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Cocaine Use May Induce Telomere Shortening in Individuals with HIV Infection

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Abstract

Background—Although cocaine use may induce/accelerate HIV-associated comorbidities in HIV-infected individuals on antiretroviral therapy (ART), and that HIV itself may accelerate aging, the issue of whether cocaine use plays a role in HIV-associated aging in HIV-infected cocaine users has not been reported. The goals of this study were (1) to explore factor(s) associated with peripheral blood leukocyte telomere length, a marker of cellular replicative history, and telomere shortening in HIV-infected individuals, and (2) to assess whether cocaine use plays a role in accelerating telomere shortening in cocaine users with HIV infection.

Methods—Between June 2010 and December 2016, 147 HIV-infected participants in Baltimore, Maryland, were enrolled in a cross-sectional study investigating factor(s) associated with telomere length. Of these 147, 93 participated in a follow-up study to examine factor(s) associated with telomere shortening. Robust regression model was used to analyze cross-sectional data and the generalized estimating equation approach was used to analyze follow-up data.

Results—Cross-sectional analyses demonstrated that (1) both daily alcohol consumption and use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) were independently associated with telomere length, and cocaine use modified the associations of daily alcohol use and NNRTI use

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Contributors

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Conflict of interest

None

with telomere length. Longitudinal analyses suggested that both daily alcohol consumption and duration of NNRTI use were independently associated with telomere shortening, and (2) cocaine use induced/accelerated telomere shortening in HIV-infected individuals.

Conclusions—Our findings suggest that cocaine use may promote premature aging in HIV-infected individuals who are on ART. Our results emphasize the importance of cocaine abstinence/reduced use, which may retard HIV-associated premature aging.

Keywords

Telomere length; telomere shortening; HIV infection; Cocaine use; HIV-associated comorbidities; Premature aging

1. Introduction

Telomeres are the repetitive DNA sequences at the distal end of chromosomes that are essential for maintenance of genomic integrity by protecting chromosomal ends from exonucleolytic degradation and preventing chromosomal fusions (Blackburn, 2001; Wong and Collins, 2003; Yeh and Wang, 2016). Telomere lengths (TLs) progressively shorten with each cell division and critical telomere shortening leads to growth arrest, cell senescence, and promotes aging (Harley et al., 1990; Blasco, 2007).

TL, a marker of cellular replicative history, has been associated with chronological aging and age-related diseases (Rizvi et al., 2014). As the age of people living with HIV has risen steadily over the past 20 years, HIV/ART-associated comorbidities represent classical aging process in those without HIV infection (Justice and Falutz, 2014). Accumulating evidence demonstrates that HIV itself may accelerate the aging processes in those with the infection. Nevertheless, several lines of evidence suggest that HIV alone may not accelerate aging (Lopez-Otin et al., 2013; Wing 2016; Wing, 2017; Antiretroviral Therapy Cohort Collaboration, 2008; May et al., 2011; May et al., 2014), implying that other factor(s) may play important roles, or perhaps modify the effect of HIV infection on aging. Although crack cocaine use was reported to be associated with telomere shortening in women in a cross-sectional study (Levandowski ey al., 2016), a longitudinal study of the association between cocaine use and telomere shortening has not been reported.

This investigation had two objectives. The first was to explore factor(s) associated with peripheral blood leukocyte telomere length and telomere shortening in HIV-infected individuals, and the second to assess whether cocaine use plays a role in accelerating telomere shortening in cocaine users with HIV infection. The data were derived from an ongoing longitudinal study examining the cardiovascular complications of HIV infection and chronic cocaine use in an African American (AA) majority population in Baltimore, Maryland, USA.

2. Methods

2.1. Participants

Between June 2004 and December 2016, 982 HIV-infected men and women, with/without chronic cocaine use, in Baltimore, Maryland, were consecutively enrolled in a prospective study investigating the effects of prolonged ART exposure and chronic cocaine use on HIV/ART-associated comorbidities. The majority of study participants were recruited from the Johns Hopkins Bartlett HIV clinic. The following data were collected: (a) behavioral, demographic, and medical data, including general medical history, use of antiretroviral therapy (detailed information about duration of each ART medication and start dates and stop dates), substance use and treatment history, health services utilization, cardiovascular risk factors, and substance use and treatment history; (b) clinical and laboratory data, including immune parameters, HIV viral load, hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections, and AIDS-related and non-AIDS-related diagnoses; laboratory tests include lipid profile (total serum cholesterol, triglyceride, high density lipoprotein cholesterol (HDL), and low density lipoprotein cholesterol (LDL), glucose, high-sensitivity C-reactive protein (*hs*CRP), and endothelial function markers (von Willebrand factor, and endothelin 1); (c) biological specimen data, including a specimen repository; and (d) contrast-enhanced coronary computed tomography (CT) angiography data. Of these 982, 147 study participants were randomly selected for a cross-sectional study of the relationship between telomere length and cocaine use. Of these 147, 93 participants were included in a follow-up study of telomere shortening in relation to cocaine use. There were no statistically significant differences in age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, *hs*CRP, glucose, total cholesterol, LDL, HDL, cardiovascular risk score, and duration of ART use between those 93 and 54 who were not included in the follow-up study.

