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Cocaine Reduces Thymic Endocrine Function: Another Mechanism for Accelerated HIV Disease Progression

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Abstract

Thymulin is a thymic peptide important for the maturation and differentiation of immature thymocytes, which have been found to be depressed in patients with low-level $CD4^+$ cell recovery despite viral control. Substance use is associated with faster progression of HIV disease, which has been ascribed to poor adherence to antiretroviral medication. Recent findings of an association between cocaine use and decline in $CD4^+$ cell counts independent of antiretroviral adherence indicate alternative mechanisms for disease progression. We evaluated the relationship between thymulin activity, $CD4^+$ and $CD8^+$ cell counts and the $CD4^+/CD8^+$ ratio, and the covariate effects of substance use cross-sectionally in 80 HIV^+ active substance users and over 12 months in 40 participants. Thymulin activity was analyzed in plasma using a modification of the sheep rosette bioassay. Thymulin activity was negatively associated with cocaine use ($\beta = -0.908$,95% CI: -1.704, -0.112; $p = 0.026$). Compared to those who do not use cocaine, cocaine users were 37% less likely to have detectable thymulin activity (RR = 0.634, 95% CI: 0.406, 0.989 $p = 0.045$) and were 75 times more likely to show a decrease in thymulin activity (OR = 74.7, 95% CI: 1.59, 3519.74; $p = 0.028$) over time. $CD4^+$ cell count was positively associated with thymulin activity ($\beta = 0.127$, 95% CI: 0.048,0.205; $p = 0.002$), detectable thymulin activity was 2.32 times more likely in those with a CD4 cell count $\geq$200 cells/μl (RR = 2.324, 95% CI: 1.196, 4.513, $p = 0.013$), and those with an increase in CD4 cell counts were more likely to show an increase in thymulin activity (OR = 1.02, 95% CI: 1.00, 1.034; $p = 0.041$) over time. Thymulin activity is predictive of HIV disease progression and is depressed in cocaine users independent of antiretroviral treatment (ART) and HIV viral load. Understanding the mechanisms for accelerated HIV disease progression provides opportunities to find alternative strategies to counteract immunosuppression.

Introduction

HIV infection is prevalent among substance abusers, and substance use is associated with faster progression to AIDS.[1–6] Use of cocaine has been associated with increased risk of progression to AIDS, AIDS-related death, and defining illnesses, faster decline of CD4 cell count, and higher HIV-1 viral load.[7–9] The effect of cocaine use on faster progression of HIV disease has been ascribed to poor antiretroviral medication adherence and decreased compliance with treatment-monitoring visits.[10–13] More recent studies, however, have shown a relationship between cocaine use and a decline of $CD4^+$ cells to $\leq$200 cells/μl that was independent of antiretroviral medication adherence.[14,15]

Cocaine is generally recognized as an immunosuppressant that results in a reduction in the number and distribution of immune cells, thymocytes, and white blood cells.[16] Numerous murine studies have shown a decrease in thymus weight, total number of thymocytes, number of immature thymocytes, and T cell response to mitogens with exposure to cocaine.[17–19] The thymic atrophy associated with cocaine appears to be due to a direct inhibition on thymocyte DNA synthesis and increased thymocyte apoptosis.[19,20] Studies with murine AIDS models have shown that cocaine use may further potentiate changes in $CD4^+$ and $CD8^+$ cell counts that occur with HIV infection.[21] The direct effect of cocaine on immune function, and the potentiation of effects of HIV on immune parameters, and on disease progression independent of antiretroviral therapy (ART) adherence, suggests that cocaine may accelerate HIV disease through an additional mechanism unrelated to antiretroviral adherence.

