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A Ten-Year Analysis of the Incidence and Risk Factors for Acute Pancreatitis Requiring Hospitalization in an Urban HIV Clinical Cohort

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Abstract

To assess the incidence of and risk factors for acute pancreatitis in HIV-infected patients in the contemporary highly active antiretroviral therapy (HAART) era, we evaluated all cases of acute pancreatitis requiring hospitalization between 1996 and 2006 in patients followed at Johns Hopkins Hospital's HIV clinic. A nested, case-control analysis was employed for initial episodes of acute pancreatitis, and conditional logistic regression was used to assess risk factors. Of 5970 patients followed for 23,460 person-years (PYs), there were 85 episodes of acute pancreatitis (incidence: 3.6 events/1000 PYs). The incidence of pancreatitis from 1996 to 2000 was 2.6 events/1000 PYs; the incidence from 2001 to 2006 was 5.1 events/1000 PYs ($p = 0.0014$, comparing rates in two time periods). In multivariate regression, factors associated with pancreatitis included female gender (adjusted odds ratio [AOR] 2.96 [1.69, 5.19]; $p = 0.001$); stavudine use (AOR 2.19 [1.16, 4.15]; $p = 0.016$); aerosolized pentamidine use (OR 6.27; [1.42, 27.63]; $p = 0.015$); and CD4 count less than 50 cells/mm³ (AOR 10.47 [3.33, 32.90]; $p = 0.001$). Race/ethnicity, HIV risk factor, HIV-1 RNA, and newer non-nucleoside reverse transcriptase inhibitors (NNRTI)- and protease inhibitor (PI)-based HAART regimens were not associated with an increased risk of pancreatitis after adjustment for the above factors. Pancreatitis remains a significant cause of morbidity in the HIV population in the HAART era. Acute pancreatitis is associated with female gender, severe immunosuppression, and stavudine and aerosolized pentamidine usage. Of note, newer antiretrovirals, particularly atazanavir, lopinavir/ritonavir, tenofovir, abacavir, and efavirenz, were not associated with an increased risk of pancreatitis.

INTRODUCTION

ACUTE PANCREATITIS is a common cause of morbidity and occasional mortality in patients infected with HIV.¹ Several retrospective studies have estimated the incidence of pancreatitis in HIV-infected individuals to be much greater than that in the general population.^{2,3} In the pre-highly active antiretroviral therapy (HAART) era, the reported incidence among HIV-infected persons has been wide-ranging. One study found an incidence of 6.7 cases per 1000 person-years (PYs) in their cohort of 939 patients followed for 7 years.² Dutta et al.³ demonstrated a much higher incidence, 140 cases per 1000 PYs, in a group of 321 patients followed for 1 year.³ A more recent study found an incidence of clinical acute pancreatitis of

6.1 per 1000 PYs, as well as a much higher rate of laboratory evidence of pancreatic abnormalities (22.3 per 1000 PYs).⁴ Chehter et al.⁵ discovered frequent pancreatic involvement (90%) in a postmortem study of AIDS-related deaths, although the majority of these patients did not have clinically apparent pancreatic disease before death.

The most common etiologies of acute pancreatitis in the HIV-infected population include alcohol, gallstones, hypertriglyceridemia, HIV-associated infections, HIV-related prophylactic medications (e.g., pentamidine), and antiretroviral medications (e.g., nucleoside reverse transcriptase inhibitors [NRTIs]).^{1,6} With the addition of protease inhibitors (PI) to the therapeutic armamentarium against HIV, several case reports of PI-associated pancreatitis have been reported in the literature.^{7–9}

The risk factors for acute pancreatitis in HIV-infected patients have not been well studied in the recent HAART era. The following study aims to describe the incidence and clinical characteristics of acute pancreatitis in HIV-infected patients and to evaluate the risk factors associated with acute pancreatitis in this population in the contemporary HAART era.