Inclusion criteria were (1) age ≥21 years; (2) HIV positivity, as determined by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot test; and (3) cocaine use: defined as use by any route for at least 6 months, administered at least 4 times/month. Infrequent users (fewer than 4 times/month, or <6 consecutive months) were not recruited. Chronic cocaine users who also used other drugs such as opiates or alcohol were included. Non-cocaine use was defined as never used cocaine or not used in the past 5 years or longer, assessment of cocaine use was based on self-reported use.

The Johns Hopkins School of Medicine Institutional Review Board approved the study protocol and consent form (IRB ID number, NA_00049791), and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines.

2.2. Assessment of relative leukocyte telomere length

Whole blood samples were collected and leukocyte deoxyribonucleic acid (DNA) was isolated from the buffy coat fraction. Quantitative polymerase chain reaction (qPCR) was used to estimate the ratio of telomeric DNA to that of a single copy gene as previously described [69], with the following modifications. Briefly, to remove potential residual PCR inhibitors, leukocyte DNA was re-purified using a DNeasy Blood and Tissue column

(Qiagen) (Bodelon at al., 2015). A total of 2 nanogram (ng) of genomic DNA was used in a 25 microliter (μl) volume for either the telomere or single copy gene (large ribosomal protein gene, RPLPO) reactions; each sample was run in triplicate. The telomere reaction mixture consisted of 1× PCR buffer, 1.5 millimolar (mM) MgCl2, 100,000 fold dilution of SyberGreen, 200 μM dNTP mix, 1 % DMSO, 100 nanomolar (nM) forward telomere primer (CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT), 900 nM reverse telomere primer (GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT), and 0.8 units (U) of Platinum Taq polymerase. The reaction proceeded for one cycle at 95 °C for 5 minutes (min), followed by 35 cycles at 95 °C for 15 seconds (s), and 54 °C for 30 s. The RPLPO reaction mixture consisted of 1× PCR buffer, 2.5 mM magnesium chloride (MgCl2), 100,000 fold dilution of SyberGreen, 200 μM deoxynucleotide triphosphate (dNTP) mix, 2 % dimethyl sulfoxide (DMSO), 250 nM forward RPLPO primer (CAGCAAGTGGGAAGGTGTAATCC), 250 nM reverse RPLPO primer (CCATTCTATCATCAACGGGTACAA), and 0.5 U of Platinum Taq polymerase. The RPLPO reaction proceeded for one cycle at 95 °C for 5 min, followed by 40 cycles at 95 °C for 15 s, 58 °C for 30 s. Each 96-well plate contained a no template negative control and two separate 5-point standard curves ranging from 0.016 to 10 nanogram (ng) using a pooled control leukocyte DNA. These standard curves allowed for the PCR efficiency to be monitored for each experimental run. Samples were repeated if the coefficient of variation (CV) of either the telomere or the β-globin reaction was equal or greater than 1% or either the telomere or the RPLPO values fell outside the range of the standard curve. The mean RPLPO cycle threshold (Ct) value and the telomere Ct value was calculated from the RPLPO and the telomere triplicate reactions, respectively. For each sample, the telomere of the experimental sample to the single copy gene telomere to single copy gene ratio (T/S ratio) (delta (change) in cycle threshold, −dCt) was calculated by subtracting the RPLPO Ct value from the telomere Ct value. The relative T/S ratio was determined by subtracting the −dCt of the corresponding pooled control leukocyte DNA. The relative T/S ratios were used in the analysis.

2.3. Statistical analysis

2.3.1. Cross-sectional analysis—Statistical analysis was performed with SAS (SAS 9.4, SAS Institute, Cary, NC). All continuous parameters were summarized by means ± standard deviations (SDs), and all categorical parameters were summarized as proportions. To compare between-group differences in demographic and clinical characteristics, lipid profiles, and other factors, the Student t-test was used for continuous variables and the Chi-square test was employed for categorical variables.

