ patients were more likely to overweight or obese (45.9%) vs. D:A:D (29.2%). Median baseline BMI was 24 (IQR, 21–26) in VACS, slightly lower than MACS (26; IQR, 24–28).[38] Previous studies have also found that HIV+ status is associated with reduced risk of DM after adjustment for established risk factors.[7,40–42]

Our analysis has important strengths. We included uninfected, demographically matched, and behaviorally similar comparators, without which we could not have determined how DM risk differs by HIV status. Additionally, risk of DM is strongly associated with advanced age. The age of our cohort more accurately estimated risk of DM in the modern era in which half those living with HIV in the United States are 50 years of age or older. Finally, after excluding prevalent cases, we used a standard biomarker for incident DM thereby eliminating possible bias introduced if general medical providers' assignment of *ICD-9* diagnostic codes differed from infectious disease providers.

Our study has limitations. Most importantly, our focus was on comparing effects of weight gain after ART among HIV-infected individuals with effects of weight gain more generally among uninfected individuals. As a result, our analyses are not well suited to determining the role of particular ART regimens in incident DM and cannot differentiate whether the differences in risk of DM associated with weight gain are due to HIV itself or to ART. It is not a simple matter to tease effects of chronic HIV from those of chronic ART exposure. Those initiating ART with a PI-based regimen differ in important ways from those who received a nonnucleoside reverse transcriptase inhibitor–based regimen. In our study, they were more likely to be HCV coinfected (33% vs. 28%), to have initiated ART in earlier years, and to be exposed to zidovudine, stavudine, or didanosine (data not otherwise shown). A careful analysis of the role of ART regimen in risk of diabetes incidence would require time updated data on ART exposure and time updated adjustment to account for confounding. Such an analysis is beyond the scope of this article.

Other limitations include that our cohort is primarily male and gender differences may be important to consider when evaluating risk of DM associated with weight change.[1,38,43] We also focused on weight change during the first 12 months of ART because that is the period in which the maximum immunologic and virologic response to ART occurs.[44] It would be interesting to see whether risk for DM remains differential by HIV status for weight gained after this 12-month window. Additionally, we did not have information on diet and exercise for this sample. A subset of our cohort was surveyed about exercise habits and, in this restricted sample, HIV+ were equally likely to exercise as uninfected individuals. While we have no data on diet, we have no reason to think that HIV+ have a worse diet than uninfected veterans. Finally, patients receiving more frequent healthcare screening may be more likely to be diagnosed with DM. HIV+ individuals received fewer A1c tests than uninfected in VACS and in sensitivity analyses, adjusted for number of glucose measurements, results were similar to our main analysis.

Whether due to increased levels of inflammation, adverse effects of ARVs, or some as yet unappreciated cause, for those aging with HIV, weight gain is associated with an even greater risk of DM than among uninfected individuals. Because it is easier to avoid weight gain than to lose weight once gained, ART initiation provides an important opportunity for clinicians to counsel patients. In conjunction with previous work, this study supports recommendations for HIV + patients initiating ART, namely (1) patients initiating ART typically gain weight in the first year beyond that observed among uninfected individuals; (2) this weight gain is associated with excess risk of diabetes compared with uninfected individuals; and (3) although gaining 10–20 pounds is associated with a survival advantage among those not overweight, there is no advantage to weight gain among overweight or obese individuals at ART initiation. To minimize DM risk after ART initiation, normal weight patients should avoid gaining more than 10 pounds; overweight or obese patients should avoid weight gain altogether.

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