MATERIALS AND METHODS

Patients and data collection

The Johns Hopkins University AIDS Service provides longitudinal primary and subspecialty care for HIV-infected patients in the Baltimore metropolitan area. At the time of registration into the clinic, patients undergo a detailed baseline assessment with collection of demographic, social, behavioral, and clinical information; they also complete a comprehensive panel of blood tests, which are then routinely monitored at 3-month intervals.

An observational database has been maintained that includes information from all patients receiving care in this practice since 1989. Trained monitors use structured data collection forms to extract extensive information, including demographic, psychosocial, clinical, laboratory, and pharmaceutical data as well as death information from clinic charts, hospital medical records, and various institutional databases. Maintenance of the database and use of its contents for analysis of patient outcomes is approved by the Institutional Review Board of the Johns Hopkins University School of Medicine and participants provided written informed consent.

For this study, we identified all cohort participants who were admitted to Johns Hopkins Hospital between January 1, 1996 and May 31, 2006 with suspected acute pancreatitis. Cases were identified using ICD-9 codes for diseases of the pancreas (577), acute pancreatitis (577.0), or elevated serum amylase or lipase enzyme levels (790.5) from hospital discharges. Charts were systematically reviewed by one of the authors (D.R.). The clinical characteristics associated with each episode of pancreatitis were recorded on structured data collection forms.

Definitions and statistical analysis

The primary outcome of interest was a clinical diagnosis of acute pancreatitis requiring hospitalization. Consistent with past research,^{10,11} a case of acute pancreatitis was defined as: a clinical history typical of acute pancreatitis with supporting biochemical evidence of pancreatitis (elevated serum amylase or lipase ≥ 3 times the upper limit of normal). In patients with multiple episodes of pancreatitis, only the first episode was included in the analysis.

For our analysis, HIV transmission risk factors included injection drug use (IDU), men who had sex with men (MSM), and heterosexual transmission (defined as either heterosexual activity with a partner at high risk for HIV or sex with an HIV-infected individual). Risk factor assignment was not mutually exclusive. In multivariate analysis, however, patients were categorized as either IDU or non-IDU.

Prior antiretroviral therapy was categorized as none, NRTIs only or HAART, according to the highest level of therapy used. HAART was defined as concomitant use of 3 or more antiretroviral drugs either from 2 or more classes (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], PIs, or a fusion inhibitor) or 3 NRTIs. Currently used antiretroviral agents were those that had been used in the 3 months prior to the pancreatitis date. Mortality was noted if the patient died during that hospitalization.

Statistical analyses were done using Stata 9.0 (Stata Corporation, College Station, TX). The mean and standard deviation were used for describing normally distributed data, whereas the median and interquartile ranges were used for describing nonparametric data. If there was a normal distribution, continuous variables were analyzed with the Student's *t* test.

Poisson regression was used to compare rates of acute pancreatitis across time. A nested case-control analysis was used to assess factors associated with the initial episode of pancreatitis. Four controls were randomly selected from the cohort population that was under observation at the time each case occurred. Controls were matched to cases by AIDS status and year of enrollment in the clinic.

Multivariate conditional logistic regression analysis was used to assess risk factors for the initial episode of pancreatitis.

RESULTS

Between January 1, 1996 and May 31, 2006, 5970 patients were followed for a total of 23,460 person-years (PYs). Five hundred eighty-three hospitalizations with the aforementioned ICD-9 codes occurred in 236 patients. First episodes of pancreatitis that met our criteria for inclusion in the analysis occurred in 85 patients, resulting in an incidence of pancreatitis over the entire study period of 3.6 events per 1000 PYs of follow-up. The incidence of pancreatitis from 1996 to 2000 was 2.6 events per 1000 PYs (95% confidence interval [CI] 1.8–3.6) while the incidence from 2001 to 2006 was 5.1 events per 1000 PYs (95% CI 3.9–6.8) of follow-up ($p = 0.0014$ for comparison of rate in 2 time periods).