The data for this investigation included sociodemographic characteristics, medical history, behaviors, including alcohol consumption, drug use, cigarette smoking, medications, and laboratory parameters, some of which may not be normally distributed and inevitably contain “outliers”. Since outliers can be masked and very hard to detect in highly structured settings, and since conventional multiple linear regression models, based on ordinary least squares, could yield misleading results if assumption of the normal distribution is not true, a robust regression model with the least trimmed squares (LTS) estimation method was used to provide robust results in the presence of outliers (Rousseeuw and Leroy, 1987). Robust

regression fits a linear regression model that is robust in the presence of outliers or high leverage points (with “extreme” or outlying values of the independent variables). Univariate robust regression models were first fitted to evaluate the crude associations between telomere length (T/S ratio) and each individual factor, including age, sex, habitual cigarette smoking, daily alcohol consumption, daily cocaine use, *hs*CRP, systolic blood pressure, diastolic blood pressure, fasting glucose, body mass index (BMI), total cholesterol, HDL, LDL, triglycerides, ACC/AHA cardiovascular risk score according to the 2013 American College of Cardiology/American Heart Association guidelines (Goff et al., 2014), years since HIV infection was diagnosed, nadir CD4 cell count (lowest CD4 cell count ever measured), maximum HIV viral load level (log-transformed) ever measured, months of NRTI (nucleoside reverse transcriptase inhibitors) use, months of NNRTI (non-nucleoside reverse transcriptase inhibitors) use, and months of PI (protease inhibitors) use. Those factors that were significant at the $p<0.10$ level in the univariate models were put into the initial multivariate robust regression model to investigate the simultaneous confounding effects of those factors on telomere length. To examine whether cocaine use was independently associated with telomere length, the importance of each variable included in the multivariate model was evaluated with 1) an examination of the Wald statistic for each variable in the model and 2) a comparison of each estimated regression coefficient in the multivariate model with the regression coefficient from the corresponding univariate model. Those variables that ceased to make significant contributions to the models based on these two criteria were deleted in a stagewise manner, and a new model was refitted. This process of eliminating, refitting, and verifying continued until all of the variables included were statistically significant, yielding a final multivariate model. The p-values reported are two-sided, and $p <0.05$ indicates statistical significance.

2.3.2. Longitudinal analysis—The generalized estimating equation (GEE) approach was used to examine whether and how cocaine use was associated with telomere shortening (Liang and Zeger, 1986). All above-mentioned variables used in the cross-sectional analysis were evaluated in multivariate GEE models, yielding a final GEE model.

3. Results

3.1. Cross-sectional analysis

3.1.1. General characteristics—General characteristics of the study participants by cocaine use status are presented in Table 1. Of the 147 participants in this study, 125 (85.0%) were chronic cocaine users. Their mean age was 50.4 (±SD, 6.9) years, and 104 (70.6%) were males. The mean duration of cocaine use was 15.1±11.6 years. The mean duration from the HIV diagnosis was 15.4 (±SD, 7.9) years. The mean nadir CD4 count was 295 (±SD, 168) cells/mm^3, and mean maximum HIV viral load (log_{10} scale) was 4.68 (±SD, 0.75) copies/mL.

There were significant differences in cigarette smoking ($p=0.01$), daily alcohol consumption ($p=0.009$), the cardiovascular risk score assessed by the 2013 ACC/AHA guideline (Goff et al., 2014) ($p=0.002$), and duration of NRTI use ($p =0\ 04$) between cocaine users and non-users.

3.1.2. Factors associated with telomere length—Among the factors investigated with the use of univariate robust regression model, cigarette smoking, daily alcohol use, cocaine use, systolic BP, diastolic BP, and low cardiovascular risk defined by the 2013 ACC/AHA cardiovascular risk score (Goff et al., 2014) were associated with telomere length (Table 2).

The final multivariate robust regression model presented in Table 2 shows that daily alcohol use (p=0.001), daily cocaine use (p=0.02), and low cardiovascular risk defined by the 2013 ACC/AHA cardiovascular risk score (p=0.02) were independently associated with telomere length. Thus, lower cardiovascular risk was associated with longer telomere length, while daily alcohol use and cocaine use were associated with shorter telomere length.

3.1.3. Cocaine use modified the effects of alcohol, cardiovascular risk and NNRTI on telomere length—Per the results of multivariate robust regression analysis presented in Table 3, daily alcohol use, and low cardiovascular risk were not associated with telomere length in those who never used cocaine, while these two factors were significantly associated with telomere length in chronic cocaine users.

3.2. Longitudinal analysis

3.2.1. General characteristics—As shown in Table 4, baseline and follow-up characteristics of the study participants are presented. Of the 93 participants in this study, 64 (68.8%) were males. At baseline, 67 (72.0%) were daily cocaine users, and 44 (47.3%) were daily alcohol drinkers. The mean duration of cocaine use was 15.7±11.7 years. The mean time interval between two visits was 1.5±0.8 years.

