

Changes in weight and weight distribution across the lifespan among HIV-infected and -uninfected men and women

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Abstract

Examine body composition changes across the lifespan of HIV-infected compared to uninfected adults. Longitudinal study of antiretroviral therapy (ART)-treated HIV-infected and uninfected participants from the Multicenter AIDS Cohort Study and Women's Interagency HIV Study. Body mass index (BMI), waist (WC), hip circumference (HC), and waist-to-height ratio (WHtR) measured at semiannual visits from 1999 to 2014. The age effect on outcomes over time was investigated using multivariate, piecewise, linear mixed-effect regression models adjusted for demographics, substance use, and comorbidities. Person-visits from 2363 men (1059

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HIV-infected/1304 HIV-uninfected) and 2200 women (1455 HIV-infected/745 HIV-uninfected), median ages 45 [IQR 39,51] and 40 [32,46], respectively, were included. BMI gains were slower among HIV-infected participants of 40 years or less ($P < 0.001$), similar between HIV-infected and uninfected persons 40 to 60 years of age, and plateaued after age 60 in both groups. WC and waist-to-height ratio (WHtR) increased across the age spectrum ($P < 0.001$) regardless of HIV serostatus, with significantly greater gains in HIV-infected men more than 60. Black race and Hispanic ethnicity were associated with greater BMI and WC. Lower BMI, WC, hip circumference, and WHtR were associated with hepatitis C infection among women only, and with substance use among all participants, and with lower CD4⁺ cell count and shorter ART duration among HIV-infected participants. Slower BMI gain among younger HIV-infected adults may be partly explained by substance use and hepatitis C infection, and suggests that lower BMI does not represent improved health. Further analysis of muscle and fat abundance and quality will advance understanding of metabolic risk over the lifespan, a key to reducing morbidity in an aging population.

Abbreviations: 3TC = lamivudine, AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, BMI = body mass index, CES-D = Center for Epidemiologic Studies Depression Scale, D4T = stavudine, FRAM Study; The Study of Fat Redistribution and Metabolic Change in HIV Infection, FTC = emtricitabine, HAART = highly active antiretroviral therapy, HC = hip circumference, HIV = human immunodeficiency virus, IQR = interquartile ratio, MACS = Multicenter AIDS Cohort Study, WC = waist circumference, WHtR = weight-to-height ratio, WIHS = Women's Interagency HIV Study, ZDV = zidovudine.

Keywords: body composition, body mass index, HIV, HIV wasting syndrome, obesity, waist circumference, weight-to-height ratio

1. Introduction

Over the past 3 decades, the association of HIV infection with body composition has evolved from the initial manifestations of severe muscle wasting in the preantiretroviral therapy (ART) era, to lipodystrophy which was most prominent after the advent of highly active ART (HAART). Today, lipodystrophy is observed primarily among adults who have aged with HIV and were treated with older ART regimens, but it continues to occur even with contemporary ART regimens.^[1] Longitudinal studies from the Fat Redistribution and Metabolic Changes in HIV (FRAM) Study, the Multicenter AIDS Cohort (MACS), and the Women's Interagency HIV Study (WIHS) have described some of these changes.^[2-4] In FRAM, HIV-infected men and women had persistently lower subcutaneous adipose tissue over 5 years of follow-up compared to HIV-uninfected participants.^[2] In the MACS and WIHS, a more rapid increase in the waist circumference (WC) or waist-to-hip ratio (WHR), but overall lower body mass index (BMI), were seen among HIV-infected men and women compared to uninfected but at-risk men and women from 1999 to 2004^[3,4]; these findings likely reflected lipoatrophy (loss of subcutaneous fat) overlying the pelvic girdle rather than increased abdominal adiposity (lipohypertrophy).

The term "return to health" weight gain was initially used to describe weight increases among profoundly immunocompromised individuals initiating ART following a period of weight loss. Weight gain with ART initiation continues to occur in the current ART era, however, despite relatively normal immune function and minimal pre-ART weight loss. A recent analysis in the Swiss HIV Cohort Study observed the most pronounced increase in weight during the first year after ART initiation, with an increase in the proportion of overweight or obese participants from 13% in 1990 to 38% in 2012.^[5] In the WIHS cohort, 40% of normal weight women became overweight and 47% of overweight women became obese following ART initiation.^[6] Cross-sectional studies of HIV-infected individuals have found rates of overweight or obesity as high as 65%.^[7-10] Thus, generalized obesity among HIV-infected persons may mirror the general population, where nearly 35% of U.S adults are obese.^[11] In the Military Natural History Study 60% of HIV-infected men and women gained weight over an average follow-up period of 6.2 years beginning in 1985, although less than 20% had an undetectable HIV-1 viral load.^[7] In a south Texas cohort

evaluated between 2007 and 2010, a quarter of HIV-infected persons (80% ART treated) were followed for a median of 3.25 years and had gains in BMI of over 3% per year.^[12] The clinical significance of these weight changes was recently demonstrated in the Veterans Aging Cohort, where weight gain among underweight or normal-weight patients initiating ART had a beneficial effect on mortality, while no mortality benefit was seen with weight gain among overweight or obese individuals.^[13] Furthermore, the impact of regional weight gain is less clear, as few studies have reported longitudinal imaging analyses. No prior studies have explored how these changes may vary by age.

