Original research

Cocaine use modifies the association of antiretroviral therapy regimens with obesity in HIV-infected adults

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A B S T R A C T

Aims: Although evidence suggests that antiretroviral therapy (ART) use may contribute to obesity in individuals with HIV infection, the alleged association between ART use and obesity in HIV-infected patients remains controversial due to differences in patient characteristics and study designs. Additionally, cocaine is commonly used among those with HIV infection and may affect body weight. The main objective of this study was to examine the interactive effects of ART regimens and cocaine use on obesity in adults with HIV infection.
Methods: Between 2003 and 2014, 672 HIV-infected study participants who resided in Baltimore, Maryland, were enrolled in a study investigating HIV/ART-associated comorbidities. Robust linear regression and multiple logistic regression models were conducted to examine whether cocaine use modified the association between antiretroviral drugs and body weight status.
Results: Adjusted regression analyses showed that duration of protease inhibitor use was significantly associated with lower BMI ($\beta = -0.012$, SE = 0.005, $p < 0.05$) and a reduced risk of obesity (OR = 0.313, 95% CI = 0.135, 0.724) in cocaine non-users, while no such association was found in cocaine users.
Conclusions: Our findings suggest that reducing cocaine use may alleviate ART-associated weight gain in adults with HIV infection.

1. Introduction

With the development and increasing availability of antiretroviral therapy (ART), life expectancy of HIV-infected patients has improved dramatically (Passaes and Saez-Cirion, 2014). Currently 1.1 million people aged 13 and older are estimated to live with HIV in the US, a half of whom are persons aged 50 years and older (Centers for Disease Control and Prevention, 2017; Huang et al., 2015). As HIV-infected people live longer, non-AIDS chronic conditions, such as coronary artery disease (CAD), diabetes mellitus, kidney disease, and cancer, have become frequent causes of death among older people with HIV infection (Effros et al., 2008). Obesity, a major public health challenge in the US, is an important modifiable risk factor for the abovementioned chronic diseases (Kearns et al., 2014).

Obesity is highly prevalent among HIV-infected people, especially among those who initiated ART treatments (Koethe et al., 2016). Existing evidence demonstrates an association between ART regimens and the development of obesity (Anuurad et al., 2010; Sharma et al., 2014). Laboratory and clinical studies have shown that protease inhibitors

(PIs) may inhibit lipoprotein lipase, impair lipoprotein catabolism and pre-adipocyte differentiation, interfere with insulin signaling pathways, and affect body fat storage and distribution (Anuurad et al., 2010). A study of 1177 females enrolled in the Women's Interagency HIV Study found that PI- and nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based drugs were significantly associated with higher BMI, but nucleoside reverse-transcriptase inhibitors (NRTIs) were associated with lower BMI (Sharma et al., 2014).

In addition to its adverse effects on HIV disease progression and prognosis (Kapadia et al., 2005), chronic cocaine use has been shown to suppress appetite, reduce fat storage, and cause weight loss in both animal and epidemiological studies (Ersche et al., 2013; Roebber et al., 2015). Although cocaine is commonly used by HIV-infected people (Kumar et al., 2015), very few studies examined possible modification effects of long-term cocaine use on ART-induced obesity in patients with HIV infection. We have reported modification effects of chronic cocaine use on HIV/ART-associated subclinical CAD and myocardial steatosis in HIV-infected adults (Lai et al., 2016, 2017). The objective of this investigation was to assess whether cocaine use modifies the

associations of various types of ART regimens with obesity in those with HIV infection, using baseline cross-sectional data from a cohort of participants aged 21 years or older in Baltimore, Maryland, USA.

2. Subjects, materials and methods

2.1. Study participants

Between August 2003 and September 2014, 1053 adult study participants with HIV infection were recruited from inner city of Baltimore, Maryland, USA to take part in an observational study that aimed to explore the impacts of HIV infection, cocaine use, ART, and other risk factors on subclinical atherosclerosis. HIV infection status was assessed by ELISA and confirmed by Western blot test. None of the participants had known or symptoms of CAD. The study protocol was approved by the Institutional Review Board at the Johns Hopkins School of Medicine. All the participants provided the written informed consent. All the study procedures followed institutional guidelines.

2.2. Substance use and ART therapy

The study participants were interviewed by trained research staff and answered questions on their cigarette smoking, alcohol consumption, duration and frequency of cocaine and other illicit drug use, medical history, and medications including HIV regimens. Cocaine use was self-reported and defined as chronic use of cocaine by any route for at least 6 consecutive months and administered at least 4 times per month. Cocaine users who used other drugs such as opiates, benzodiazepines, or methamphetamine were included. Infrequent cocaine users other than chronic cocaine users (< 6 consecutive months or < 4 times per month) were excluded from the final analyses. Individuals who reported never using cocaine were considered cocaine non-users. The final sample included 672 subjects, i.e., 408 cocaine users and 264 cocaine non-users.

Medical charts were reviewed to confirm information on self-reported medical history and medications administered. ART regimens were categorized into three types: PIs, NRTIs, and NNRTIs. Durations of ART regimens were measured in months. According to median values, ART use was dichotomized as > 12 months vs. ≤12 months for PIs, > 24 months vs. ≤24 months for NRTIs, and > 0 months vs. = 0 month for NNRTIs.