There were significant differences in age (p=0.001), daily cocaine use (p<0.0001), cigarette smoking (p=0.002), hypertension (p<0.0001), systolic BP (p=0.04), diastolic BP (p=0.025), months of NNRTI use, the cardiovascular risk score assessed by the 2013 ACC/AHA guideline (Goff et al., 2014) (p=0.002), and duration of NRTI use (p =0.009) between baseline and follow-up visits. The follow-up telomere length was also significantly shorter than that at the baseline (p=0.001).

3.2.2. Factors associated with telomere shortening—By univariate GEE analysis, advanced age, and duration of NNRTI use were associated with telomere shortening (Table 5). The final GEE analysis indicated that advanced age (p=0.03), daily alcohol use (p=0.02) and duration of NNRTI use (p=0.002) were independently associated with telomere shortening (Table 5).

3.2.3. Cocaine use modified the effects of age, alcohol, and duration of NNRTI use on telomere shortening—The results of the multivariate GEE regression analysis presented in Table 6 demonstrate that advanced age, daily alcohol use and duration of NNRTI use were not associated with telomere shortening in those who had never used cocaine, while duration of NNRTI use was significantly associated with telomere length in chronic cocaine users. Since the size of the cocaine never use group was small, we also performed stratified GEE regression analysis by daily cocaine use. While both daily alcohol use and duration of NNRTI use were significantly associated with telomere shortening in

those who used cocaine daily, these two factors were not associated with telomere shortening in those who had never used cocaine or had used cocaine less frequently than daily (Table 6).

4. Discussion

4.1. Major findings

In this study, we report that (1) daily alcohol use and duration of NNRTI use were associated with telomere shortening, (2) chronic cocaine use modified the associations of alcohol use and duration of NNRTI use with telomere shortening - ART and alcohol appeared to be toxic only in cocaine users.

4.2. Factors associated with telomere length

We found that among the factors investigated, daily alcohol consumption and NNRTI use were independently associated with telomere length. Prior reports of the impact of alcohol consumption on telomere length are inconsistent. While several failed to find significant association between alcohol consumption and telomere length (Hou, et al., 2009; Mirabello, et al., 2009; Needham, et al., 2013; Sun, et al., 2012; Weischer, et al., 2014), a significant association between alcohol consumption, even minor use, and shorter telomere length in businessmen (mean age: 76 years) was reported (Strandberg, et al., 2012). However, the association between alcohol consumption and telomere length in the HIV-infected population has not been reported. An investigation of the effects of chronic binge alcohol consumption in simian immunodeficiency virus (SIV)-infected male rhesus macaques showed that chronic binge alcohol consumption increased cytotoxic T-cell activation in the intestinal mucosa and the peripheral blood, and increased senescent cells in the blood and lymph nodes, suggesting that chronic binge alcohol use may augment immune activation and immunesenescence in those with HIV infection (Katz, et al., 2015).

Our study suggests that duration of NNRTI use was independently associated with telomere length, which has not been reported previously. Antiretroviral drugs could cause mitochondrial DNA damage and alter mitochondrial morphology and function (Smith et al., 2013). A randomized clinical trial in non-symptomatic ART-naïve patients demonstrated that long-term exposure to PIs or NNRTIs is associated with disrupted glucose transport as well as disrupted lipid metabolism with increased insulin resistance (Shlay et al., 2007). A recent study indicates that efavirenz, the most widely used NNRTI, is associated with mitochondrial toxicity in its present therapeutic concentration, and that toxicity increases with longer duration of drug treatment in different types of cells (Ganta et al., 2017). The mitochondrial toxicity may contribute to premature and accelerated aging in NNRTI-treated patients (Smith et al., 2013). Further studies will be needed to confirm this finding.

4.3. Cocaine use modified the associations of cardiovascular risk, alcohol consumption and NNRTI use with telomere length

The results of this study show that the effect of alcohol consumption and NNRTI use on telomere length may depend on cocaine use status: in those who had never used cocaine, the associations of alcohol consumption, NNRTI use, and cardiovascular risk with telomere

length were not significant, while in chronic cocaine users, all of these three factors were independently associated with telomere length (Table 3). We previously reported that cocaine use may modify the association between obesity measures and myocardial triglyceride content (Lai et al., 2015), and cocaine use may also modify HIV/ART-associated myocardial and hepatic steatosis (Lai et al., 2017).

Cocaine use has been reported to accelerate cellular aging among women (Levandowski et al, 2016). However, the potential interactions between cocaine use and other factors have also not been thoroughly investigated.

4.4. Factors associated with telomere shortening

We found that in addition to age, alcohol consumption and duration of NNRTI use were independently associated with telomere shortening. These findings were not reported before and further studies are needed to confirm these findings.