The objectives of the present study were to describe the changes in BMI, WC, hip circumference (HC), and waist-to-height ratio (WHtR) that occur across the adult lifespan (from ages 18 to 75 years) of HIV-infected men and women on HAART; compare these changes to those in similar people without HIV infection; and determine factors associated with BMI, WC, HC, and WHtR trajectories. Identification of populations at high risk for gain or loss in these variables may guide age- and gender-specific obesity prevention programs and identify potential mechanisms for the body composition changes with aging.

2. Methods

2.1. Study population

The MACS and the WIHS are ongoing, multicenter, prospective cohort studies of the natural and treated histories of men and women, respectively, with or at risk for HIV infection in the United States. The MACS began in 1984, and has enrolled 7343 men from sites in Baltimore, MD/ Washington DC; Chicago, IL; Pittsburgh, PA; and Los Angeles, CA. The WIHS has enrolled 4,856 women since 1994, from sites in Atlanta, GA; Birmingham, AL; Bronx/Manhattan and Brooklyn, NY; Chapel Hill, NC; Chicago, IL; Jackson, MS; Los Angeles and San Francisco, CA; Miami, FL; and Washington, DC. Study design and participant characteristics of both studies have been described.^[14-16] Each semiannual MACS and WIHS visit includes a physical examination, collection of blood for laboratory studies including CD4⁺ T cell count and plasma HIV-1 RNA determination, and completion of questionnaires that provide data on demographics, health status, and use of antiretroviral medications. Measurements of WC and HC were added to semi-annual visits beginning

Table 1**Baseline characteristics of study participants.**

Characteristics	HIV- men (N=1304)	HIV+ men (N=1059)	HIV- women (N=745)	HIV+ women (N=1455)
Age, y (mean, SD)	45.6 (10.6)	44.1 (8.5)*	35.9 (9.9)	41 (8.6)*
Age, %, ≤40 years	362 (27.8)	352 (33.2)	520 (69.8)	748 (51.4)
40–60 years	849 (65.1)	675 (63.7)	222 (29.8)	690 (47.4)
>60 years	93 (7.1)	32 (3.0)	3 (0.4)	17 (1.2)
BMI (mean, SD)	26.7 (4.8)	25.3 (4)*	30 (8.2)	28.8 (7.2)*
Waist circumference, cm (mean, SD)	94.7 (13.3)	90.5 (10.9)*	92.3 (17.6)	92.3 (15.3)*
Hip circumference, cm (mean, SD)	100.9 (9.8)	95.8 (7.8)*	106.3 (15.5)	102.8 (14.6)*
Race (%), White	70.3	59.2*	10.3	13.1*
Black	20.3	25.5	60.7	55.9
Hispanic	8.1	13.5	24.6	27.9
Other	1.3	1.8	4.4	3.1
Number of drinks/week, %, 0	15.9	19.1*	43.1	57.5
1–3	42	52.1	43.5	36.2
4–13	34	24	3.8	2.9
≥14	8.1	4.8	9.7	3.4
Smoking, %, never smoker	31.3	28*	29.1	34.4
Former smoker	39.5	37.2	16.2	23.8
Current smoker	29.2	34.8	54.6	41.8
Marijuana use, %	30.7	36.4*	32.5	15.9*
Stimulant use, %	13	18.3*	22.3	7.4*
Hepatitis C virus infection, %	4.7	9.8*	11.9	19*
Hepatitis B virus infection, %	1.8	5.3*	0.4	2.1*
Depression, %	24.8	26.6*	37.7	37.3
Current CD4+ T-cell count <200 cells/μL, %	–	7.6	–	10.7
200–499 cells/μL	–	44.6	–	47.8
≥ 500 cells/μL	–	47.7	–	41.5
Lowest prior CD4+ T-cell count <200 cells/μL, %	–	35.5	–	36.8
200–499 cells/μL	–	52.8	–	46.1
≥ 500 cells/μL	–	11.6	–	17
Clinical AIDS, %	–	11.8	–	33.8
Years from ART initiation, %, <5	–	78.3	–	69.7
5–10	–	18.5	–	26
>10	–	3.2	–	4.4

* P value for the difference between HIV-infected and -uninfected less than 0.001.

BMI=body mass index, SD=standard deviation, HIV=human immunodeficiency virus.

in 1999. The institutional review boards at each site approved study protocols and forms, and each participant provided written informed consent.

The current analysis included participants who were between ages 18 and 75 years, were receiving at least 2 ART agents with an HIV-1 RNA less than 400 copies/mL at baseline (for HIV-infected participants), and had at least 3 measurements of BMI, WC, and HC. Person-visits were excluded if BMI, WC, and HC were not measured, covariates of interest (alcohol use, smoking, marijuana and stimulant use, hepatitis B virus infection, hepatitis C virus infection, and depression) were not measured, or if the age of the participant at the visit was more than 75 years (see Supplementary material for a flow chart of participant selection, <http://links.lww.com/MD/B398>).