2.3. Body weight measurements as outcome variables

Body weight and height were measured by nurses at the clinical research unit and used to calculate body mass index (BMI, kg/m^2). Weight status was classified as underweight if BMI $< 18.5\,kg/m^2$, normal weight if $18.5\,kg/m^2 \leq BMI < 25\,kg/m^2$, overweight if $25\,kg/m^2 \leq BMI < 30\,kg/m^2$, and obesity if BMI $\geq 30\,kg/m^2$ (World Health Organization, 2000).

2.4. Covariates

During face-to-face interviews, participants answered questions on their sociodemographic characteristics such as marital status, employment, education level, and annual household income. Participants were asked to recall their weight at age 20 and BMI at age 20 was calculated accordingly. Baseline CD4 cell counts and HIV viral loads were abstracted from medical charts. Blood samples were obtained after overnight fasting. Blood hemoglobin levels were measured with complete blood count by Quest Diagnostics (Baltimore, Maryland).

2.5. Statistical analyses

Descriptive and regression analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC). Medians and interquartile ranges (IQRs) were calculated for continuous variables, e.g., age, BMI, and durations of ART regimens. Distributions of selected demographic and lifestyle characteristics were described using proportions. The continuous and categorical variables were compared between cocaine use subgroups using the nonparametric Wilcoxon rank-sum test and chi-square test, respectively.

All the models were fitted for overall subjects, cocaine users, and cocaine non-users, separately. The associations of lifestyle and clinical risk factors with BMI were examined using linear regression models. As compared to conventional multiple linear regression models based on least squares, least trimmed squares (LTS) estimation method was less sensitive to outliers and high leverage points (Rousseeuw and Leroy, 1987). Given the presence of non-normal distributions and outliers of our data, robust linear regression models using LTS were built to provide robust estimates of explanatory variables. Logistic regression models were performed to examine the associations between various risk factors and obesity.

Univariate regression models were first fitted to evaluate the unadjusted associations between body weight status and individual risk factor, i.e., age, gender, current cigarette smoking, current alcohol use, years of cigarette smoking, years of alcohol consumption, marital status, employment, education, annual household income, BMI at age 20, blood hemoglobin, baseline CD4 cell count, baseline HIV viral load level, durations of PI use, durations of NRTI use, and durations of NNRTI use. Those factors that were significant at the $p < 0.15$ level in the univariate models were included in the multivariate regression models to investigate the combined effects of these risk factors on BMI and obesity. By repeating the process of eliminating, refitting, and verifying, the variables were removed in a stage wise manner and the final models only contained the variables that made significant contributions. All the tests were two-sided and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Selected characteristics by cocaine use status

Among the 672 participants with HIV infection, 60.7% were cocaine users, 62.7% were male, 63.7% were current cigarette smokers, 66.4% were never married, and 81.1% were unemployed (Table 1). Approximately 95% of the participants were African Americans; therefore race/ethnicity was not adjusted in the regression models. The median value was 47 years (IQR 42–51 years) for age and $25.3\,kg/m^2$ (IQR 22.2–29.5 kg/m^2) for BMI. Cocaine users were significantly older, more likely to currently smoke, and have longer-term cigarette smoking and alcohol drinking as compared to cocaine non-users (all $p < 0.05$). Gender, current alcohol consumption, blood hemoglobin levels, BMI, and durations of ART treatments did not significantly differ between two subgroups (all $p > 0.05$). The overall prevalence rates of obesity and overweight were 23.2% and 28.9% respectively, which did not significantly differ between cocaine users and non-users ($p > 0.05$). The prevalence of underweight was 4.6% and combined with normal weight group in the final analyses.

3.2. The associations of durations of ART regimens with BMI, stratified by cocaine use status

The associations between ART durations and BMI were presented in Table 2. The multivariate robust regression analyses of the overall sample showed that being female ($\beta = 3.171$, SE = 0.461, $p < 0.05$), current cigarette smoking ($\beta = -1.807$, SE = 0.436, $p < 0.05$), BMI at age 20 ($\beta = 0.628$, SE = 0.052, $p < 0.05$), and blood hemoglobin levels ($\beta = 0.576$, SE = 0.143, $p < 0.05$) were significantly associated with BMI. Cocaine use modified the associations between duration of PI use and BMI. Although multivariate analyses showed that durations of ART regimens were not independently associated with BMI in cocaine

Table 1

Characteristics of study participants by cocaine use status (n = 672).[a]