The thymus is directly affected by HIV infection and plays a role in immune recovery upon initiation of ART. HIV infection leads to a decrease in thymic function and the thymus

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itself can be infected by HIV.[22,23] Although progressive thymic involution occurs throughout life, the thymus has been shown to be functional well into adulthood.[24,25] Upon initiation of ART, the thymus is the primary site of *de novo* T cell production. Recovery of thymic output has been demonstrated with initiation of ART using both the measurement of excisional DNA products of TCR-gene rearrangement (TREC) in naive $CD4^+$ cells[26] and through thymic scan.[27] TREC number increased in naive $CD4^+$ cells and greater thymic tissue was correlated with higher naive T cell counts with initiation of ART. Additionally, decreased thymic volume predicts a faster decline of the $CD4^+$ cell count to ≤ 350 cells/μl in HIV^+ patients who had stopped ART.[28]

In addition to thymus volume and naive T cell output, thymic endocrine function may play a role in the failure to restore $CD4^+$ cell counts in patients on ART who attain viral control.[29] Thymulin is produced exclusively by the reticuloepithelial cells of the thymus and is an important factor for evaluating thymic endocrine activity.[30] Thymulin is biologically active only when coupled with zinc in an equimolar ratio, and functions in T cell differentiation within the thymus and systemically.[31] Active thymulin modulates cytokine release by peripheral blood mononuclear cells (PBMCs), induces proliferation of $CD8^+$ T cells in combination with interleukin (IL)-2, and the expression of the IL-2 receptor on T cells.[32,33] A progressive decline of circulating zinc-bound active thymulin levels has been demonstrated in HIV and AIDS.[34,35] The relationship between substance use and thymulin activity in the context of HIV disease, however, has not been clearly elucidated. This study evaluated the relationship between levels of active thymulin, immune parameters of HIV disease progression, and substance use.

Materials and Methods

Study design

A retrospective, cross-sectional analysis of the relationship between thymulin activity and $CD4^+$ and $CD8^+$ cell counts and the $CD4^+/CD8^+$ ratio was performed in 80 HIV-seropositive men and women randomly selected from a cohort of 222 HIV-infected drugs users who had participated in an 18-month nutritional study conducted on a cohort of 222 HIV-infected drug users recruited between March 2002 and December 2005.[36] The independent and covariate effects of substance use on these parameters were also investigated. The relationship between change of thymulin activity over a 12-month period and change in $CD4^+$ cell count was evaluated in 40 participants randomly selected from the original 80. Thymulin activity was analyzed in plasma samples stored at -80°C from HIV-seropositive participants, who were age 18 years or older, and were active substance users (determined by urine drug toxicology). The study protocol was approved by the Florida International University Internal Review Board, and the Animal Care and Use Committee.

Participant examination protocol

Participant information was available from the prospective study cohort that had the following examination protocol. Demographics were collected at the initial screening visit and participants were followed for 18 months. Assessment visits were conducted every 6 months at which time a physical examination and medical history were performed by a nurse practitioner. The medical history included a medication history of all prescribed medications used in the previous 6 months, including ART. Participants were asked to bring the medications they were currently taking to each assessment visit, and the type of antiretrovirals and schedule of intake, as well as changes in ART prescription or intake in the past 6 months (initiation, switches, and discontinuation) were identified through review of records from the previous 6 month interview. Participants were asked if they had been taking ART as prescribed in the previous 6 months. For analysis, the participants were classified at each study visit as reporting adherence with ART. Every 6 months, blood was drawn for assessment of $CD4^+$ and $CD8^+$ cell counts and HIV viral load. Questionnaires on history of alcohol and drug use in the preceding 6 months were also administered at this time.

Evaluation of alcohol and illicit drug use

A drug use questionnaire was administered verbally that detailed the type, frequency, mode of administration, quantity of alcohol, and illicit drug use in the previous 6 months. At the same visit, urine samples were taken and analyzed for the presence of barbiturates, benzodiazepines, cannabinoids, hallucinogens, morphine, and amphetamines.

Cytometric assays

Lymphocyte phenotype was determined with a four-color immunophenotyping panel of monoclonal antibodies. Differential counts were determined using a Coulter MaxM hematology instrument and corroborated with cytocentrifuge smears. Viral load was obtained by the reverse transcriptase polymerase reaction using the Roche Amplicor reagents and protocol. All assays were performed by LabCorp. (Tampa, Florida).