2.2. Outcomes: BMI, WC, HC, WHtR

At each visit, BMI was determined by dividing the body weight (kilograms) by height (meters) squared, and categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥ 30 kg/m²). WC and HC measurements from both cohorts were obtained in the standing position, using standardized procedures.^[17] WHtR was calculated by dividing the WC by the height. All examiners underwent a standardized training.

2.3. Exposure: HIV status

All HIV-uninfected men and women were assessed for HIV positivity by ELISA. Positive results were confirmed by Western blot. Persons who seroconverted were included in the appropriate group because of and following seroconversion.

2.4. Covariates

Age was measured via self-reported date of birth and categorized into decades of age. Cigarette exposure was categorized as never, former, or current smoker; alcohol use was categorized as none, mild (1–3 drinks/week), moderate (4–13 drinks/week), or heavy (14 or more drinks/week). Education was categorized as ≤ high school, any college, or graduate school. Marijuana and stimulant (including cocaine or methamphetamine) use were dichotomized as any or no use within the prior 6 months. Hepatitis C infection was defined as a detectable hepatitis C RNA in serum, and hepatitis B virus infection as a positive hepatitis B virus surface antigen. Depressive symptoms were defined by a score of 16 or greater using the Center for Epidemiological Studies-Depression (CES-D) questionnaire.^[18] Entry into the MACS or WIHS was dichotomized as before or after 2001. History of an acquired immunodeficiency syndrome (AIDS)-defining illness was measured according to the Centers for Disease Control and Prevention definition^[19]; AIDS defined by a nadir CD4⁺ T-cell