Characteristics	All		Cocaine use		Cocaine non-use		P value[b]
N (%)	672		408	(60.7)	264	(39.3)	
Age (years)	47	(42–51)	48	(44–52)	45	(36–51)	< **0.001**
Male (%)	421	(62.7)	255	(62.5)	166	(62.9)	0.921
Race (%)							0.072
Non-Hispanic black	638	(94.9)	392	(96.1)	246	(93.2)	
Non-Hispanic white and others	34	(5.1)	16	(3.9)	18	(6.8)	
Current cigarette smoking (%)	428	(63.7)	310	(76.0)	118	(44.7)	< **0.001**
Years of cigarette smoking	24	(7–32)	29	(20–35)	10	(0–25)	< **0.001**
Current alcohol use (%)	234	(34.8)	139	(34.1)	95	(36.0)	0.611
Years of alcohol use	18	(3–29)	20	(7–30)	10	(1–21)	< **0.001**
Never married	446	(66.4)	266	(65.2)	180	(68.2)	0.424
Unemployed	545	(81.1)	363	(89.0)	182	(68.9)	< **0.001**
Education < high school	254	(37.8)	191	(46.8)	63	(23.9)	< **0.001**
Annual household income < $5000	260	(38.7)	192	(47.1)	68	(25.8)	< **0.001**
Body mass index at age 20 (BMI, kg/m^2)	22.9	(20.7–25.3)	22.8	(20.7–25.1)	23.1	(20.6–25.5)	0.372
Hemoglobin (g/dL)	13.1	(12.1–14.2)	13.1	(12.1–14.1)	13.4	(12.2–14.3)	0.130
CD4 count at baseline (cells/mm^3)	345	(213–565)	331	(206–563)	373	(230–567)	0.320
HIV RNA load at baseline (copies/mL)	1440	(202–43762)	2750	(220–53858)	400	(202–28104)	0.179
Duration of ART therapy (months)	36.0	(5.9–86.5)	36.0	(5.9–84.0)	36.0	(8.4–96.0)	0.378
Duration of PI therapy (months)	12.0	(0–53.0)	12.0	(0–48.0)	12.0	(0–60.0)	0.553
Duration of NRTI therapy (months)	24.0	(1.9–70.0)	24.0	(1.9–61.0)	25.5	(0.9–82.5)	0.369
Duration of NNRTI therapy (months)	0	(0–15.0)	0	(0–12.0)	0	(0–20.5)	0.098
Body mass index (BMI, kg/m^2)	25.3	(22.2–29.5)	25.1	(22.3–29.0)	25.6	(22.1–30.7)	0.545
Body weight status							0.164
Obesity	156	(23.2)	84	(20.6)	72	(27.3)	
Overweight	194	(28.9)	127	(31.1)	67	(25.4)	
Normal weight	291	(43.3)	177	(43.4)	114	(43.2)	
Underweight	31	(4.6)	20	(4.9)	11	(4.1)	

[a] Median (interquartile range) was presented for continuous variables, and proportion (%) was presented for categorical variables.

[b] Nonparametric Wilcoxon rank-sum test was used to compare continuous variables. Chi-square test was used to compare categorical variables.

users, duration of PI use was significantly associated with lower BMI (β = −0.012, SE = 0.005, p < 0.05) in the individuals who had never used cocaine. No such association was found for NRTIs or NNRTIs.

3.3. The associations of durations of ART regimens with obesity, stratified by cocaine use status

According to logistic regression models (Table 3), being female (OR = 4.433, 95% CI = 2.695, 7.291) and BMI at age 20 (OR = 1.394, 95% CI = 1.289, 1.508) were significantly associated with increased risk of obesity in the overall sample. Multiple logistic regression analyses showed that duration of PI use was significantly associated with a lower risk of obesity (OR = 0.313, 95% CI = 0.135, 0.724) in cocaine non-users.

4. Discussion

This study examined whether chronic cocaine use may modify ART-induced obesity in individuals with HIV infection. We found that (1) duration of PI-based therapy was inversely associated with BMI and obesity in those who had never used cocaine (both p < 0.05); (2) no such association was observed for the use of NRTIs or NNRTIs (all p > 0.05); and (3) chronic cocaine use was not associated with BMI and obesity in adults with HIV infection (all p > 0.05).

Much attention has been paid to metabolic adverse effects of ART regimens since their clinical application in HIV-infected patients. PIs have strong affinity for the catalytic site of HIV-1 protease enzyme (da Cunha et al., 2015), which is approximately 60% homologous to two important proteins involved in lipid metabolism, i.e., cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP) (Navia et al., 1989). It is hypothesized that PIs may bind to CRABP-1 and LRP, impair differentiation of peripheral adipocytes, reduce triglyceride storage, inhibit hepatic uptake of chylomicrons, and then lead to peripheral lipodystrophy and central adiposity (Carr et al., 1998). NRTIs interfere with HIV reverse transcriptase activity via phosphorylation (Jiang et al., 2007). Intracellular and intramitochondrial phosphorylation of NRTIs may inhibit pol-γ, deplete mtDNA, and induce mitochondrial dysfunction in various tissues including adipose tissue (Lewis and Dalakas, 1995). NNRTIs do not require phosphorylation to achieve antiviral activities, and are considered substitutes for NRTIs and PIs in HIV-infected patients prone to atherosclerosis (Kline and Sutliff, 2008). However, NNRTIs have been shown to strongly impair lipid metabolism and adipocyte differentiation in vitro (Erlandson and Lake, 2016; Minami et al., 2011).

The findings on ART-associated obesity have remained inconclusive. A multi-center randomized trial suggested immediate weight gain following ART initiation in treatment-naïve patients with HIV infection (Gallant et al., 2004). A study among ART-naïve patients observed significantly positive associations of BMI change with the use of PIs but not with other ART agents after 6 and 24 months of ART initiation (Tate et al., 2012). The Women's Interagency HIV Study showed that PIs and NNRTIs were significantly associated with higher BMI, while NRTIs were associated with lower BMI (Sharma et al., 2014). A longitudinal study of 495 HIV-infected patients observed a significant increase in body weight after switching from NNRTI-based to PI-based ART regimens (Norwood et al., 2017). However, an observational cohort study of 1214 HIV-infected adults indicated no significant associations between any ART drugs including PIs and weight gain (Taylor et al., 2014). Furthermore, a prospective study of 1682 patients from the US Military HIV Natural History Study found that NRTI agents were significantly associated with weight loss, and there was no association of PIs and NNRTIs with weight gain (Crum-Cianflone et al., 2010).