Among the 85 cases, most were male (51.8%), of African-American race/ethnicity (88.2%), and had IDU or high-risk heterosexual behavior as their primary HIV risk factor (Table 1). The median patient age was 36 years (range, 21–53 years).

This study population had advanced HIV disease with 82.4% of patients being AIDS defined. The majority of patients (57.5%) had a CD4 count less than 200 cells/mm³ at the time of their episode of pancreatitis, and the median CD4 count at the time of pancreatitis was 160 cells/mm³. The median HIV-1 RNA was 4.4 log₁₀ copies/mL; 29.1% had an HIV-1 RNA >5 log₁₀ copies/mL but 19.0% had an undetectable level (i.e., < 2.6 log₁₀ copies/mL) at the time of pancreatitis. The majority of cases (55.3%) and controls (59.7%) were on HAART at the time of pancreatitis (Table 1).

Among the cases of pancreatitis, the median amylase level was 445 u/L (range, 73–4924 u/L), and the median lipase level was 393 u/L (range, 39–7770 u/L) (Table 2). The mean Ranson score was 0.5 (median, 0; range, 0–3). Other laboratory values are shown in Table 2. Five patients died of pancreatitis during their hospitalization, yielding an in hospital mortality of 5.9% for acute pancreatitis.

In bivariate analysis, risk factors for acute pancreatitis included female sex (OR 2.58; 95% CI [1.58, 4.24]; $p < 0.01$), African-American race/ethnicity (OR 1.99; [0.98, 4.06]; $p = 0.058$); HIV-1 RNA > 5 log₁₀ copies/mL (OR 2.33; [1.27, 4.28]; $p = 0.006$) compared with an HIV-1 RNA ≤ 5 log₁₀ copies/mL; stavudine use (OR 1.74; [1.00, 3.02]; $p = 0.050$); didanosine use

(OR 1.91; [1.01, 3.63]; $p = 0.048$); and hydroxyurea use (OR 4.53; [1.20, 17.09]; $p = 0.026$) (Table 3). Receipt of opportunistic infection (OI) prophylactic medications also increased the risk of acute pancreatitis: trimethoprim-sulfamethoxazole use (OR 1.56; [0.87, 2.80]; $p = 0.136$); dapsone use (OR 2.95; [1.25, 6.94]; $p = 0.013$); and aerosolized pentamidine use (OR 9.33; [2.41, 36.09]; $p = 0.001$). Those patients with the greatest levels of immunosuppression, i.e., $CD4 < 50$ cells/mm³, had the highest risk of acute pancreatitis (OR 10.77; [95% CI 3.52, 33.03]; $p < 0.001$) compared to those with CD4 counts over 500 cells/mm³.

In multivariate regression, factors that remained significantly associated with pancreatitis included female gender (adjusted odds ratio 2.96; [95% CI 1.69, 5.19]; $p < 0.001$); stavudine use (AOR 2.19; [1.16, 4.15]; $p = 0.016$); aerosolized pentamidine use (AOR 6.27; [1.42, 27.63]; $p = 0.015$); and $CD4 < 50$ cells/mm³ (AOR 10.47; [3.33, 32.90]; $p < 0.001$). After adjustment for other factors, African American race/ethnicity; HIV-1 RNA; and didanosine, hydroxyurea, dapsone, and trimethoprim-sulfamethoxazole usage were no longer significantly associated with an increased risk of acute pancreatitis. Age and HIV risk factor were not associated with an increased risk of pancreatitis in bivariate or multivariate analyses. No specific PI or NNRTI, nor usage of any PI or NNRTI, was significantly associated with an increased odds of pancreatitis.