4.5. Cocaine use may trigger the toxic effects of NNRTI

Perhaps the most provocative finding of this investigation is that chronic cocaine use may trigger the telomere shortening associated with NNRTI toxicity. We recently reported that long-term (>36 months, 36 was the median of ART use duration in our study population) use of ART was independently associated with a higher risk of subclinical atherosclerosis in cardiovascularly asymptomatic African Americans with HIV infection, and that cocaine use may trigger and/or exacerbate subclinical atherosclerosis in those who had used ART for longer than 36 months (Lai et al., 2016). Taken together, these studies consistently suggest that (1) although ART substantially reduces HIV/AIDS-related mortality, long-term exposure to ART may be associated with comorbidities, including subclinical atherosclerosis, myocardial and hepatic steatosis, and telomere shortening, and (2) these ART-associated comorbidities could potentially be reduced or minimized in cocaine users with HIV infection if cocaine abstinence or even reduced use could be achieved. Although cocaine is highly addictive, we have demonstrated that cocaine abstinence or reduced use can be achieved with the use of a cash-based incentive intervention, and that cocaine abstinence or reduced use lowers a marker of endothelial dysfunction and is associated with coronary plaque regression (Lai, et al., 2015; Sandfort, et al., 2017). Despite the absence of FDA-approved medications for cocaine dependence, several candidate medications have demonstrated promising results in clinical trials (Kampman, 2009; Kampman, et al., 2015; Nuijten, et al., 2016). Thus, further studies on whether reduced cocaine use leads to reduced HIV/ART-associated comorbidities and premature aging should be a high priority for managing HIV disease.

4.6. Limitations

There are some potential major limitations of this study, which merit discussion. First, because the large majority of the study participants were African Americans in the United States, the results derived from this investigation may not be generalized to other race/ethnic groups without caution. Further studies may be warranted to examine any racial/ethnic differences in the effect of cocaine use on telomere length and telomere shortening. Second, the sample size of this study is relatively small. Studies with larger sample size are needed to

confirm the findings of this investigation. Lastly, since the sample size is not large enough, we could not estimate the years of ageing attributed to cocaine use.

5. Conclusions

The study results suggest that duration of alcohol consumption and duration of NNRTI use may be associated with telomere shortening in HIV-infected individuals, although larger longitudinal studies are needed to confirm this finding.

The results of this study also indicate that cocaine use may induce the toxicity of alcohol and NNRTI in HIV-infected cocaine users. These findings, although preliminary, are sufficient to alert health care providers to inform their patients with HIV infection of the very real risks and consequences of cocaine use and, specifically, that cocaine use is associated with premature aging, and the likely consequent HIV/aging-associated comorbidities.

Cocaine use is prevalent in the U.S. and worldwide, especially in those with HIV infection. Since premature aging may lead to co- and multi-morbidities, such as cardiovascular disease, diabetes, cognitive impairment, and osteoporosis (Guaraldi, et al., 2011), and since abstinence from cocaine use or even reduced cocaine use can be achieved in African Americans with HIV infection, a randomized clinical trial should be conducted to address the important issue of whether reduced cocaine use improves HIV/AIDS-associated premature aging.

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Highlights

- Daily alcohol use and duration of NNRTI use were independently associated with telomere shortening in HIV-infected individuals Duration of PI use is independently associated with hepatic triglyceride in cocaine users, but not in cocaine never-users.
- Cocaine use modified the associations of alcohol use and duration of NNRTI use with telomere shortening.
- Health care providers to inform their patients with HIV infection of the very real risks and consequences of cocaine use and, specifically, that cocaine use is associated with premature aging, and the likely consequent HIV/aging-associated comorbidities.