A major finding of this investigation was that the ART-associated obesity was significantly modified by cocaine use of HIV-infected patients. Both multivariate linear and logistic regression analyses suggested that cocaine reduced use may minimize adverse effects of PI-based therapy by decreasing the likelihood of developing obesity. The results of this investigation were consistent with our prior findings, which have reported that cocaine abstinence or reduced use may

Table 2

The associations of demographic and clinical characteristics with body mass index (BMI, kg/m^2) by cocaine use status, robust regression.

Characteristics	Univariate model			Final multivariate model		
	Estimate	SE	P value	Estimate	SE	P value
All						
Age	0.004	0.025	0.868			
Female	2.118	0.419	**< 0.001**	3.171	0.461	**< 0.001**
Current cigarette smoking	−1.849	0.420	**< 0.001**	−1.807	0.436	**< 0.001**
Years of cigarette smoking	−0.038	0.014	**0.009**			
Current alcohol use	−1.363	0.420	**0.001**			
Years of alcohol use	−0.017	0.015	0.278			
Long-term cocaine use	−0.261	0.413	0.528			
Never married vs. married or other marital status	−1.746	0.423	**< 0.001**			
Unemployed vs. employed	−0.994	0.515	**0.054**	−1.112	0.561	**0.048**
Education < high school vs. High school diploma, GED or above	0.455	0.417	0.276			
Annual household income < $5000 vs. annual household income ≥ $5000	−0.353	0.414	0.394			
BMI at age 20 (kg/m^2)	0.612	0.047	**< 0.001**	0.628	0.052	**< 0.001**
Hemoglobin (g/dL)	0.367	0.140	**0.009**	0.576	0.143	**< 0.001**
CD4 count at baseline (cells/mm^3)	0.001	0.001	0.572			
HIV RNA load at baseline (copies/mL, log transformed)	−0.136	0.106	0.199			
Duration of PI therapy (months)	−0.007	0.004	**0.067**			
Duration of NRTI therapy (months)	−0.007	0.004	**0.052**	−0.015	0.004	**< 0.001**
Duration of NNRTI therapy (months)	−0.018	0.007	**0.007**			
Cocaine use						
Age	−0.030	0.040	0.463			
Female	1.449	0.522	**0.006**	2.966	0.526	**< 0.001**
Current cigarette smoking	−1.355	0.587	**0.021**	−1.691	0.553	**0.002**
Years of cigarette smoking	−0.031	0.021	**0.145**			
Current alcohol use	−1.389	0.523	**0.008**			
Years of alcohol use	−0.007	0.019	0.713			
Long-term cocaine use	NA					
Never married vs. married or other marital status	−0.675	0.524	0.198			
Unemployed vs. employed	−0.782	0.795	0.326			
Education < high school vs. High school diploma, GED or above	0.442	0.502	0.379			
Annual household income < $5000 vs. annual household income ≥ $5000	−0.093	0.502	0.853			
BMI at age 20 (kg/m^2)	0.549	0.062	**< 0.001**	0.580	0.066	**< 0.001**
Hemoglobin (g/dL)	0.447	0.167	**0.008**	0.663	0.160	**< 0.001**
CD4 count at baseline (cells/mm^3)	0.000	0.001	0.932			
HIV RNA load at baseline (copies/mL, log transformed)	−0.145	0.129	0.260			
Duration of PI therapy (months)	−0.003	0.005	0.543			
Duration of NRTI therapy (months)	−0.007	0.005	0.181			
Duration of NNRTI therapy (months)	−0.018	0.009	**0.035**			
Cocaine non-use						
Age	0.035	0.035	0.317			
Female	3.174	0.694	**< 0.001**	1.871	0.624	**0.003**
Current cigarette smoking	−2.504	0.674	**< 0.001**	−1.742	0.585	**0.003**
Years of cigarette smoking	−0.069	0.025	**0.005**			
Current alcohol use	−1.444	0.711	**0.042**			
Years of alcohol use	−0.028	0.027	0.308			
Long-term cocaine use	NA					
Never married vs. married or other marital status	−3.531	0.699	**< 0.001**	−1.820	0.640	**0.004**
Unemployed vs. employed	−1.024	0.734	0.163			
Education < high school vs. High school diploma, GED or above	0.574	0.803	0.475			
Annual household income < $5000 vs. annual household income ≥ $5000	−0.695	0.784	0.375			
BMI at age 20 (kg/m^2)	0.872	0.072	**< 0.001**	0.742	0.068	**< 0.001**
Hemoglobin (g/dL)	0.210	0.254	0.409			
CD4 count at baseline (cells/mm^3)	0.002	0.002	0.213			
HIV RNA load at baseline (copies/mL, log transformed)	−0.103	0.189	0.584			
Duration of PI therapy (months)	−0.013	0.006	**0.033**	−0.012	0.005	**0.025**
Duration of NRTI therapy (months)	−0.010	0.006	**0.087**			
Duration of NNRTI therapy (months)	−0.020	0.011	**0.075**			

Bold indicates Significance level: p < 0.15 in the univariate models, and p < 0.05 in the final multivariate models

alleviate ART-associated coronary stenosis, myocardial and hepatic steatosis, and dyslipidemia (Lai et al., 2016, 2017; Li et al., 2018). The mechanisms underlying the modification effects of chronic cocaine use on the relationships between ART treatments and obesity remain unclear. Existing literature has suggested that cocaine use may alter body weight by dysregulating transcript peptides in discrete hypothalamic nuclei associated with eating, lowering circulating leptin levels, and impairing energy balance (Ersche et al., 2013; Roebber et al., 2015). Increasing evidence also indicates relationships of ART treatments with changes in appetite and fat storage (Anuurad et al., 2010; Rehman et al., 2015; Sharma et al., 2014). Therefore, we postulated that alterations in appetite, food preference and eating habits as well as

Table 3
The associations of demographic and clinical characteristics with obesity by cocaine use status, logistic regression.