DISCUSSION

This study has several important findings. First, the overall incidence rate of acute pancreatitis requiring hospitalization among our urban cohort of HIV patients was found to be 3.6 per 1000 PYs of follow-up, which is greater than 10 times the incidence in the non-HIV population found by Andersson et al.¹¹ (0.3 cases per 1000 PYs). Moreover, during the 10-year HAART period, the incidence rates actually increased significantly. In this study in multivariate analysis, acute pancreatitis was associated with female sex, severe immunosuppression (i.e., $CD4 < 50$ cells/mm³), and both aerosolized pentamidine and stavudine usage. Of note, we found no evidence that newer antiretroviral drugs including PIs (e.g., atazanavir and lopinavir/ritonavir), NRTIs (e.g., tenofovir and abacavir), or NNRTIs (e.g., efavirenz), were associated with an increased risk of pancreatitis.

Incidence and risk factors for pancreatitis

The incidence of acute pancreatitis in the HAART era has not been recently described. Reisler et al.⁴ examined rates of pancreatitis by pooling data from 20 Adult AIDS Clinical Trials Group studies. The incidence rate of pancreatitis in this study was 6.1 cases per 1000 PYs for clinical pancreatitis, defined as elevated serum amylase and a compatible clinical syndrome of nausea, vomiting, and/or abdominal pain, and 22.3 episodes per 1000 PYs for chemical pancreatitis, grade 3 or 4 elevations of amylase and/or lipase. Both definitions were likely to overestimate the number of cases of pancreatitis by favoring sensitivity over specificity. Another study by Guo et al.¹² found an incidence of acute pancreatitis of 19.5 cases per 1000 PYs by searching the Ohio Medicaid claims database for ICD9 codes indicative of HIV infection and acute pancreatitis. However, because this study was limited to administrative data, the authors were unable to validate their diagnoses by confirming elevated levels of serum amylase or lipase or a corroborating clinical syndrome.

The incidence of pancreatitis in our 10 year study, 3.6 cases per 1000 PYs, was similar to that found in the pre-HAART era in this same urban Baltimore cohort—7.65 cases per 1000 PYs.⁶ One possible explanation for the slightly lower incidence of pancreatitis in this current study is that only patients with acute pancreatitis of sufficient severity to require hospitalization were included for analysis; this criterion may have led to a lower incidence than that found in other studies where nonhospitalized patients with less severe or only chemical pancreatitis were included. Another potential reason for the lower incidence of pancreatitis in the current era in

this study is that fewer patients are now taking NRTIs (e.g., didanosine, stavudine, and hydroxyurea) which were strongly associated with the development of pancreatitis in previous studies. As providers are recommended to prescribe these NRTIs less frequently,¹³ a relative decrease in the number of pancreatitis cases resulting from their use could be expected.

The link between NRTIs and acute pancreatitis was first noted shortly after they were introduced for the treatment of HIV.^{14–17} Our findings support the link between pancreatitis and NRTIs,⁶ with the strongest association between stavudine and acute pancreatitis. The specific mechanism for NRTI-induced pancreatitis is not fully known, but it is generally ascribed to mitochondrial toxicity caused by inhibition of host mitochondrial DNA polymerase gamma.¹⁸ The reason that didanosine was not found to have a stronger association with pancreatitis in this study may be related to declining use of this drug in accord with more recent antiretroviral therapy guidelines,¹³ use of a different formulation, use of lower doses (e.g., with tenofovir), and black-box warnings¹⁹ increasing awareness of this side effect that might lead to earlier discontinuation of the drug.

Since PI-based HAART therapy was first introduced in 1996, three studies^{4,20,21} have evaluated whether the etiologies of acute pancreatitis could be changing. These studies have had conflicting results as to the impact of PIs on the development of pancreatitis, however. Two case reports^{7,8} have suggested a causal mechanism between PI-induced hypertriglyceridemia and acute pancreatitis, while a third case report of PI-associated acute pancreatitis was not associated with a rise in serum triglycerides.⁹ Neither Reisler et al.,⁴ nor Bush and Kosmiski,²⁰ found significant increases in hypertriglyceridemic pancreatitis after the introduction and widespread use of PIs. Manfredi et al.²¹ demonstrated an increased risk of pancreatitis with PI-based HAART exposure; however, this study included both clinical and subclinical (i.e., laboratory only—at least a threefold increase in serum pancreatic isoamylase and/or lipase levels) episodes in the analysis. Though we did not have data on triglyceride levels on all cases, our study did not show an increased risk of pancreatitis in patients receiving a PI, which was consistent with Reisler et al.⁴ and Bush and Kosmiski.²⁰