Table 1

Characteristics of 147 HIV-infected participants by cocaine use status *

Characteristic	Never use cocaine	Chronic cocaine use	Total	P-value
	N=22	N=125	N=147	
Age (year)	50.4±6.9	53.1±6.9	52.7±6.32	0.07
African American race (%)	95.5	96.0	95.9	0.96
Male sex (%)	63.6	72.0	70.6	0.43
Cigarette smoking (%)	36.4	65.6	61.2	0.01
Daily alcohol use (%)	13.6	43.2	38.8	0.009
Daily cocaine use	0.0	72.8	61.9	
Hypertension (%)	4.5	19.2	17.0	0.09
Diabetes (%)	4.6	8.9	8.2	0.50
BMI (kg/m^2)	26.0±6.7	27.9±6.1	27.4±6.4	0.32
Systolic BP (mm Hg)	118±15	122±17	121±17	0.32
Diastolic BP (mm Hg)	70±9	74±25	74±23	0.11
hsCRP (mg/dL)	5.3±7.4	4.7±6.5	4.6±6.6	0.57
Total cholesterol (mg/dL)	174±49	171±45	172±46	0.80
LDL-C (mg/dL)	94±38	87±40	88±40	0.45
HDL-C (mg/dL)	55±21	57±22	56±22	0.69
Triglycerides (mg/dL)	127±71	146±115	143±110	0.29
The 2013 risk (%)	6.0±4.7	10.0±7.4	9.4±7.2	0.002
Low 2013 risk	63.4	42.4	45.6	0.065
Years since HIV was diagnosed	17.7±8.6	14.4±7.6	15.4±7.9	0.13
CD4 nadir ($cells/mm^3$)	295±168	194±129	204±136	0.12
Maximum HIV RNA (copies/mL), log_{10} scale	4.68±0.75	4.67±1.00	4.47±1.0	0.98
Months of ART use	100.0±97.3	62.5±66.6	68.1±72.8	0.09
Months of NRTI use	95.8±99.8	46.9±59.1	54.2±68.6	0.04
Months of NNRTI use	24.9±65.5	10.2±26.2	12.4±35.1	0.31
Months of PI use	74.6±95.8	44.0±64.7	48.6±70.7	0.16
Telomere length (T/S ratio)	0.93±0.28	0.77±0.21	0.79±0.23	0.02

* Mean (±standard deviation) for continuous variables, proportion (%) for categorical variables.

Abbreviations: BMI, body mass index (kg/m^2); hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; glucose, fasting glucose; the 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., 2014), low 2013 risk, the 2013 risk<0.075% (Goff et al., 2014), CD4 nadir, the lowest CD4 cell count recorded, maximum HIV RNA, the highest HIV viral load level recorded, ART, antiretroviral therapy, NRTI, *nucleoside reverse transcriptase inhibitor, NNRTI, non-nucleoside reverse transcriptase inhibitor, PI, protease inhibitor.*

Table 2

Factors associated with telomere length (T/S ratio), robust regression analyses*

Characteristic	Univariate model	Initial multivariate model	Final multivariate model
	Regression	Regression	Regression
	coefficient (95%CI) p-value	coefficient (95%CI) p-value	coefficient (95%CI) p-value
Age (year)	−0.0025(−0.0079, 0.0028) 0.36		
Male sex (%)	−0.0012(−0.0749, 0.0724) 0.97		
Cigarette smoking	−0.1222(−0.2130,−0.0314) 0.008	−0.0292(−0.1240,0.0656) 0.54	
Daily alcohol use	−0.1143(−0.1813,−0.0473) 0.0008	−0.1125(−0.1829,−0.0422) 0.002	−0.1109(−0.1778,−0.0441) 0.001
Cocaine use	−0.1126(−0.2091,−0.0161) 0.02	−0.0607(−0.1320,0.0105) 0.09	−0.0781(−0.1454,−0.0108) 0.02
Daily cocaine use	−0.0692(−0.1373,−0.0012) 0.046		
BMI (kg/m^2)	0.0018(−0.0093, 0.0129) 0.75		
Systolic BP (mm Hg)	−0.0019(−0.0039, 0.0001) 0.06	−0.0015(−0.0038,0.0008) 0.21	
Diastolic BP (mm Hg)	−0.0028(−0.0059, 0.0003) 0.08	0.0001(−0.0014,0.0017) 0.88	
hsCRP (mg/dL)	0.0022(−0.0027,0.0071) 0.38		
Glucose (mg/dL)	−0.0006(−0.0023, 0.0010) 0.46		
Total cholesterol (mg/dL)	0.0000(−0.0007, 0.0008) 0.93		
LDL-C (mg/dL)	0.0000(−0.0008, 0.0009) 0.91		
HDL-C (mg/dL)	−0.0011(−0.0026, 0.0005) 0.18		
Triglycerides (mg/dL)	−0.0001(−0.0005, 0.0004) 0.72		
The 2013 risk (%)	−0.4600(−0.9312, 0.0111) 0.055		
Low 2013 risk	0.0759(0.0085, 0.1433) 0.027	0.0585(−0.0168,0.1338) 0.13	0.0771(0.0116,0.1427) 0.02
Years since HIV was diagnosed	0.0044(−0.0029, 0.0117) 0.24		
CD4 nadir ($cells/mm^3$)	−0.0003(−0.0008, 0.0002) 0.23		
Maximum HIV RNA (copies/mL, $\log_{10}$ scale)	−0.0228(−0.0894, 0.0438) 0.50		
Months of NRTI use	−0.0001(−0.0006, 0.0004) 0.80		
Months of NNRTI use	0.0003(−0.0007, 0.0013) 0.60		

Characteristic	Univariate model	Initial multivariate model	Final multivariate model
	Regression	Regression	Regression
	coefficient (95%CI) p-value	coefficient (95%CI) p-value	coefficient (95%CI) p-value
Months of PI use	−0.0002(−0.0006, 0.0003) 0.50		