Assay of thymulin activity

Plasma samples frozen at -80°C from the 12 month assessment visit of the 80 participants, and from the baseline assessment visit of 40 of these same participants, were analyzed for thymulin activity using a modification of the rosette inhibition assay described by Bach.[37] Thymulin exists in two forms in the plasma, an inactive form and a zinc-bound active form. The rosette inhibition bioassay is the only assay currently available that is specific for the zinc-bound active form of thymulin. This technique has been shown to be specific for, and a valid test of, thymulin activity because the assay is unaffected by other thymic hormones, and the rosette-inducing activity is removed completely by passing plasma samples through an antithymulin immunoabsorbent. The bioassay has a sensitivity allowing for the detection of 1 pg/ml synthetic thymulin (Sigma, USA). Reliability of the bioassay has been demonstrated as two consecutive blind assays showed a difference of no more than one $\log_2$ in all samples.[31]

Briefly, plasma samples were thawed and ultrafiltered at 4°C to remove nonspecific high-molecular-weight (MW) molecules of extrathymic origin that have been shown to inhibit the assay.[38] Spleen cells from male C57BL/6 mice that had been thymectomized at 5 weeks of age were collected and suspended in Hanks' solution at a concentration of 4.3×10^7 cells/ml. Duplicate 60-μl aliquots of serial $\log_2$ dilutions of

plasma filtrate made with Hanks' solution were mixed with 60 μl of spleen cells, and 60 μl of azathioprine solution at a concentration of 0.02 mg/ml were incubated in a water bath at 37°C for 75 min. A 1% sheep red blood cell suspension was added and allowed to incubate 5 min at 37°C, after which the cells were centrifuged at 4°C at 150×g for 5 min and placed on ice. Cells were gently resuspended and rosette-forming cells counted in a hemocytometer. The maximum dilution that induced azathioprine sensitivity in 50% of the rosette-forming spleen cells was taken as the active thymulin titer, and was expressed as $\log_2$ of the inverse of the dilution.

Statistical analysis

Descriptive statistics were used to characterize the population. Data were assessed for normality of distribution, and transformations performed on variables when appropriate. HIV viral load was log transformed and the square root of $CD4^+$ and $CD8^+$ cell counts taken to normalize the distribution. Undetectable thymulin activity levels were given a value of 1 for univariate and linear regression analyses.

Univariate analyses of the association between the active thymulin titer and $CD4^+$ cell counts, $CD8^+$ cell counts, and the $CD4^+/CD8^+$ ratio were performed on data from the 12-month visit using Pearson's correlations. Significant differences in the mean active thymulin titer, $CD4^+$ and $CD8^+$ cell counts, and the $CD4^+/CD8^+$ ratio by single and combination drug use were evaluated using analysis of variance (ANOVA) and the Mann–Whitney U test. For these analyses, participants were classified as a "user" of a particular drug or drug combination if they reported any use of that drug or drug combination within the past 6 months, and a "nonuser" if they reported no use of that drug or drug combination within the past 6 months.

Linear regression models were constructed to further evaluate the relationship between the active thymulin titer and the immune parameters. A regression model was constructed for those immune parameters that showed a correlation with the active thymulin titer at a significance of $p \leq 0.25$. Additionally, models were constructed that included those drugs and drug combinations that showed a relationship with thymulin activity or immune parameters in the ANOVA with a significance of $p \leq 0.25$. HIV viral load, age, gender, and antiretroviral use at the 12-month visit were included in all models as control variables. Relative risk analysis was performed on immune parameters and illicit drugs showing a significant relationship with thymulin activity in the linear regression models. For this analysis, binary variables were created. Thymulin was categorized as detectable and undetectable activity, and CD4 cell count was categorized as $<$200 cells/μl and $\geq$200 cells/μl. Relative risk analysis was controlled for race, ART use, and change in viral load.