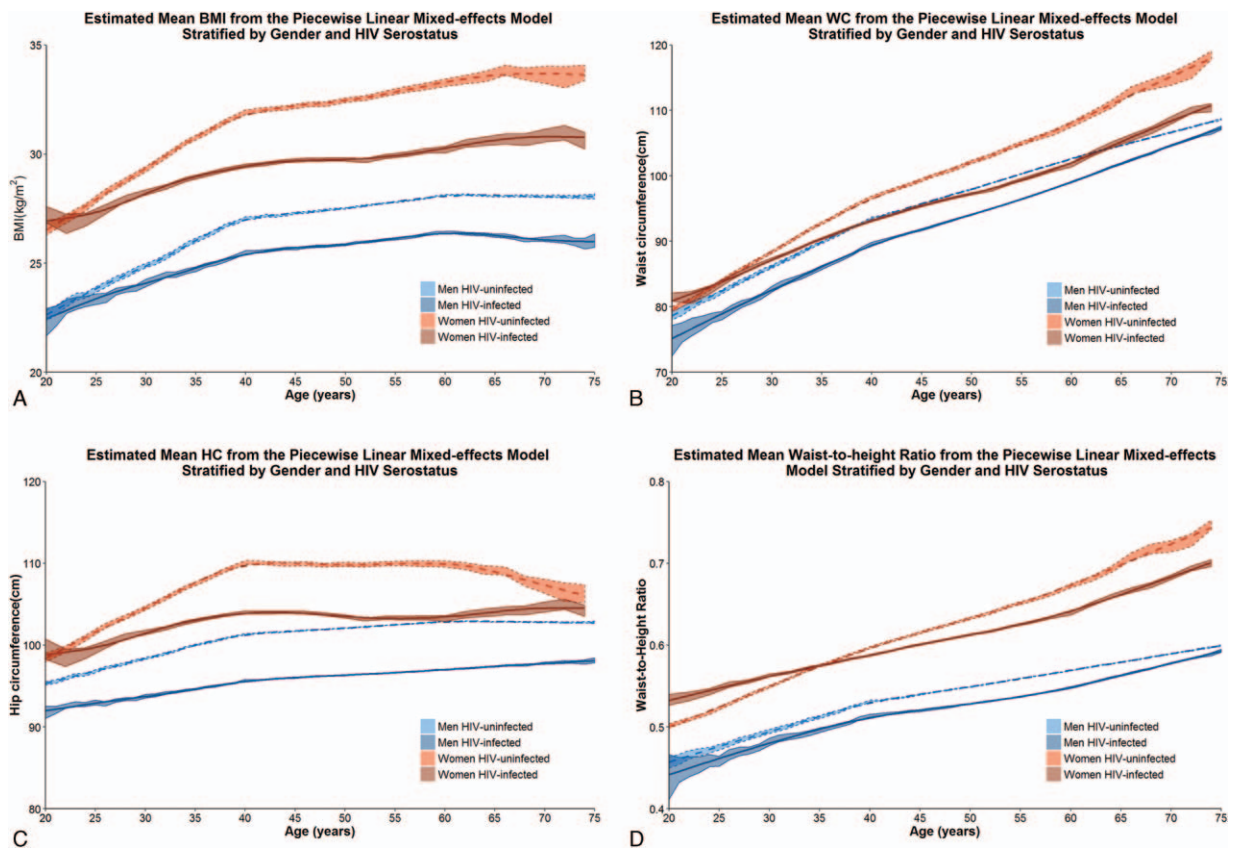


Figure 1. Mean body mass index (1A), waist circumference (1B), hip circumference (1C), and WHtR by age, estimated using multivariate piecewise linear mixed-effect regression models, and adjusted for age at visit, HIV infection on effective antiretroviral therapy, the interaction between age at visit and HIV infection on effective antiretroviral therapy, race, cigarette exposure, alcohol use, marijuana and stimulant use, hepatitis C and B viral infection, and depression. WHtR = waist-to-height ratio.

count less than 200 cells/ μ L was included as a separate variable. The definition of HAART was guided by the Department of Health and Human Services/Kaiser Panel guidelines.^[20] Years from ART initiation was categorized as less than 5, 5 to 10, or more than 10 years.

2.5. Statistical analysis

To assess changes in body composition over time, multivariate, piecewise, linear mixed-effect regression models were implemented by employing the SAS PROC Mixed procedure (SAS Institute, Cary, NC). Separate models were constructed for each outcome (BMI, WC, HC, and WHtR). Our *a priori* hypothesis was that age modified the effect of treated HIV infection on our outcomes of interest. Covariates were selected based on statistically significant univariate associations with HIV status ($P < 0.10$) and literature review to identify potential confounders. The following covariates were included in the models: age at visit (as the time scale), HIV serostatus, an interaction term for age and HIV serostatus, race, cigarette exposure, alcohol use, marijuana and stimulant use, hepatitis B or hepatitis C infection, and depression. Additional variables were tested but not included in multivariate analyses as all P values were more than 0.10 in univariate analyses: enrollment into the MACS/WIHS before or after 2001; education; physical activity; cumulative use of zidovudine (ZDV), stavudine (D4T), lamivudine (3TC), or emtricitabine (FTC); nadir CD4⁺ T-cell count while under observation; and history of an AIDS-defining illness. Because the

trajectories of outcomes across time were nonlinear, a spline term for age with knots at 40 and 60 years of age was used to allow for different outcomes over time in different age ranges. Different effects of baseline age and HIV serostatus on trajectories of outcomes were explored by using interactions. For HIV-infected participants, a separate model was built including HIV-related variables, CD4⁺ T cell count, and years from ART initiation.

These models were constructed to fit the data with random intercept allowing for individual differences at baseline visit, and random slope, reflecting individual rate of change over time (by age). Parameters including unstructured covariance of random coefficient and constant error variances, and the restricted maximum likelihood method were applied to estimate regression coefficients. The models accounted for correlation among repeated measurements from the same participants. These models provided estimates of the average rate of change of each outcome over time. $P < 0.05$ was considered as statistical significance for all of analyses. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 2363 men (1059 HIV-infected contributing 13,965 person visits, and 1304 HIV-uninfected contributing 20,652 visits) and 2200 women (1455 HIV-infected contributing 16,472 person-visits, and 745 HIV-uninfected contributing 11,763 person-visits) were included in the analyses; participant characteristics from the first available visit are detailed in Table 1.

Table 2
Effects on BMI by piecewise linear mixed-effects models, stratified by sex and HIV serostatus.

	All men Estimate [†]	All women Estimate [†]	HIV-infected men only Estimate [†]	HIV-infected women only Estimate [†]
A. HIV serostatus and age effects on BMI trajectories (kg/m ² change per year of age)				
HIV-uninfected, ≤40 years	0.21**	0.27**		
HIV-infected, ≤40 years	0.15**	0.15**	0.11**	0.18**
HIV-uninfected, age 40–60 years	0.07**	0.08**		
HIV-infected, age 40–60 years	0.05**	0.06**	0.03*	0.03*
HIV-uninfected, age >60 years	−0.01	−0.01		
HIV-infected, age >60 years	−0.03	0.00	−0.04*	−0.11**
B. Effects of HIV and other covariates on average BMI ^{††} stratified by sex and HIV serostatus				
Average BMI ^{††}	28.35**	32.87**	26.67**	30.16**
HIV infection	−2.05**	−3.61**		
Hispanic (vs non-Hispanic)	0.97*	1.83*	0.90*	1.63*
Black (vs Caucasian)	1.37**	2.92**	1.10**	3.22**
Other race (vs Caucasian)	0.49	2.54*	0.15	1.52
1–3 alcohol drinks/week (vs none)	−0.11**	−0.19**	−0.13*	−0.17*
4–13 alcohol drinks/week (vs none)	−0.02	−0.28**	−0.06	−0.20
>13 alcohol drinks/week (vs none)	0.13*	−0.22*	−0.03	−0.35*
Former smoker (vs never smoker)	0.12	−0.13	−0.02	−0.21
Current smokers (vs never smoker)	−0.34**	−0.80**	−0.43*	−1.08**
Marijuana use (vs none)	−0.16**	−0.56**	−0.16**	−0.70**
Stimulant use	−0.23**	−1.25**	−0.25**	−1.03**
Hepatitis C virus infection	−0.12	−1.78*	−0.29	−2.65**
Hepatitis B virus infection	−0.05	1.39	−0.54*	1.52
Depressive symptoms	−0.08**	−0.24**	−0.10**	−0.15*
CD4 T-cell count <200 cells/μL			−0.51**	−1.31**
CD4 T-cell count 200–499 cells/μL			−0.23**	−0.56**
Highly active ART for < 5 years			−0.24**	−0.20
Highly active ART for 5–10 years			−0.15**	−0.32**