*Abbreviations: BMI, body mass index (kg/m^2); hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; glucose, fasting glucose; the 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., 2014), low 2013 risk, the 2013 risk<0.075% (Goff et al., 2014), CD4 nadir, the lowest CD4 cell count recorded, maximum HIV RNA, the highest HIV viral load level recorded, ART, antiretroviral therapy, NRTI, *nucleoside reverse transcriptase inhibitor, NNRTI, non-nucleoside reverse transcriptase inhibitor, PI, protease inhibitor.*

Table 3

Factors associated with telomere length (T/S ratio) by cocaine use status, robust regression analyses *

Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
Never cocaine use (N=22)			
Daily alcohol use	−0.0510(−0.4024, 0.0305) 0.77	−0.0548(−0.4210, 0.3114) 0.77	
Low 2013 risk	0.0223(−0.2287, 0.2734) 0.86	0.0586(−0.2111, 0.3283) 0.67	
NNRTI use	0.1759(−0.1020, 0.4538) 0.21	0.1983(−0.1029, 0.4995) 0.20	
Chronic cocaine use (N=125)			
Daily alcohol use	−0.1118(−0.1801,−0.0435) 0.001	−0.1174(−0.1819,−0.0529) 0.0004	−0.1174(−0.1819,−0.0529) 0.0004
Low 2013 risk	0.0884(0.0187, 0.1581) 0.01	0.0917(0.0270, 0.1563) 0.005	0.0917(0.0270, 0.1563) 0.005
NNRTI use	0.1007(0.0103, 0.1910) 0.029	0.0865(0.0032,0.1699) 0.04	0.0865(0.0032,0.1699) 0.04

* low 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk≤7.5% (Goff et al., 2014),

NNRTI, *non-nucleoside reverse transcriptase inhibitor*.

Table 4

Baseline and follow-up characteristics of 93 HIV-infected participants*

Characteristic	Baseline (N=93)	Follow-up (N=93)	P-value
Age (year)	52.8±7.3	54.2±7.0	0.001
African American race (%)	95.7	95.7	-
Male sex (%)	68.8	68.8	-
Daily cocaine use (%)	72.0	75.3	<0.0001
Cigarette smoking (%)	64.5	67.7	0.002
Daily alcohol use (%)	47.3	30.1	0.059
Hypertension (%)	21.5	27.0	<0.0001
Diabetes (%)	4.4	4.4	-
BMI (kg/m^2)	26.9±6.0	27.0±7.1	0.94
Systolic BP (mm Hg)	123±18	127±19	0.04
Diastolic BP (mm Hg)	73±12	76±12	0.025
hsCRP (mg/dL)	4.5±6.5	6.3±10.4	0.05
Glucose (mg/dL)	87±39	87±17	0.98
Total cholesterol (mg/dL)	171±45	169±35	0.59
LDL-C (mg/dL)	87±39	87±32	0.83
HDL-C (mg/dL)	59±23	58±20	0.81
Triglycerides (mg/dL)	133±84	118±57	0.11
The 2013 risk (%)	10.1±7.6	10.4±7.4	0.002
Low 2013 risk (%)	39.8	40.9	0.06
Months of ART use	52.7±70.8	74.4±80.5	0.38
Months of NRTI use	35.8±70.8	45.1±60.0	0.28
Months of NNRTI use	5.9±21.6	16.2±39.2	0.009
Months of PI use	35.7±64.8	49.6±78.9	0.15
Telomere length (T/S ratio)	0.71±0.16	0.64±0.17	0.001

*Mean ± standard deviation for continuous variables, proportion (%) for categorical variables.

Abbreviations: BMI, body mass index (kg/m^2); hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; glucose, fasting glucose; the 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., 2014), low 2013 risk, the 2013 risk<0.075% (Goff et al., 2014), CD4 nadir, the lowest CD4 cell count recorded, maximum HIV RNA, the highest HIV viral load level recorded, ART, antiretroviral therapy, NRTI, *nucleoside reverse transcriptase inhibitor, NNRTI, non-nucleoside reverse transcriptase inhibitor, PI, protease inhibitor.*