Change in thymulin activity between the baseline and 12-month assessment visits and the relationship with change in $CD4^+$, $CD8^+$ cell count, and $CD4^+/CD8^+$ ratio was evaluated. ANOVA was used to assess differences in mean change in immune parameters in relation to change in thymulin activity, and logistic regression models were controlled for alcohol and drug use, age, antiretroviral use, and change in HIV viral load. The association of change in thymulin activity with substance use was evaluated using Pearson's chi-square. For these analyses, participants were categorized as a "consistent user" of a particular drug if they indicated that they were using the drug at both the baseline visit and the 12-month visit, as an "inconsistent user" if they reported use at one but not the other visit, and as a "nonuser" if they reported no use of the particular drug at either visit. Drugs showing a relationship with change in thymulin activity with a significance of $p \leq 0.25$ were included in the logistic regression models. To assess model fit, the Hosmer-Memeshow Test of Goodness-of-Fit was performed. Standardized residuals were calculated to test for the effect of outliers. A residual larger than 3.0 or smaller than -3.0 was considered an outlier. All analyses were conducted using the SPSS-15 for Windows statistical software package (Pearson Prentice Hall, Inc.)

Results

Population characteristics

This was a population of active alcohol and illicit drug users randomly selected from a larger cohort of participants in a previously performed nutritional study, the majority of whom were black (82.5%) and male (68%). Over half were homeless (53%). The median $CD4^+$ cell count at the 12-month visit was 292 cells/μl (6, 1173) with 67.5% of participants reporting ART at that time (Table 1). Over half of the participants reported receiving ART at both the baseline and the 12-month visit ($N = 46$, 57.5%), with 20% reporting ART at one or the other timepoints and 21% reporting no ART at either timepoint.

Substance use patterns

The major substances of use in this population were alcohol, marijuana, and cocaine, with minimal use of heroin and speedball. The percentages of participants using these substances at the baseline and 12-month visits, respectively, were 25% and 34% for alcohol, 7% and 15% for marijuana, and 69% and 50% for cocaine. Cocaine was used most consistently with 92.5% of those using cocaine at the 12-month visit also having used it at baseline. Alcohol and marijuana showed relatively consistent use as well at 78% and 65%, respectively. Approximately one-third of participants who reported using alcohol and cocaine at the 12-month visit reported using

Table 1. Month 12 Population Statistics ($N = 80$)

Characteristic	*Statistic*
Mean age (years, ± SD)	43.1 ± 6.7
Male	68%
Race	
White, non-Hispanic	5%
White, Hispanic	12.5%
Black	82.5%
Homeless	53%
Gross monthly income[a]	$0 ($0, $1260)
Level of education (years)[a]	12 (0,16)
Antiretroviral use	67.5%
$CD4^+$ cells (cells/μl)[a]	292 (6, 1173)
$CD8^+$ cells (cells/μl)[a]	701.5 (150, 2993)
CD4/CD8 ratio (±SD)	0.497 (±0.340)
Viral load (copies/ml)[a]	7120 (399, 750,001)
Log_2 active thymulin titer (±SD)	2.37 (±1.5)

[a]Median (min, max).

Table 2. Participant Drug Use at 12-Month Assessment Visit and Consistency of Use Across Time

Substance	*Percentage users* (N = *80)*	*Proportion of heavy use*[a]	*Proportion of consistent use*[b]
Alcohol	40% ($N=32$)	34.4% ($N=11$)	78.1% ($N=25$)
Marijuana	32.5% ($N=26$)	15.4% ($N=4$)	65.4% ($N=17$)
Cocaine	50% ($N=40$)	27.5% ($N=11$)	92.5% ($N=37$)
Heroin	3.75% ($N=3$)	66.7% ($N=2$)	33.3% ($N=1$)
Speedball	2.5% ($N=2$)	50% ($N=1$)	50% ($N=1$)

[a]Proportion of users that used the substance more than daily.
[b]Proportion of substance users at 12 months also reporting use at baseline.

heavily, defined as more than once a day (Table 2). The most common drug combinations were alcohol and marijuana ($N=12$, 16.25%), alcohol and cocaine ($N=22$, 27.5%), and marijuana and cocaine ($N=16$, 20%).