* $P < 0.05$.

** $P < 0.001$.

† Estimate interpreted as the change in the slope (kg/m² per year of age) for part A, and the effect on the average BMI at age 44 for part B.

†† Average BMI is at age 44 (mean age of the entire sample).

ART = antiretroviral therapy, BMI = body mass index, HIV = human immunodeficiency virus.

Briefly, HIV-infected men were younger and black, smoked cigarettes and used marijuana or stimulants, and had hepatitis B or C infection compared to HIV-uninfected men. In contrast, HIV-infected women were older, white, and/or Hispanic, less likely to smoke or consume alcohol, marijuana, or stimulants, but more had hepatitis B or C infection than HIV-uninfected women.

3.1. BMI, WC, HC, and WHtR Trajectories

As shown in Fig. 1A, BMI increased significantly ($P < 0.001$) among both HIV-infected and HIV-uninfected men and women until 60 years of age, and then stabilized after age 60. Compared to HIV-uninfected men, HIV-infected men gained BMI significantly more slowly before age 40 (0.15 kg/m²/year in HIV-infected vs 0.21 kg/m²/year in HIV-uninfected; $P < 0.001$); yearly changes in BMI did not differ by HIV status after age 40 (Table 2A). Similar changes were seen among the women: BMI change differed by HIV serostatus only among those less than 40 years during which time HIV-uninfected women experienced nearly double the rate of BMI increase of HIV-infected women (0.15 kg/m²/year in HIV-infected vs 0.27 kg/m²/year in HIV-uninfected; < 0.001). Similar changes by age were seen in models restricted to HIV-infected participants with further adjustment for HIV-specific variables (Table 2A) except that the decrease in BMI trajectory among women more than 60 years strengthened (from 0 to −0.11 kg/m²/year) and was statistically significant (P value < 0.001 ; Table 2A).

WC (Fig. 1B; Table 3A) increased among both men and women across each age category regardless of HIV serostatus ($P < 0.001$). The increases in WC were similar between HIV-infected and -uninfected men until age 60; thereafter, HIV-infected men increased more rapidly (0.56 cm/y) compared to HIV-uninfected men (0.39 cm/y; $P = 0.021$). In contrast, the HIV-uninfected women of 40 years or less experienced a significantly greater gain in WC (0.86 cm/y) compared to HIV-infected women (0.64 cm/y; $P = 0.002$); no significant differences by HIV serostatus were seen in other age groups ($P \geq 0.57$). Similar changes were observed in analyses restricted to HIV-infected men and HIV-infected women.

Small but significant increases in HC (Fig. 1C, Table 4A) were seen among men until age 60; these changes did not differ by HIV serostatus ($P = 0.09$ for age ≤ 40 , $P = 0.38$ for age 40–60, and $P = 0.12$ for age > 60). Women also had significant increases in HC until age 40, which were significantly greater among HIV-uninfected (0.57 cm/y) versus HIV-infected women (0.27 cm/y; $P < 0.001$). In models restricted to HIV-infected participants, similar changes in HC occurred among men; HC increased significantly in women up to age 40, and then decreased significantly after age 40 ($P < 0.001$; Table 4A).

Change in WHtR were similar to the WC (Fig. 1D; Table 5A), and increased among both men and women across each age category regardless of HIV serostatus (all $P < 0.001$). Changes between HIV-infected and uninfected men were similar until age 60, when HIV-infected men experienced greater increases in WHtR (0.003/y vs 0.002/y, $P = 0.020$). In contrast, HIV-infected women experienced

Table 3

Effects on WC by piecewise linear mixed-effects models, stratified by sex and HIV serostatus.