Characteristics	Univariate model			Final multivariate model		
	OR	95% CI	P value	OR	95% CI	P value
All						
Age	1.007	(0.983, 1.031)	0.593			
Female	3.345	(2.246, 4.982)	**< 0.001**	4.433	(2.695, 7.291)	**< 0.001**
Current cigarette smoking	0.491	(0.330, 0.731)	**0.001**	0.441	(0.268, 0.726)	**0.001**
Years of cigarette smoking	0.987	(0.973, 1.000)	**0.055**			
Current alcohol use	0.554	(0.361, 0.849)	**0.007**			
Years of alcohol use	0.991	(0.976, 1.005)	0.203			
Long-term cocaine use	0.740	(0.503, 1.089)	**0.127**			
Never married vs. married or other marital status	0.573	(0.383, 0.856)	**0.007**			
Unemployed vs. employed	0.833	(0.514, 1.351)	0.460			
Education < high school vs. High school diploma, GED or above	1.111	(0.752, 1.641)	0.598			
Annual household income < $5000 vs. annual household income ≥$5000	1.068	(0.722, 1.578)	0.743			
BMI at age 20 (kg/m^2)	1.333	(1.244, 1.428)	**< 0.001**	1.394	(1.289, 1.508)	**< 0.001**
Hemoglobin (g/dL)	1.088	(0.949, 1.247)	0.229			
CD4 count at baseline (cells/mm^3)	1.001	(0.999, 1.002)	0.321			
HIV RNA load at baseline (copies/mL, log transformed)	0.907	(0.804, 1.023)	**0.111**			
Longer use of PI therapy (> 12 months)	0.702	(0.476, 1.035)	**0.074**			
Longer use of NRTI therapy (> 24 months)	0.994	(0.677, 1.460)	0.977			
Longer use of NNRTI therapy (> 0 months)	0.612	(0.402, 0.931)	**0.022**	0.542	(0.320, 0.916)	**0.022**
Cocaine use						
Age	0.986	(0.945, 1.029)	0.513			
Female	2.836	(1.676, 4.798)	**< 0.001**	7.899	(3.646, 17.115)	**< 0.001**
Current cigarette smoking	0.546	(0.303, 0.983)	**0.044**			
Years of cigarette smoking	0.990	(0.969, 1.011)	0.348			
Current alcohol use	0.566	(0.320, 1.004)	**0.052**			
Years of alcohol use	0.994	(0.975, 1.014)	0.568			
Long-term cocaine use	NA					
Never married vs. married or other marital status	0.886	(0.519, 1.515)	0.659			
Unemployed vs. employed	1.014	(0.425, 2.417)	0.975			
Education < high school vs. High school diploma, GED or above	1.118	(0.671, 1.864)	0.668			
Annual household income < $5000 vs. annual household income ≥$5000	1.111	(0.666, 1.852)	0.688			
BMI at age 20 (kg/m^2)	1.277	(1.168, 1.397)	**< 0.001**	1.360	(1.220, 1.516)	**< 0.001**
Hemoglobin (g/dL)	1.177	(0.983, 1.409)	**0.076**	1.370	(1.080, 1.738)	**0.009**
CD4 count at baseline (cells/mm^3)	1.001	(0.999, 1.002)	0.416			
HIV RNA load at baseline (copies/mL, log transformed)	0.921	(0.800, 1.061)	0.254			
Longer use of PI therapy (> 12 months)	0.783	(0.467, 1.311)	0.352			
Longer use of NRTI therapy (> 24 months)	0.962	(0.576, 1.607)	0.883			
Longer use of NNRTI therapy (> 0 months)	0.543	(0.304, 0.969)	**0.039**			
Cocaine non-use						
Age	1.022	(0.992, 1.053)	**0.146**	1.049	(1.003, 1.097)	**0.035**
Female	4.309	(2.320, 8.003)	**< 0.001**	5.205	(2.171, 12.480)	**< 0.001**
Current cigarette smoking	0.471	(0.260, 0.854)	**0.013**			
Years of cigarette smoking	0.988	(0.968, 1.010)	0.281			
Current alcohol use	0.535	(0.281, 1.018)	**0.057**			
Years of alcohol use	0.991	(0.969, 1.014)	0.451			
Long-term cocaine use	NA					
Never married vs. married or other marital status	0.296	(0.156, 0.559)	**< 0.001**	0.364	(0.150, 0.880)	**0.025**
Unemployed vs. employed	0.874	(0.470, 1.625)	0.670			
Education < high school vs. High school diploma, GED or above	1.334	(0.700, 2.543)	0.381			
Annual household income < $5000 vs. annual household income ≥$5000	1.178	(0.622, 2.228)	0.615			
BMI at age 20 (kg/m^2)	1.408	(1.258, 1.575)	**< 0.001**	1.460	(1.282, 1.663)	**< 0.001**
Hemoglobin (g/dL)	0.958	(0.770, 1.191)	0.698			
CD4 count at baseline (cells/mm^3)	1.001	(0.999, 1.002)	0.566			
HIV RNA load at baseline (copies/mL, log transformed)	0.869	(0.687, 1.099)	0.240			
Longer use of PI therapy (> 12 months)	0.610	(0.337, 1.102)	**0.101**	0.313	(0.135, 0.724)	**0.007**
Longer use of NRTI therapy (> 24 months)	1.043	(0.582, 1.867)	0.888			
Longer use of NNRTI therapy (> 0 months)	0.682	(0.368, 1.265)	0.225			

Bold indicates Significance level: p < 0.15 in the univariate models, and p < 0.05 in the final multivariate models

impaired fat storage and distribution processes may be involved in possible interactions between cocaine use and antiretroviral regimens with regard to weight gain and obesity.