Relationship between the active thymulin titer, immune parameters, and substance use

Univariate correlations between the active thymulin titer and immune parameters showed a significant direct correlation with $CD4^+$ cell counts ($r=0.298$, $p=0.008$) and nonsignificant direct correlations with $CD8^+$ cell count and the $CD4^+/CD8^+$ cell ratio (Table 3).

Analysis of differences in the mean active thymulin titer and immune parameters by substance use showed that only cocaine use was significantly associated with a lower mean active thymulin titer (2.775 vs. 1.975, $p=0.042$). There were no significant associations between any other substance of abuse or substance combination and thymulin activity or immune parameters. Cocaine users showed a lower mean $CD8^+$ cell count but it was not significant (899.5 vs. 738.4, $p=0.076$) (Table 4).

Separate linear regression models were constructed for the $CD4^+$ cell count, $CD8^+$ cell count, and the $CD4^+/CD8^+$ cell ratio on the active thymulin titer. Cocaine was included as a covariate, with HIV viral load, age, gender, and ART use as control variables. $CD4^+$ cell count was a significant positive predictor and cocaine use a significant negative predictor of the active thymulin titer, with a model including both of these parameters explaining 18.8% of the variance in thymulin activity. There was no significant relationship between $CD8^+$ cell count or the $CD4^+/CD8^+$ ratio and the active thymulin titer (Table 5). Relative risk analysis showed that individuals who used cocaine were 37% less likely to have detectable thymulin activity (RR = 0.634, 95% CI: 0.406, 0.989, $p=0.045$) compared to those who did not use cocaine. Detectable thymulin activity was 2.32 times more likely in those with a CD4 cell count ≥ 200 cells/μl (RR = 2.324, 95% CI: 1.196, 4.513, $p=0,013$) compared to those with CD4 cell counts <200 cells/μl.

Table 3. Unadjusted Correlation Between Log_2 Active Thymulin Titer and Immune Parameters

Immune parameter	*Pearson correlation coefficient (r)*	*Significance (2-tailed)*
$CD4^+$ cell count	0.298	0.008
$CD8^+$ cell count	0.160	0.162
$CD4^+/CD8^+$	0.137	0.230

Relationship between change in thymulin activity, change in immune parameters, and substance use

Analysis of variance of the difference in mean change in immune parameters over 12 months by change in thymulin activity showed decreasing $CD4^+$ cell count with decreasing thymulin activity. There was a significantly greater decline in $CD4^+$ cell count (–46.46 vs. +73.85, $p=0.034$) and $CD8^+$ cell count (–175.15 vs. +198.92, $p=0.040$) between those with a decrease in thymulin activity compared to those with an increase in thymulin activity. Change in the $CD4^+/CD8^+$ cell ratio was not significantly different for the change in thymulin categories (Table 6).

Change in thymulin activity by substance use was evaluated using Chi square. Consistent cocaine users ($N=21$) were more likely to have a decline in thymulin activity when compared to nonusers ($N=9$, $p=0.046$), and when compared to inconsistent and nonusers combined ($N=19$, $p=0.056$).

Logistic regression showed that individuals with an increase in $CD4^+$ cell count over the 12 months were more likely to have an increase in thymulin activity (OR = 1.02, 95% CI: 1.00, 1.044; $p=0.05$), and consistent cocaine users were 75 times more likely to show a decrease in thymulin activity compared to those who did not use cocaine consistently, independent of change in viral load, antiretroviral use, gender, age, alcohol, and marijuana (OR = 74.7, 95% CI: 1.59, 3519.74; $p=0$ .028). Change in viral load was not significantly associated with change in thymulin activity in this model. Models of change in $CD8^+$ cell count on change in thymulin activity were not significant.

Discussion

Our results show a direct relationship between thymulin activity levels and severity of HIV disease measured by $CD4^+$ cell count, and an independent association of lower thymulin activity with cocaine use. Thymulin activity levels were not significantly associated with HIV viral load. A decline in thymulin activity was associated with a decline in $CD4^+$ cell count, and consistent cocaine users were 75 times more likely to have a decline in thymulin activity over a 12-month period compared to inconsistent and nonusers combined, independent of change in viral load and antiretroviral medication use.