	All men Estimate [†]	All women Estimate [†]	HIV-infected men only Estimate [†]	HIV-infected women only Estimate [†]
A. HIV serostatus and age effects on WC trajectories (cm per year of age)				
HIV-uninfected, ≤40 years	0.76**	0.86**		
HIV-infected, ≤40 years	0.76**	0.64**	0.65**	0.59**
HIV-uninfected, age 40–60 years	0.46**	0.61**		
HIV-infected, age 40–60 years	0.49**	0.52**	0.42**	0.38**
HIV-uninfected, age >60 years	0.39**	0.63**		
HIV-infected, age >60 years	0.56**	0.54**	0.52**	0.15*
B. Effects of HIV and other covariates on average WC ^{††} stratified by sex and HIV serostatus				
Average WC ^{††}	99.71**	102.4**	96.66**	98.43**
HIV infection	-4.14**	-5.74**		
Hispanic (vs non-Hispanic)	3.00*	2.08	2.26*	1.76
Black (vs Caucasian)	0.59	3.82**	0.51	5.10**
Other race (vs Caucasian)	-0.14	3.51	-2.01	1.54
1–3 alcohol drinks/week (vs none)	-0.63**	-0.54**	-0.61**	-0.59**
4–13 alcohol drinks/week (vs none)	-0.33*	-0.70**	-0.38*	-0.61
> 13 alcohol drinks/week (vs none)	0.27	-0.63**	-0.04	-0.58
Former smoker (vs never smoker)	0.53*	0.73	-0.08	0.21
Current smokers (vs never smoker)	-0.64*	-0.77	-1.10*	-2.03**
Marijuana use (vs none)	-0.47*	-1.25**	-0.54**	-1.65**
Stimulant use	-0.82*	-2.74**	-0.85**	-1.86**
Hepatitis C virus infection	-0.32	-5.12**	-0.85	-5.12**
Hepatitis B virus infection	-0.32	2.28	-0.94	2.85
Depressive symptoms	-0.11	-0.45**	-0.08	-0.17
CD4 T-cell count <200 cells/μL			-1.38**	-2.89**
CD4 T-cell count 200–499 cells/ μL			-0.61**	-1.42**
Highly active ART for < 5 years			-0.88**	-1.53**
Highly active ART for 5–10 years			-0.43**	-1.38**

* $P < 0.05$.

** $P < 0.001$.

[†] Estimate interpreted as the change in the slope (cm per year of age) for part A, and the effect on the average WC at age 44 for part B.

^{††} Average WC is at age 44 (mean age of the entire sample).

ART = antiretroviral therapy, HIV = human immunodeficiency virus, WC = waist circumference.

slower WHtR until age 40 (0.004/y vs 0.005/y, $P = 0.005$). Findings were similar in models restricted to HIV-infected participants.

3.2. Covariate effects on BMI, WC, HC, and WHtR at age 44, the mean age of the study population

The effects of covariates on BMI among men and women in multivariate analyses are shown in Tables Table 2B to 5B. Black race and Hispanic ethnicity were both associated with greater BMI; the association with WC was only seen among Hispanic men and black women, while the association with WHtR was seen among Hispanic, but not black, men and women. The association with HC was only seen among black men and women. Alcohol intake, marijuana use, and stimulant use were all associated with lower BMI, WC, HC, and WHtR; current smoking was associated with lower WC and WHtR in men and lower HC in men and women. Lower BMI, WC, HC, and WHtR were associated with hepatitis C infection among women only. Depressive symptoms were associated with significantly lower BMI among both men and women, and lower WC, HC, and WHtR among women only.

3.3. HIV-related effects on BMI, WC, HC, and WHtR at age 44, the mean age of the study population

Among HIV-infected men and women, a lower CD4⁺ T-cell count and shorter duration of ART tended to be associated with lower BMI, WC, HC, and WHtR (Tables 2–5B).

In a sensitivity analysis, we restricted the analysis to participants who were virologically suppressed (HIV-1 RNA <400 copies/mL) at all available visits (608 HIV-infected men and 580 HIV-infected women). The estimates of BMI, WC, and HC trajectories were similar to point estimates in the overall cohort, as shown in the Supplemental Table, <http://links.lww.com/MD/B398>. In separate sensitivity analysis, adjustment for the baseline outcome (ie, BMI, WC, or HC) did not appreciably change the effects of age and/or HIV status.

4. Discussion

We provide the first comparisons of body composition trajectories from ages 18 to 75 among both HIV-infected and -uninfected men and women. Similar to prior findings among HIV-uninfected US adults,^[21–23] we found that gains in BMI and WC were the steepest in the youngest participants. BMI increases continued until age 60 and then plateaued, whereas WC and WHtR increased across the age spectrum and irrespective of HIV serostatus, but with slower gains among younger HIV-infected women and faster gains among older HIV-infected men. These changes in WC in those more than 60 years with a leveling off of BMI suggest a concomitant loss of lean mass (an estimate of skeletal muscle) that may have important clinical consequences in an aging population: changes in WC are highly correlated with changes in trunk fat by dual-energy absorptiometry and with visceral adipose tissue area by computed tomography scan (Priya

Table 4
Effects on HC by piecewise linear mixed-effects models, stratified by sex and HIV serostatus.