Our data indicated that female patients were more likely to develop obesity than their male counterparts, which was consistent with the findings of previous studies (Guehi et al., 2016; Koethe et al., 2016).

Such a gender difference may be attributed to genetic and hormone factors (Bouchard, 1996; Perusse et al., 1997). BMI at age 20 and blood hemoglobin levels were significantly associated with greater risks of obesity in our study. Cumulative studies have demonstrated that obesity in childhood and youth may track into adulthood (Evensen et al., 2016; Ronque et al., 2018; Yang et al., 2007), and hemoglobin levels

were higher in obese individuals than in normal-weight ones (Akter et al., 2017; Rao and Morghom, 1986). Obesity prevention interventions along with ART initiation may be beneficial in HIV-infected patients who are female, obese in childhood or youth, and have high hemoglobin levels.

5. Limitations

This study has several limitations. First, our findings are derived from a cross-sectional analysis of baseline data, and these findings cannot uncover causal associations of ART use and cocaine use with body weight. Longitudinal studies are needed to investigate whether ART and cocaine influence body weight in adults with HIV infection. Second, evidence has shown that food intake and physical activity are strongly correlated with obesity (Westerterp, 2010). However, we did not collect data on participants' usual dietary intake and physical activity levels. Third, we evaluated general obesity in this study but did not have measures of participants' body fat distribution. In addition, body weight at age 20 was self-reported by study participants. Although validation research has shown that men tended to over-report their weight and women likely underestimated their weight, self-reported body weight and height have been widely used in national surveys and epidemiological studies (Merrill and Richardson, 2009; Poston et al., 2014; Watson et al., 2015). Fourth, the participants' drug use was also self-reported in this study. The information on never use of cocaine cannot be validated. Lastly, all of the study participants resided in Baltimore city and some of them may use multiple drugs. Potential confounding effects of other illicit drugs were tested in our models and none of them was statistically significant.

6. Conclusions

Although no association between chronic cocaine use and weight loss was uncovered in this study, our data suggested that cocaine abstinence or reduced use may alleviate ART-associated adverse effects on body weight status. Additionally, being female, youth obesity, and high hemoglobin levels are independent predictors for obesity in those with HIV infection. Biomedical and longitudinal studies are warranted to confirm our findings. Given the high prevalence of cocaine use in people with HIV infection, treating cocaine addiction may be considered as an important component of the comprehensive management and care of HIV-infected patients with obesity and obesity-related diseases.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

Acknowledgements

References

Akter, R., Nessa, A., Sarker, D., Yesmin, M., 2017. Effect of obesity on hemoglobin concentration. Mymensingh Med. J. : MMJ 26, 230–234.

Anuurad, E., Bremer, A., Berglund, L., 2010. HIV protease inhibitors and obesity. Curr. Opin. Endocrinol. Diabetes Obes. 17, 478–485. https://doi.org/10.1097/MED.0b013e32833dde87.

Bouchard, C., 1996. The causes of obesity: advances in molecular biology but stagnation on the genetic front. Diabetologia 39, 1532–1533.

Carr, A., Samaras, K., Chisholm, D.J., Cooper, D.A., 1998. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet 351, 1881–1883. https://doi.org/10.1016/S0140-6736(98)03391-1.

Centers for Disease Control and Prevention, 2017. HIV in the United States: at A Glance. https://www.cdc.gov/hiv/statistics/overview/ataglance.html, Accessed date: 30 August 2018.

Crum-Cianflone, N., Roediger, M.P., Eberly, L., Headd, M., Marconi, V., Ganesan, A., Weintrob, A., Barthel, R.V., Fraser, S., Agan, B.K., Infectious Disease Clinical Research Program, H.I.V.W.G., 2010. Increasing rates of obesity among HIV-infected persons during the HIV epidemic. PLoS One 5, e10106. https://doi.org/10.1371/journal.pone.0010106.

da Cunha, J., Maselli, L.M., Stern, A.C., Spada, C., Bydlowski, S.P., 2015. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: old and new drugs. World J. Virol. 4, 56–77. https://doi.org/10.5501/wjv.v4.i2.56.

Effros, R.B., Fletcher, C.V., Gebo, K., Halter, J.B., Hazzard, W.R., Horne, F.M., Huebner, R.E., Janoff, E.N., Justice, A.C., Kuritzkes, D., Nayfield, S.G., Plaeger, S.F., Schmader, K.E., Ashworth, J.R., Campanelli, C., Clayton, C.P., Rada, B., Woolard, N.F., High, K.P., 2008. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin. Infect. Dis. : Off. Publ. Infect. Dis. Soc. Am. 47, 542–553. https://doi.org/10.1086/590150.