Cocaine is a recognized immunosuppressant and has been demonstrated in murine models to have a direct effect on the thymus.[19–21] Our results demonstrate that cocaine use is also associated with depressed thymic endocrine function. The association of cocaine use with both lower thymulin activity and a greater decline in thymulin activity over time was independent of viral load and ART. This suggests that cocaine

Table 4. Mean of Log_2 Active Thymulin Titer, $CD4^+$ and $CD8^+$ Cell Count, and $CD4^+/CD8^+$ Ratio and Viral Load by Substance Use

Drug	N	*Log_2 thymulin titer [mean (SD)]*	*$CD4^+$ cell count [mean (SD)]*	*$CD8^+$ cell count [mean (SD)]*	*$CD4^+/CD8^+$ [mean (SD)]*	*Viral load (copies/ml) [mean (SD)]*
Alcohol						
No	48	2.54 (1.88)	204.20 (29.79)	415.71 (60.64)	0.49 (0.32)	8.8E4 (1.9E5)
Yes	32	2.12 (1.56)	273.70 (48.38)	569.44 (102.27)	0.50 (0.37)	7.3E4 (1.6E5)
Marijuana						
No	54	2.43 (1.79)	359.67 (259.53)	844.63 (511.15)	0.48 (0.33)	8.6E4 (1.9E5)
Yes	26	2.27 (1.73)	318.08 (168.76)	761.42 (419.91)	0.53 (0.36)	7.5E4 (1.8E5)
Cocaine						
No	40	2.77 (1.94)[a]	364.88 (212.96)	899.50 (520.63)	0.47 (0.30)	7.1E4 (1.8E5)
Yes	40	1.97 (1.48)	327.57 (252.87)	738.42 (433.20)	0.53 (0.38)	9.4E4 (1.9E5)
Alcohol and marijuana						
No	67	2.45 (1.78)	357.53 (243.59)	832.34 (504.72)	0.51 (0.34)	8.3E4 (1.9E5)
Yes	13	2.00 (1.68)	287.38 (166.97)	739.69 (348.42)	0.45 (0.33)	8.2E4 (1.5E5)
Alcohol and cocaine						
No	58	2.57 (1.85)	347.70 (203.21)	828.25 (490.87)	0.49 (0.31)	7.9E4 (1.8E5)
Yes	22	1.86 (1.39)	341.54 (303.28)	788.00 (466.77)	0.52 (0.40)	9.1E4 (1.9E5)
Marijuana and cocaine						
No	64	2.44 (1.82)	356.14 (248.68)	858.66 (509.15)	0.48 (0.33)	8.6E4 (1.9E5)
Yes	16	2.12 (1.50)	306.00 (158.85)	655.06 (317.62)	0.56 (0.38)	6.9E4 (1.43E5)

[a]Significantly different at $p < 0.05$ (Mann–Whitney U test).

decreases thymic function through an action independent of effects of cocaine use on ART adherence or viral load.

Previous *in vitro* and animal studies have demonstrated that cocaine, as well as other substances of abuse, stimulates HIV replication in peripheral blood mononuclear cells.[39–42] Higher HIV-1 viral loads (>100,000 copies/ml) were recently reported in women from a multicohort study reporting cocaine use, as well as a higher frequency of $CD4^+$ cell counts $\leq$200 cells/μl, independent of adherence to antiretroviral treatment,[14] providing evidence of the association between cocaine use, HIV viral load, and $CD4^+$ cell counts. That cocaine may affect $CD4^+$ cell counts independently of HIV viral load is shown in a study of African-American HIV^+ women who smoked crack. This study found lower $CD4^+$ cell counts for a given HIV viral load as cocaine use increased.[43] Our data suggest that cocaine may have an independent effect on $CD4^+$ cell count through a suppressive action on thymic function that is additive to the effects of the HIV virus. These results are consistent with findings of reduced thymic function implicated in the inability to fully reconstitute the $CD4^+$ cell count in patients who have complete HIV RNA replication control and are on ART.[44]