	Men	Women	HIV-infected men only	HIV-infected women only
	Estimate [†]	Estimate [†]	Estimate [†]	Estimate [†]
HIV Serostatus and age effects on HC trajectories (cm change per year of age)				
HIV-uninfected, ≤40 years	0.27**	0.57**		
HIV-infected, ≤40 years	0.17**	0.27**	0.14*	0.16**
HIV-uninfected, age 40–60 years	0.08**	0.02		
HIV-infected, age 40–60 years	0.06*	0.02	0.05*	−0.08**
HIV-uninfected, age >60 years	−0.02	−0.33*		
HIV-infected, age >60 years	0.06	−0.01	0.04	−0.27**
Effects of HIV and other covariates on average HC ^{††} stratified by sex and HIV serostatus				
Average HC ^{††}	103.7**	112.8*	97.40**	105.4
HIV infection	−6.31**	−8.82**		
Hispanic (vs non-Hispanic)	−0.22	1.71	0.67	0.68
Black (vs Caucasian)	1.15*	5.25**	1.82*	6.18**
Other race (vs Caucasian)	−0.57	2.25	−1.04	2.66
1–3 alcohol drinks/week (vs none)	−0.46**	−0.53**	−0.36**	−0.29*
4–13 alcohol drinks/week (vs none)	−0.23*	−0.71**	−0.12	−0.51
> 13 alcohol drinks/week (vs none)	−0.01	−0.68**	0.05	−0.75*
Former smoker (vs never smoker)	0.24	0.63	−0.05	−0.26
Current smokers (vs never smoker)	−0.53*	−0.93*	−0.67*	−2.14**
Marijuana use (vs none)	−0.29**	−1.26**	−0.22*	−1.57**
Stimulant use	−0.59**	−2.66**	−0.64**	−2.03**
Hepatitis C virus infection	0.19	−4.58**	−0.42	−4.36**
Hepatitis B virus infection	−0.51	3.80	−0.35	3.98
Depressive symptoms	−0.09	−0.51**	−0.01	−0.30*
CD4 T-cell count <200 cells/μL			−0.60*	−2.07**
CD4 T-cell count 200–499 cells/ μL			−0.33**	−0.82**
Highly active ART for < 5 years			−0.22	−1.65**
Highly active ART for 5–10 years			−0.24*	−1.45**

* P < 0.05.

** P < 0.001.

† Estimate interpreted as the change in the slope (kg/m² per year of age) for part A, and the effect on the average HC at age 44 for part B.

†† Average HC is at age 44 (mean age of the entire sample).

ART = antiretroviral therapy, HIV = human immunodeficiency virus, HC = hip circumference.

Bhagwat, et al; *Measurement of Abdominal Fat Changes in HIV-Infected Individuals Initiating Therapy*; Abstract #704, presented at Conference on Retroviruses and Opportunistic Infections; Boston, MA 2/2016). Moreover, central obesity has negative metabolic effects and has been associated with increased mortality^[24] and neurocognitive impairment^[25] in addition to fatty liver disease^[26] and liver stiffness among HIV-infected individuals.^[27]

Although published data on WHtR is very limited in adults with HIV infection, this measurement has been associated with mortality and metabolic risk in HIV-uninfected populations.^[28,29] A value of 0.5 or greater has been proposed as an indicator of increased metabolic risk,^[30] and this cut-off value allows for a simple bedside test to determine whether a piece of string measured at one-half of a person’s height will fit around the person’s waist.^[30] As expected, WC and WHtR changes with age were quite similar in our population (Fig. 1D). Although further studies are needed to verify the predictive value of this measure in HIV-infected populations, the findings are notable for the average WHtR well above 0.5 among both HIV-infected and uninfected men and women in this study population.

The greatest differences in BMI, WC, HC, and WHtR occurred among ethnic and/or racial minorities, suggesting a need for targeted lifestyle interventions in these high-risk populations. Depressive symptoms were associated with significantly lower BMI, WC, HC, and WHtR in nearly all models. Prior studies have shown an association between depression and both weight

loss and weight gain,^[31] and between depressive symptoms and weight loss.^[32] This relationship may be complex, with the most severe symptoms in underweight older adults and less severe symptoms among overweight or obese individuals.^[33] Thus, in our cohort, weight loss may be a sign of more severe depression.

The present findings in the HIV-infected participants are also notable: although weight gain is often attributed to a “return to health” following ART initiation, our findings suggest that greater BMI, WC, HC, and WHtR are found many years after immune reconstitution, including among participants with CD4 T-cell counts more than 500 cells/μL and with over 10 years of ART. These findings likely reflect the overall increasing rates of obesity in the general population. Alternatively, they could suggest that many years of suppressive ART are needed before the elevated resting energy expenditure associated with HIV is reversed, an inflammatory state persists during the first 5 to 10 years of ART and blunts weight gain, or the development of abdominal lipohypertrophy is most pronounced after a longer duration (>10 years) of ART. Furthermore, the effects of age were similar among those with consistent HIV virologic suppression and in the overall cohort with intermittent viremia.

HIV-infected adults generally gained weight and girth at a slower pace than HIV-uninfected individuals. This may be somewhat reassuring, in the midst of a growing obesity epidemic. However, a less steep BMI and WC trajectory is not necessarily equivalent to maintaining a “healthy” weight or improved health outcomes, as suggested by the observed strong association of

Table 5

Effects on waist-to-height ratio by piecewise linear mixed-effects models, stratified by sex and HIV serostatus.