Consistent with prior studies,^{3,6,21,22} this study demonstrated an increased risk of pancreatitis with worsening immunosuppression, particularly at the lowest CD4 counts, even after adjustment for HAART use. There are multiple potential causes for this association. At low CD4 counts (i.e., < 200 cells/mm³), HIV patients are more susceptible to OIs. Numerous OIs, including cytomegalovirus,^{23–25} varicella-zoster virus,²⁶ *Mycobacterium tuberculosis*,^{27–29} *Mycobacterium avium*,^{29,30} toxoplasmosis,^{27,31} cryptococcosis,^{32,33} and *Pneumocystis jirovecii* (formerly *carinii*),^{33,34} have all been associated with pancreatic involvement. Medications for OI treatment and prevention, including pentamidine^{35–37} and trimethoprim-sulfamethoxazole,^{38–40} have also been associated with pancreatitis, and these medications are predominantly prescribed for patients with the lowest CD4 counts. This study also demonstrated an increased risk of pancreatitis in those patients who received aerosolized pentamidine in the year prior to presentation that was independent of the CD4 count. The severe metabolic changes that occur in AIDS patients may play a role in the ultra-structural histologic changes found in the pancreas,⁵ making these patients more prone to clinical pancreatitis. Last, CD4 lymphocytes could be important in preventing the acinar cell necrosis which leads to clinical acute pancreatitis.³ Any or all of these factors might increase the likelihood of acute pancreatitis in HIV patients with the greatest level of immunosuppression.

Consistent with some prior studies, we found an association between female gender and acute pancreatitis.^{6,41} Previous studies hypothesized that smaller body mass might increase the toxicity of NRTIs. However, several other studies^{3,21,22} found no association between gender and risk of pancreatitis. Cappell and Marks² found an increased risk for pancreatitis in males.

The relationship between gender and pancreatitis will need to be reevaluated with the introduction of newer antiretroviral agents.

The association of race and risk of pancreatitis has been mixed, and several studies have not found race to be a significant risk factor for development of pancreatitis.^{3,6,22} Guo et al.¹² found a 36%–54% higher risk for non-white patients. In our study, African American race/ethnicity was associated with acute pancreatitis in bivariate analysis but not in multivariate analysis. This suggests that other factors, such as immunosuppression and NRTI usage, may have confounded the observed association.

There are several potential limitations to our study. First, these results are based on patients from a single institution with a high proportion of IDUs and indigent patients, although the population is representative of HIV in urban settings. Second, cases of pancreatitis for which a patient was admitted to another hospital may have been missed by this analysis; however, our hospital serves as the primary care center for these patients, and a recent analysis demonstrated 96% of all admissions occurred at our hospital. Third, although there is no consensus definition of acute pancreatitis, we used one that favored specificity over sensitivity and is consistent with past literature.^{10,11} We counted cases only when the serum amylase or lipase levels were elevated 3 or more times the upper limit of normal *and* when patients were hospitalized for their symptoms. Thus, episodes of pancreatitis not severe enough to cause marked enzyme elevations or those not requiring hospitalization would have been excluded. A small number of cases (10.6%) were identified by elevations in only the amylase level 3 or more times the upper limit of normal, which could potentially lead to misclassification due to the lack of specificity of this enzyme for acute pancreatitis; however, these cases did have elevations in lipase, though not 3 or more times the upper limit of normal, as well as a compelling clinical presentation for acute pancreatitis, which makes these cases unlikely to have been misclassified. The incidence found in this study may have been higher if these definitions and inclusions had been altered to increase sensitivity at the expense of specificity. Fourth, we did not have alcohol consumption data available for this study; however, previous studies^{42,43} have demonstrated alcohol utilization rates in HIV patients are similar to that of the general United States population. Last, we did not count recurrent episodes of pancreatitis in this analysis, and risk factors for subsequent pancreatitis episodes could be different than those for the first episode.