Table 5

Factors associated with telomere shortening, GEE regression analyses*

Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
Age (year)	−0.0046(−0.0046, −0.0004) 0.03	−0.0033(−0.0081, 0.0016) 0.19	−0.0045(−0.0087,−0.0004) 0.03
Male sex (%)	−0.0012(−0.0597, 0.0620) 0.97		
Cigarette smoking	−0.0443(−0.1252,−0.0365) 0.28		
Daily alcohol use	−0.0442(−0.0917, 0.0032) 0.07	−0.0506(−0.0998, −0.0015) 0.043	−0.0547(−0.1017,−0.0077) 0.02
Cocaine use	−0.0947(−0.2327,−0.0432) 0.18		
Daily cocaine use	−0.0428(−0.1062, 0.0205) 0.19		
BMI (kg/m^2)	0.0032(−0.0009, 0.0073) 0.12		
Systolic BP (mm Hg)	−0.0006(−0.0018, 0.0007) 0.37		
Diastolic BP (mm Hg)	−0.0016(−0.0033, 0.0001) 0.06	−0.0009(−0.0032, 0.0014) 0.44	
hsCRP (mg/dL)	0.0012(−0.0015, 0.0039) 0.38		
Glucose (mg/dL)	− 0.0003(−0.0016, 0.0009) 0.60		
Total cholesterol (mg/dL)	0.0003(−0.0005, 0.0011) 0.50		
LDL-C (mg/dL)	0.0005(−0.0003, 0.0013) 0.22		
HDL-C (mg/dL)	−0.0010(−0.0021, 0.0002) 0.09	−0.0005(−0.0017, 0.0007) 0.39	
Triglycerides (mg/dL)	0.0002(−0.0003, 0.0007) 0.49		
The 2013 risk (%)	−0.3250(−0.6693, 0.0193) 0.06	−0.0738(−0.5558, 0.4082) 0.76	
Low 2013 risk	0.0296(−0.0249, 0.0841) 0.29		
Years since HIV was diagnosed	0.0044(−0.0031, 0.0018) 0.25		
CD4 count at baseline ($cells/mm^3$)	0.0000(−0.0001, 0.0002) 0.62		
HIV RNA at baseline (copies/mL, $\log_{10}$ scale)	−0.0044(−0.0315, 0.0228) 0.75		
Months of ART use	− 0.0002(−0.0004, 0.0001) 0.16		
Months of NRTI use	−0.0000(−0.0004, 0.0003) 0.90		
Months of NNRTI use	−0.0007(−0.0011, −0.0002) 0.002	−0.0007(−0.0011,−0.0002) 0.005	−0.0007(−0.0011,−0.0003) 0.002

Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
Months of PI use	−0.0000(−0.0003, 0.0002) 0.85		

*Abbreviations: BMI, body mass index (kg/m^2); hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; glucose, fasting glucose; the 2013 risk, cardiovascular risk defined by the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (Goff et al., 2014), low 2013 risk, the 2013 risk<0.075% (Goff et al., 2014), CD4 nadir, the lowest CD4 cell count recorded, maximum HIV RNA, the highest HIV viral load level recorded, ART, antiretroviral therapy, NRTI, *nucleoside reverse transcriptase inhibitor, NNRTI, non-nucleoside reverse transcriptase inhibitor, PI, protease inhibitor.*

Table 6

Factors associated with telomere shortening by cocaine use status, GEE analyses*

Characteristic	Univariate model Regression coefficient (95%CI) p-value	Initial multivariate model Regression coefficient (95%CI) p-value	Final multivariate model Regression coefficient (95%CI) p-value
Never cocaine use (N=6)			
Age	−0.0104(−0.0267, 0.0059) 0.21		
Daily alcohol use	0.0353(−0.1430. 0.2136) 0.70		
Duration of NNRTI use	0.0027(−0.0013, 0.0067) 0.18		
Chronic cocaine use (N=87)			
Age	−0.0032(−0.0077, 0.0013) 0.16		
Daily alcohol use	−0.0377(−0.0849, 0.0096) 0.12		
Duration of NNRTI use	−0.0008(−0.0012,−0.0004) <0.0001	−0.0008(−0.0012,−0.0004) <0.0001	−0.0008(−0.0012,−0.0004) <0.0001
Never cocaine use or used less than daily (N=26)			
Age	−0.0074(−0.0143,−0.0005) 0.04	−0.0074(−0.0143,−0.0005) 0.04	−0.0074(−0.0143,−0.0005) 0.04
Daily alcohol use	−0.0411(−0.1388, 0.0566) 0.41		
Duration of NNRTI use	0.0007(−0.0009, 0.0023) 0.40		
Daily cocaine use (N=67)			
Age	−0.0018(−0.0061,0.0025) 0.42		
Daily alcohol use	−0.0497(−0.1048, 0.0053) 0.08	−0.0591(−0.1150,−0.0031) 0.04	−0.0591(−0.1150,−0.0031) 0.04
Duration of NNRTI use	−0.0008(−0.0012, −0.0004) <0.0001	−0.0009(−0.0013,−0.0005) <0.0001	−0.0009(−0.0013,−0.0005) <0.0001

*Abbreviations: *NNRTI, non-nucleoside reverse transcriptase inhibitor.*