	All men	All women	HIV-infected men only	HIV-infected women only
	Estimate [†]	Estimate [†]	Estimate [†]	Estimate [†]
HIV serostatus and age effects on waist-to-height ratio trajectories (cm per year of age)				
HIV-uninfected, ≤40 years	0.004**	0.005**		
HIV-infected, ≤40 years	0.004**	0.004**	0.003**	0.004**
HIV-uninfected, age 40–60 years	0.003**	0.004**		
HIV-infected, age 40–60 years	0.003**	0.003**	0.002**	0.002**
HIV-uninfected, age >60 years	0.002**	0.004**		
HIV-infected, age >60 years	0.003**	0.004**	0.003**	0.002**
Effects of HIV and other covariates on average waist-to-height ratio ^{††} stratified by sex and HIV serostatus				
Average WHtR ^{††}	0.561**	0.631**	0.546**	0.617**
HIV infection	-0.021**	-0.030**		
Hispanic (vs non-Hispanic)	0.032**	0.027**	0.031**	0.017
Black (vs Caucasian)	0.004	0.012	0.001	0.016
Other race (vs Caucasian)	0.001	0.035*	-0.026	0.015
1–3 alcohol drinks/week (vs none)	-0.003**	-0.004**	-0.003*	-0.005**
4–13 alcohol drinks/week (vs none)	-0.001	-0.005**	-0.001	-0.007*
>13 alcohol drinks/week (vs none)	0.002*	-0.005**	0.001	-0.007*
Former smoker (vs never smoker)	0.003	0.005	-0.003	0.008
Current smokers (vs never smoker)	-0.004*	-0.003	-0.009*	-0.005
Marijuana use (vs none)	-0.003**	-0.007**	-0.003*	-0.012**
Stimulant use	-0.004**	-0.018**	-0.003*	-0.012**
Hepatitis C virus infection	-0.002	-0.020*	-0.006	-0.028*
Hepatitis B virus infection	0.001	0.024**	0.004	0.032
Depressive symptoms	0.000	-0.004**	0.000	-0.002*
CD4 T-cell count <200 cells/μL			-0.009**	-0.009*
CD4 T-cell count 200–499 cells/μL			-0.004**	-0.003*
Highly active ART for < 5 years			-0.005**	-0.012**
Highly active ART for 5–10 years			-0.002*	-0.009**

* $P < 0.05$.

** $P < 0.001$.

[†] Estimate interpreted as the change in the slope (cm per year of age) for part A, and the effect on the average WHtR at age 44 for part B.

^{††} Average WHtR is at age 44 (mean age of the entire sample).

ART = antiretroviral therapy, HIV = human immunodeficiency virus, HC = hip circumference, WHtR = waist-to-height ratio.

substance abuse and hepatitis C infection with lower BMI and WC. BMI is a rough estimate of overall obesity-related risk particularly among older adults, as aging is associated with decreased muscle and increased fat^[34–36] and BMI by itself therefore likely underestimates the extent of adiposity.^[37] Indeed, the steady increase in WC but not BMI or HC after age 60 in the present study suggests a gain in central adiposity and loss of lean mass. This finding is worrisome, because a normal or stable BMI may not prompt diet and physical activity counseling by healthcare providers despite underlying potentially harmful body composition changes that would benefit from these interventions.^[38] Lastly, an obesity paradox may exist among older adults, where a greater BMI is associated with improved survival.^[39,40] Consistent with this paradox, a lower BMI throughout the age trajectory may suggest less reserve and lower survival benefit among older populations.

We acknowledge several limitations of the current analysis. First, we did not have body composition imaging to distinguish whether the gain in abdominal fat was subcutaneous or visceral, or if the gain in fat was associated with a loss of lean body mass. We also did not have detailed dietary intake, food security assessments, or physical activity measurements that were comparable and consistent in both cohorts. However, the large numbers of visits and participants, the use of clinically feasible and inexpensive anthropomorphic measurements, the inclusion of racially and ethnically diverse men and women, and the restriction of some analyses to virologically suppressed partic-

ipants on ART expand greatly upon previously reported BMI trajectory data, and are strengths of the study.

Routine measurement and monitoring of BMI, WC, and HC trajectories may provide important insights and identify opportunities for interventions. Counseling should be provided to all HIV-infected patients, regardless of BMI, on the importance of a lifestyle factors (healthy diet, physical activity) to maintain a normal weight. Particular attention should be directed toward younger individuals, racial/ethnic minorities, and individuals initiating ART at high CD4⁺ T cell counts. An unintentional negative BMI trajectory might serve as a prompt for screening for depressive symptoms, substance abuse, or hepatitis C infection, and may be a marker of loss of lean mass. Further analysis of the changes in muscle and fat compartments complemented by studies of muscle and fat quality will advance the understanding of the metabolic risk over the lifespan, a key to extending longevity and compressing morbidity in an aging population.

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