CONCLUSION

This study has several important implications. In the current era of HAART, the incidence of acute pancreatitis is relatively unchanged from the pre-HAART era. Neither PIs nor NNRTIs appear to have led to an increased incidence despite earlier fears and occasional case reports associated with PI-induced hypertriglyceridemia. Acute pancreatitis remains a significant cause of morbidity and mortality, even in the HAART era. Future studies should continue to evaluate the risk of developing pancreatitis, particularly in women and immunosuppressed patients, as new antiretroviral medicines continue to be introduced.

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Table 1

Demographic and Clinical Characteristics of Cases with Acute Pancreatitis and Controls

Characteristic	Case (n = 85)	Control (n = 340)
Median age [years (range)]	36 (21–53)	38 (19–76)
Gender [No. (%)]		
Male	44 (51.8)	249 (73.2)
Female	41 (48.2)	91 (26.8)
Race [No. (%)]		
African American	75 (88.2)	269 (79.1)
Non-African American	10 (11.8)	71 (20.9)
HIV risk factor ^a [No. (%)]		
Injection drug use	47 (55.3)	174 (51.2)
MSM	13 (15.3)	95 (27.9)
Heterosexual sex	44 (51.8)	139 (40.9)
Hepatitis C antibody		
Positive [no. (%)]	46 (54.1)	169 (49.7)
Negative [no. (%)]	32 (37.7)	138 (40.6)
Unknown [no. (%)]	7 (8.2)	33 (9.7)
CD4 (cells/mm ³) at episode [No. (%)]	(n = 80)	(n = 338)
≤50	23 (28.8)	34 (10.1)
51–200	23 (28.8)	79 (23.4)
201–350	17 (21.2)	89 (26.3)
350–500	11 (13.7)	70 (20.7)
>500	6 (7.5)	66 (19.5)
HIV-1 RNA at episode [No. (%)]	(n = 79)	(n = 331)
≤5 log ₁₀ copies/mL	56 (70.9)	278 (84.0)
>5 log ₁₀ copies/mL	23 (29.1)	53 (16.0)
Prophylaxis in the prior year		
Trimethoprim-sulfamethoxazole	35 (41.2)	115 (33.8)
Dapsone	11 (12.9)	18 (5.3)
Aerosolized pentamidine	7 (8.2)	3 (0.9)
Previous ART [no. (%)]		
None	8 (9.4)	38 (11.2)
NRTIs only	9 (10.6)	44 (12.9)
HAART	68 (80.0)	258 (75.9)
Individual ART components [no. (%)]		
Stavudine	25 (29.4)	67 (19.7)
Didanosine	15 (17.7)	33 (9.7)
Hydroxyurea	5 (5.9)	5 (1.5)
Tenofovir	5 (5.9)	25 (7.4)
Efavirenz	14 (16.5)	63 (18.5)
Indinavir	2 (2.4)	22 (6.5)
Lopinavir/ritonavir	8 (9.4)	38 (11.2)
Atazanavir	1 (1.2)	6 (1.8)
On HAART [No. (%)]		
NNRTI-based regimen	17 (20.0)	77 (22.6)
PI-based regimen	27 (31.8)	122 (35.9)

^aHIV risk factors were not mutually exclusive categories.