Our findings of an increase in thymulin activity with an increase in $CD4^+$ cell count is similar to previous results from a population of HIV-infected individuals in advanced stages of the disease.[45] We did not find an association of $CD8^+$ cell counts or the CD4/CD8 ratio with thymulin activity, however. This may be explained by early findings in which TREC, the episomal fragments generated by rearrangement of T cell receptor genes during T cell maturation in the thymus,[26] correlated inversely with HIV viral load[46] and positively with $CD4^+$ cell counts and naive T cells.[46,47] The TREC-containing $CD4^+$ cells correlated with the number of naive $CD4^+$ cells, while the TREC-containing $CD8^+$ cells did not correlate with the number of naive CD8 cells in this study. Sustained proliferation of $CD8^+$ cells in response to HIV infection, which causes a consequent

Table 5. Linear Regression of $CD4^+$ Cell Count and Cocaine Use on the Active Thymulin Titer

Variable name[a]	*β*	p	*Standardized β*	*95% CI*	
Immune parameter					
$CD4^+$ (squared root)	0.127	0.002	0.457	0.048	0.205
Drug variables					
Cocaine	−0.908	0.026	−0.261	−1.704	−0.112
Control variables					
Log viral load	0.332	0.177	0.197	−0.154	0.818
Age	−0.010	0.731	−0.039	−0.068	0.048
Gender	−0.371	0.381	−0.100	−1.210	0.468
Antiretroviral	0.835	0.083	0.226	−0.112	1.781
R^2			0.188		
F			2.736		
p value			0.019		

[a]Dependent variable: log_2 active thymulin titer.

Table 6. Mean Immune Parameter Change by Active Thymulin Titer Change

Immune parameter	*Thymulin change*	N	*Mean (SD)*
Change in $CD4^+$ cell count	Decrease	13	−46.46 (167.21)[a]
	No change	14	−27.64 (129.44)
	Increase	13	73.84 (116.94)
Change in $CD8^+$ cell count	Decrease	13	−175.15 (450.12)[a]
	No change	14	−14.43 (428.41)
	Increase	12	198.92 (437.41)
Change in CD4/CD8	Decrease	13	0.077 (0.220)
	No change	14	−0.014 (0.185)
	Increase	12	0.058 (0.150)

[a]Significant difference at $p < 0.05$ between decrease and increase.

reduction in the proportion of TREC-containing $CD8^+$ cells, was proposed as the reason for the lack of an association.[48]

There is substantial evidence that cocaine use accelerates HIV disease progression. The factors affecting this acceleration appear to be a combination of lifestyle factors, adherence to antiretroviral medication, and a more direct effect of cocaine on HIV viral replication and $CD4^+$ cell depletion. Our findings demonstrate an effect of cocaine on thymic endocrine function, which offers an additional mechanism for accelerated HIV disease progression. Our study is limited due to the nonspecific measures of immune function evaluated, i.e., $CD4^+$ and $CD8^+$ cell count, and the limitations of the thymulin bioassay. The study was also unable to evaluate for significant differences in immune function with varying frequencies and quantity of drug use, alcohol and marijuana use, and the effect of drug use combinations due to the sample size. An appropriately powered, prospective study to evaluate the relationship of thymic function, measured using TREC and/or thymus volume and including other drugs of abuse, needs to be conducted to substantiate our current findings.

For HIV treatment to be successful in this population, programs that address the problem of continued cocaine use must be an integral part of the medical treatment of HIV. Programs to reduce overall drug abuse are needed because even a modest reduction in frequency of substance abuse improves antiretroviral compliance and is associated with slower HIV disease progression.[12,49] Alternative therapies to counteract the immunosuppressive effects of cocaine may have beneficial effects, although further research is needed.[50]

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Author Disclosure Statement

No competing financial interests exist.

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