Erlandson, K.M., Lake, J.E., 2016. Fat matters: understanding the role of adipose tissue in health in HIV infection. Current HIV/AIDS reports 13, 20–30. https://doi.org/10.1007/s11904-016-0298-8.

Ersche, K.D., Stochl, J., Woodward, J.M., Fletcher, P.C., 2013. The skinny on cocaine: insights into eating behavior and body weight in cocaine-dependent men. Appetite 71, 75–80. https://doi.org/10.1016/j.appet.2013.07.011.

Evensen, E., Wilsgaard, T., Furberg, A.S., Skeie, G., 2016. Tracking of overweight and obesity from early childhood to adolescence in a population-based cohort - the Tromso Study, Fit Futures. BMC Pediatr. 16, 64. https://doi.org/10.1186/s12887-016-0599-5.

Gallant, J.E., Staszewski, S., Pozniak, A.L., DeJesus, E., Suleiman, J.M., Miller, M.D., Coakley, D.F., Lu, B., Toole, J.J., Cheng, A.K., Study, G., 2004. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. Jama 292, 191–201. https://doi.org/10.1001/jama.292.2.191.

Guehi, C., Badje, A., Gabillard, D., Ouattara, E., Koule, S.O., Moh, R., Ekouevi, D., Ahibo, H., N'Takpe, J.B., Menan, G.K., Deschamps, N., Lecarrou, J., Eholie, S., Anglaret, X., Danel, C., 2016. High prevalence of being overweight and obese HIV-infected persons, before and after 24 months on early ART in the ANRS 12136 temprano trial. AIDS Res. Ther. 13, 12. https://doi.org/10.1186/s12981-016-0094-y.

Huang, M.B., Ye, L., Liang, B.Y., Ning, C.Y., Roth, W.W., Jiang, J.J., Huang, J.G., Zhou, B., Zang, N., Powell, M.D., Liang, H., Bond, V.C., 2015. Characterizing the HIV/AIDS epidemic in the United States and China. Int. J. Environ. Res. Public Health 13https://doi.org/10.3390/ijerph13010030. ijerph13010030.

Jiang, B., Hebert, V.Y., Li, Y., Mathis, J.M., Alexander, J.S., Dugas, T.R., 2007. HIV antiretroviral drug combination induces endothelial mitochondrial dysfunction and reactive oxygen species production, but not apoptosis. Toxicol. Appl. Pharmacol. 224, 60–71. https://doi.org/10.1016/j.taap.2007.06.010.

Kapadia, F., Vlahov, D., Donahoe, R.M., Friedland, G., 2005. The role of substance abuse in HIV disease progression: reconciling differences from laboratory and epidemiologic investigations. Clin. Infect. Dis. : Off. Publ. Infect. Dis. Soc. Am. 41, 1027–1034. https://doi.org/10.1086/433175.

Kearns, K., Dee, A., Fitzgerald, A.P., Doherty, E., Perry, I.J., 2014. Chronic disease burden associated with overweight and obesity in Ireland: the effects of a small BMI reduction at population level. BMC Public Health 14, 143. https://doi.org/10.1186/1471-2458-14-143.

Kline, E.R., Sutliff, R.L., 2008. The roles of HIV-1 proteins and antiretroviral drug therapy in HIV-1-associated endothelial dysfunction. J. Investig. Med. : Off. Publ. Am. Fed. Clin. Res. 56, 752–769. https://doi.org/10.1097/JIM.0b013e3181788d15.

Koethe, J.R., Jenkins, C.A., Lau, B., Shepherd, B.E., Justice, A.C., Tate, J.P., Buchacz, K., Napravnik, S., Mayor, A.M., Horberg, M.A., Blashill, A.J., Willig, A., Wester, C.W., Silverberg, M.J., Gill, J., Thorne, J.E., Klein, M., Eron, J.J., Kitahata, M.M., Sterling, T.R., Moore, R.D., North American, A.C.C.o.R., Design, 2016. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. AIDS Res. Hum. Retrovir. 32, 50–58. https://doi.org/10.1089/aid.2015.0147.

Kumar, S., Rao, P.S., Earla, R., Kumar, A., 2015. Drug-drug interactions between antiretroviral therapies and drugs of abuse in HIV systems. Expert Opin. Drug Metabol. Toxicol. 11, 343–355. https://doi.org/10.1517/17425255.2015.996546.

Lai, H., Moore, R., Celentano, D.D., Gerstenblith, G., Treisman, G., Keruly, J.C., Kickler, T., Li, J., Chen, S., Lai, S., Fishman, E.K., 2016. HIV infection itself may not Be associated with subclinical coronary artery disease among African Americans without cardiovascular symptoms. J. Am. Heart Assoc. 5, e002529. https://doi.org/10.1161/JAHA.115.002529.

Lai, S., Gerstenblith, G., Moore, R.D., Celentano, D.D., Bluemke, D.A., Treisman, G., Liu, C.Y., Li, J., Chen, S., Kickler, T., Lai, H., 2017. Cocaine use may modify HIV/ART-associated myocardial steatosis and hepatic steatosis. Drug Alcohol Depend. 177, 84–92. https://doi.org/10.1016/j.drugalcdep.2017.03.029.

Lewis, W., Dalakas, M.C., 1995. Mitochondrial toxicity of antiviral drugs. Nat. Med. 1,

417–422.

Li, J., Lai, H., Chen, S., Lai, S., 2018. Impact of cocaine use on protease inhibitor-associated dyslipidemia in HIV-infected adults. Int. J. STD AIDS 29, 781–789. https://doi.org/10.1177/0956462418757126.

Merrill, R.M., Richardson, J.S., 2009. Validity of self-reported height, weight, and body mass index: findings from the National Health and Nutrition Examination Survey, 2001-2006. Prev. Chronic Dis. 6, A121.

Minami, R., Yamamoto, M., Takahama, S., Ando, H., Miyamura, T., Suematsu, E., 2011. Comparison of the influence of four classes of HIV antiretrovirals on adipogenic differentiation: the minimal effect of raltegravir and atazanavir. J. Infect. Chemother. : official journal of the Japan Society of Chemotherapy 17, 183–188. https://doi.org/10.1007/s10156-010-0101-5.

Navia, M.A., Fitzgerald, P.M., McKeever, B.M., Leu, C.T., Heimbach, J.C., Herber, W.K., Sigal, I.S., Darke, P.L., Springer, J.P., 1989. Three-dimensional structure of aspartyl protease from human immunodeficiency virus HIV-1. Nature 337, 615–620. https://doi.org/10.1038/337615a0.

Norwood, J., Turner, M., Bofill, C., Jenkins, C., Bebawy, S., Rebeiro, P., Hulgan, T., Raffanti, S., Haas, D., Sterling, T.R., Koethe, J., 2017. Weight gain after switch from Efavirenz-based to integrase inhibitor-based regimens. Open Forum Infect Di 4 (Suppl. 1), S433 doi:410.1093/ofid/ofx1163.1094.

Passaes, C.P., Saez-Cirion, A., 2014. HIV cure research: advances and prospects. Virology 454–455, 340–352. https://doi.org/10.1016/j.virol.2014.02.021.

Perusse, L., Chagnon, Y.C., Dionne, F.T., Bouchard, C., 1997. The human obesity gene map: the 1996 update. Obes. Res. 5, 49–61.

Poston, W.S., Jitnarin, N., Haddock, C.K., Jahnke, S.A., Day, R.S., 2014. Accuracy of self-reported weight, height and BMI in US firefighters. Occup. Med. 64, 246–254. https://doi.org/10.1093/occmed/kqu040.

Rao, G.M., Morghom, L.O., 1986. Effect of obesity on erythrocyte count and hemoglobin levels in Libyan diabetic patients. Clin. Physiol. Biochem. 4, 277–280.

Rehman, A.M., Woodd, S., Chisenga, M., Siame, J., Sampson, G., PrayGod, G., Koethe, J.R., Kelly, P., Filteau, S., 2015. Appetite testing in HIV-infected African adults recovering from malnutrition and given antiretroviral therapy. Public Health Nutr. 18, 742–751. https://doi.org/10.1017/S1368980014000718.

Roebber, J.K., Izenwasser, S., Chaudhari, N., 2015. Cocaine decreases saccharin preference without altering sweet taste sensitivity. Pharmacol. Biochem. Behav. 133, 18–24. https://doi.org/10.1016/j.pbb.2015.03.010.

Ronque, E.R.V., Werneck, A.O., Bueno, M.R.O., Cyrino, E.S., Stanganelli, L.C.R., Arruda, M., 2018. Tracking of body adiposity indicators from childhood to adolescence: mediation by BMI. PLoS One 13, e0191908. https://doi.org/10.1371/journal.pone.0191908.

Rousseeuw, P.J., Leroy, A.M., 1987. Robust Regression and Outlier Detection. Wiley, New York.

Sharma, A., Bynum, S.A., Schneider, M.F., Cox, C., Tien, P.C., Hershow, R.C., Gustafson, D., Plankey, M.W., 2014. Changes in body mass index following HAART initiation among HIV-infected women in the women's interagency HIV study. J. AIDS Clin. Res. 5. https://doi.org/10.4172/2155-6113.1000323.

Tate, T., Willig, A.L., Willig, J.H., Raper, J.L., Moneyham, L., Kempf, M.C., Saag, M.S., Mugavero, M.J., 2012. HIV infection and obesity: where did all the wasting go? Antivir. Ther. 17, 1281–1289. https://doi.org/10.3851/IMP2348.

Taylor, B.S., Liang, Y., Garduno, L.S., Walter, E.A., Gerardi, M.B., Anstead, G.M., Bullock, D., Turner, B.J., 2014. High risk of obesity and weight gain for HIV-infected uninsured minorities. J. Acquir. Immune Defic. Syndr. 65, e33–40. https://doi.org/10.1097/QAI.0000000000000010.

Watson, K.B., Frederick, G.M., Harris, C.D., Carlson, S.A., Fulton, J.E., 2015. U.S. Adults' participation in specific activities: behavioral risk factor surveillance system–2011. J. Phys. Act. Health 12 (Suppl. 1), S3–S10. https://doi.org/10.1123/jpah.2013-0521.

Westerterp, K.R., 2010. Physical activity, food intake, and body weight regulation: insights from doubly labeled water studies. Nutr. Rev. 68, 148–154. https://doi.org/10.1111/j.1753-4887.2010.00270.x.

World Health Organization, 2000. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation. World Health Organization, Geneva, pp. 253.

Yang, X., Telama, R., Leskinen, E., Mansikkaniemi, K., Viikari, J., Raitakari, O.T., 2007. Testing a model of physical activity and obesity tracking from youth to adulthood: the cardiovascular risk in young Finns study. Int. J. Obes. 31, 521–527. https://doi.org/10.1038/sj.ijo.0803459.