MSM, men who have sex with men; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2**Laboratory Values of Pancreatitis Cases**

	Median (range) <i>n</i> = 85
Amylase (U/L)	445 (73–4924)
WBC (No./mm ³)	6000 (1290–30,460)
AST (U/L)	91.0 (19–2820)
Glucose (mg/dL)	110 (65–674)
Bicarbonate (mEq/L)	22.0 (5–31)
Lipase (U/L)	<i>n</i> = 84
	393 (39–7770)
Triglyceride (mg/dL)	<i>n</i> = 51
	146 (45–1278)
Lactate (mmol/L)	<i>n</i> = 32
	1.8 (0.7–19.3)
LDH (U/L)	<i>n</i> = 31
	349 (127–1702)
Median Ranson score	0 (0–3)

WBC, white blood cell count; AST, aspartate amino transferase; LDH, lactate dehydrogenase. Of the 85 total cases, 9 (10.6%) had only amylase elevated ≥ 3 times the upper limit of normal, 27 patients (31.8%) had only lipase elevated ≥ 3 times the upper limit of normal, while the remainder (49 patients [57.6%]) had both enzymes elevated ≥ 3 times the upper limit of normal.

Table 3

Bivariate and Multivariate Conditional Logistic Regression Analysis for Factors Associated with Pancreatitis

Characteristic	Bivariate analysis		Multivariate analysis ^a	
	OR (95% CI)	p value	AOR (95% CI)	p value
Female	2.58 (1.58–4.24)	<0.001	2.96 (1.69–5.19)	<0.001
African American race	1.99 (0.98–4.06)	0.058	—	—
HIV risk group				
IDU	1.18 (0.73–1.90)	0.496	—	—
MSM	0.47 (0.25–0.88)	0.019	—	—
Heterosexual sex	1.54 (0.96–2.48)	0.074	—	—
Hepatitis C antibody positive	1.04 (0.71–1.52)	0.846	—	—
CD4 (cells/mm ³) at episode				
≤50	10.77 (3.52–33.03)	30.001	10.47 (3.33–32.90)	<0.001
51–200	4.81 (1.58–14.66)	0.006	4.76 (1.53–14.84)	0.005
201–350	2.51 (0.87–7.26)	0.088	2.59 (0.89–7.57)	0.074
350–500	2.09 (0.72–6.05)	0.175	2.10 (0.71–6.21)	0.124
>500	1.0 reference	—	1.0 reference	—
HIV-1 RNA				
≤5 log ₁₀ copies/mL	1.0 reference	—	—	—
>5 log ₁₀ copies/mL	2.33 (1.27–4.28)	0.006	—	—
Prophylaxis in the prior year				
Trimethoprim-sulfamethoxazole	1.56 (0.87–2.80)	0.136	—	—
Dapsone	2.95 (1.25–6.94)	0.013	—	—
Aerosolized pentamidine	9.33 (2.41–36.09)	0.001	6.27 (1.42–27.63)	0.015
Previous ART				
None	1.0 reference	—	—	—
NRTIs only	0.94 (0.31–2.84)	0.909	—	—
HAART	1.30 (0.56–3.02)	0.543	—	—
Individual ART components				
Stavudine	1.74 (1.00–3.02)	0.050	2.19 (1.16–4.15)	0.016
Didanosine	1.91 (1.01–3.63)	0.048	—	—
Hydroxyurea	4.53 (1.20–17.09)	0.026	—	—
Tenofovir	0.76 (0.27–2.19)	0.614	—	—
Efavirenz	0.84 (0.42–1.68)	0.631	—	—
Indinavir	0.35 (0.08–1.51)	0.158	—	—
Lopinavir/ritonavir	0.82 (0.36–1.86)	0.631	—	—
Atazanavir	0.67 (0.08–5.54)	0.707	—	—
Usage of any NNRTI	0.83 (0.44–1.57)	0.573	—	—
Usage of any PI	0.83 (0.50–1.38)	0.472	—	—

^a AOR not displayed in the Table were not included in the final multivariate model.

OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval; IDU, injection drug use; MSM, men who have sex with men; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy.