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HIV Infection and the Risk of Diabetes Mellitus

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Abstract

Background—The influence of HIV infection on the risk of diabetes is unclear. We determined the association and predictors of prevalent DM in HIV infected and uninfected veterans.

Methods—We determined baseline prevalence and risk factors for diabetes among HIV infected and uninfected veterans in the Veterans Aging Cohort Study. Logistic regression was used to determine the odds of diabetes in HIV infected and uninfected persons.

Results—We studied 3,327 HIV-infected and 3,240 HIV-uninfected subjects. HIV infected subjects were younger, more likely to be black race, male, have HCV coinfection and a lower body mass index (BMI). HIV infected subjects had a lower prevalence of diabetes at baseline (14.9% vs. 21.4%, $P < 0.0001$). After adjustment for known risk factors, HIV infected individuals had a lower risk of diabetes (OR 0.84, 95% CI 0.72-0.97). Increasing age, male gender, minority race, and BMI were associated with an increased risk. The odds ratio for diabetes associated with increasing age, minority race and BMI were greater among HIV infected veterans. HCV coinfection and nucleoside and non-nucleoside reverse transcriptase inhibitor therapy were associated with a higher risk of diabetes in HIV infected veterans.

Conclusion—While HIV infection itself is not associated with increased risk of diabetes, increasing age, HCV coinfection and BMI have a more profound effect upon the risk of diabetes among HIV infected persons. Further, long term ARV treatment also increases risk. Future studies will need to determine whether incidence of DM differs by HIV status.

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Keywords

HIV; diabetes; HCV; risk; antiretroviral therapy

Introduction

The association between human immunodeficiency virus (HIV) infection and diabetes mellitus (DM) is poorly understood and complicated by the differential prevalence of risk factors for DM in HIV infected persons compared with HIV uninfected persons.¹⁻³ There is general agreement that the traditional risk factors for DM (increasing age, minority race, obesity) are still responsible for most of the increased risk in the HIV infected population.⁴ However, the role of more novel risk factors (e.g. hepatitis C virus [HCV] coinfection, combination antiretroviral therapy [CART]) is less clear. Few studies have directly compared HIV infected subjects with HIV uninfected, and the results are conflicting. For example, in the Multicenter AIDS Cohort Study (MACS), 5% of the HIV uninfected and 7% of the HIV infected subjects not taking CART had prevalent diabetes at baseline, compared with 14% of subjects who were on CART.⁵ The prevalence of HCV was very low in this cohort. In contrast, HIV infection was not associated with an increased incidence of DM in the Women's Interagency HIV Study or the Community Programs for Clinical Research of AIDS (CPCRA) study.^{6, 7}

The role of HCV coinfection in HIV infected persons is also unclear. In the FIRST study, HCV coinfection was associated with a higher risk of DM in the antiretroviral-naïve HIV infected population who were < 50 years old,⁸ while no increased risk was found in the Swiss HIV Cohort Study⁹ or an urban cohort of HIV infected persons in New York city.¹⁰ While it is generally accepted that protease inhibitor use, or care in the CART era is associated with an increased risk of DM,⁴ at least two studies do not support this assertion.^{10, 11}

We determined the association of HIV infection itself with DM, and studied the factors that predicted DM in HIV infected and uninfected groups in the Veterans Aging Cohort Study (VACS), which is one of the largest prospective studies of HIV infected persons and uninfected controls.

Methods

The Veterans Aging Cohort Study (VACS) has been described in detail in previous publications.^{1, 12-15} Briefly, VACS is a live prospective cohort study being conducted at eight Veterans Affairs (VA) facilities in the United States (Atlanta, GA; Baltimore, MD; Bronx, NY, Houston, TX; Los Angeles, CA; New York City, NY; Pittsburgh, PA and Washington, DC). Enrollment in VACS began in June 2002 and reached its initial target of 3000 HIV infected subjects and 3000 HIV uninfected controls in August 2004, and continues ongoing enrollment. HIV infected subjects are recruited from the Infectious Diseases clinics at the participating sites. All patients presenting to each participating site are eligible and a majority of the patients in care at the sites are enrolled in the study. HIV uninfected controls are recruited from the General Internal Medicine clinics at the same site, and are targeted to match the demographics of the ID clinics on 5-year age blocks, race and gender. At enrollment, the subjects complete a comprehensive survey which includes demographic information and information on tobacco and drug use, comorbidities, height and weight. It also includes the 3-item AUDIT C,^{16, 17} and the Alcohol Dependence Scale (ADS). Complete electronic medical records data (including data prior to enrollment in VACS) are also routinely collected from each local site and includes laboratory information with dates, values, and reference range for all lab tests. Outpatient pharmacy information is collected nationally through the VA Pharmacy Benefits Management (PBM) program (Hines, IL) and includes medication name, dose, number

dispensed and number of refills ordered. An advantage of national pharmaceutical data is the ability to capture outpatient prescriptions filled by any VA facility.

For the purpose of our study, all subjects enrolled in VACS were eligible to be included in the analysis. HIV infection was defined based on ICD-9 codes and verified by an antibody test with a Western blot confirmation. The primary outcome was diabetes at baseline, which was defined as having any of the following: 1) Glucose ≥ 200 mg/dl on two separate occasions; 2) ICD-9 codes (two outpatient OR one inpatient) PLUS treatment with an oral hypoglycemic or insulin for ≥ 30 days; 3) ICD-9 codes (two outpatient OR one inpatient) PLUS glucose ≥ 126 mg/dl on two separate occasions; 4) Glucose ≥ 200 mg/dl on one occasion PLUS treatment with an oral hypoglycemic or insulin for ≥ 30 days. We created this multifaceted definition to avoid biases that might be introduced by an exclusive focus on ICD-9 diagnostic codes. Diabetes medication prescription and ICD-9 codes have previously been used as diagnostic criteria for diabetes in the veterans.¹⁸ We compared our definition with presence of at least one inpatient or at least 2 outpatient codes for diabetes. Our definition had a sensitivity of 86.6%, specificity of 97.5%, agreement of 95.5% with a kappa value of 0.85 (95% CI 0.83-0.86), suggesting excellent agreement beyond chance. Lab data were obtained closest to the baseline date. Over 94% of the subjects had a biochemical profile performed within 360 days prior to the baseline visit. HCV coinfection was determined based on at least one inpatient or 2 outpatient ICD-9 codes. Quantity and frequency of alcohol use was determined using the AUDIT-C instrument. Illicit drug use was determined by subject self report of presence of at least one inpatient or 2 outpatient ICD-9 codes for drug abuse or dependence. Height and weight were measured as a part of routine clinical care and extracted from subject medical records at the enrolment date. Hypoglycemic medication and antiretroviral use and duration at baseline was determined and calculated from the subjects' electronic medical records retrieved locally and through the PBM database.

We conducted analyses on all subjects stratified by HIV infection. We also conducted analyses including alanine and aspartate aminotransferase levels with and without HCV in the model, as well as separate comparative analyses on subjects with and without alcohol and drug use to explain some of the observed differences in the risk of DM. Subjects were considered to have received CART if they received ≥ 3 drugs from ≥ 2 classes of antiretrovirals. Individual class use was calculated as the cumulative number of days each class of antiretrovirals (nucleoside reverse transcriptase inhibitors [NRTI], non-nucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor [PI]) was used in any given subject. We analysed antiretroviral use as "any CART", "use of each class per year", as well as combinations of classes for ≥ 1 year to understand fully the role of antiretroviral therapy upon the risk of DM within the HIV-infected group.

We compared baseline demographic, clinical and laboratory characteristics of HIV infected and uninfected subjects, and subjects with and without DM at baseline using chi-square and student's t-test as appropriate. Univariable and multivariable logistic regression analysis was used to determine factors associated with the risk of DM. We used Stata® 8.2 (Stata Corp., College Station, TX) for all statistical analyses.

RESULTS

There were 3,327 HIV infected subjects and 3,240 HIV uninfected controls. HIV infected subjects were younger, more likely to be black race, male, and have HCV coinfection and had a significantly lower body mass index (BMI) compared with HIV uninfected controls. In addition, HIV infected patients had less use of alcohol but more drug use. (Table 1) The baseline prevalence of diabetes was 14.9% in the HIV infected and 21.4% in the HIV uninfected group

($P < 0.0001$). Most of this difference was driven by the difference in the category with the lowest BMI.

In a univariable logistic regression model, HIV was associated with a lower risk of DM at baseline (OR 0.64, 95% CI 0.56-0.73). (Table 2) In the overall group, increasing age, male gender, minority race, and BMI were associated with an increased risk of DM. Increasing amount of alcohol use and a history of drug abuse or dependence were associated with a lower risk of DM. The effect of increasing age, minority race and BMI were more pronounced in the HIV infected group compared with HIV uninfected controls. HCV coinfection was associated with a higher risk of DM in the HIV infected, but not in the HIV uninfected group. (Table 2)

In multivariable analysis, HIV was still associated with a lower risk of DM (OR 0.84, 95% CI 0.72-0.97). (Table 3) Other factors associated with DM were similar to the univariable analysis. Increasing age and BMI had a more pronounced effect on the risk of diabetes in the HIV infected compared to HIV uninfected persons. HCV remained a significant predictor only in the HIV infected group.

In the HIV infected group use of CART was associated with a higher risk of DM (OR 1.11, 95% CI 1.05-1.17, result not otherwise shown). While each class of CART was associated with a higher risk of DM in the univariable model, only NRTI and NNRTI use was associated with a higher risk in the multivariable model. (Tables 2 and 3). When we analyzed various combinations of CART classes for varying durations (≤ 1 year vs. > 1 year), cumulative use of NRTI or PI or both was associated with a significantly higher risk of DM compared with the group of subjects with cumulative exposure to both classes for ≤ 1 year. (data not shown) Increasing CD4+ lymphocyte count was associated with an increased risk in univariable analysis, but not in the multivariable analysis. There was no association of DM with HIV RNA levels (data not shown).

Alcohol consumption was associated with a lower risk of DM in both HIV infected and uninfected persons. The lower risk was more pronounced in HIV infected group, and this risk decreased with increasing amount of alcohol consumption, except in those who consumed > 60 drinks per month. (table 4) Compared with non-drinkers, the odds of DM in HIV infected person who consumed 31-60 drinks per months were 0.40 (95% CI 0.22-0.72). To further understand the lower risk of DM associated with alcohol use, we analyzed this variable by age and BMI. There was no difference in BMI among persons with varying quantity/frequency of alcohol use. However, a higher proportion of non-drinkers were > 60 years old, and conversely, a smaller proportion among the older age groups were moderate to heavy drinkers. (data not shown) We also categorized alcohol use by AUDIT score and into three categories – never used, used > 12 months ago, and used in the past 12 months. Compared with never drinkers, those who drank > 12 months ago did not have a significantly lower risk but those who reported drinking in the past 12 months had markedly lower odds of DM (OR 0.46, 95% CI 0.32-0.67) in the multivariable model. (data not shown) Since alcohol and drug abuse and/or dependence frequently coexist, we determined prevalence of DM in subjects who used neither, both or either alcohol or drugs. The prevalence of DM was highest in those who used neither (22.5%) compared with those who used both (12.9%), alcohol alone (20%) or drugs alone (15.7%). (Overall $P < 0.001$)

DISCUSSION

We determined the relationship between HIV infection and other risk factors for prevalent diabetes in one of the largest prospective cohorts of HIV infected persons and HIV uninfected controls and found that HIV infection *per se* was not associated with a higher risk of DM. In fact, the risk of DM at baseline was lower in the HIV infected (OR 0.84, 95% CI 0.72-0.97)

compared with HIV uninfected persons. Most of this difference was driven by the difference in the group with lowest BMI suggesting a role of improving health status leading to a higher risk. This observation is further strengthened by the association of higher CD4+ lymphocyte counts with an increased risk of diabetes. There were many differences in the prevalence of risk factors for DM in the HIV infected and uninfected persons. HIV infected persons were younger and had a lower BMI, which decreases the risk for DM, but were more likely to be racial minorities and had a higher prevalence of HCV, which increases risk. Even after adjusting for these risk factors, HIV was associated with a lower risk of DM. We believe that the net risk of DM is determined by a complex interplay of individual factors, with the traditional risk factors dominating the profile leading to an overall lower risk in HIV infected persons. Lower prevalence and risk in the HIV infected group may also reflect a referral/diagnostic bias, with more people in the general medicine clinics seeking care for evaluation and treatment of DM. Another possible mechanism is the differential level of immune activation and inflammatory response in HIV infected and uninfected persons. While HIV infected persons may have higher levels of high sensitivity C-reactive protein levels, those with HCV/HIV coinfection have lower levels than uninfected persons.^{19, 20} How these interact in a given patient to determine the net risk of diabetes require further study.

We found that HCV infection is associated with a higher risk of DM in the HIV infected group, and demonstrated a similar trend in the uninfected group in multivariable analysis (although this trend did not reach statistical significance, the effect size was similar). This confirms the suggestion from some previous studies that HCV affects the risk of DM in a complex manner, and such risk is influenced significantly by other more traditional risk factors.^{10, 21} In our analysis, the risk conferred by HCV is not altered by the presence of liver damage as measured by elevated alanine and aspartate aminotransferase levels. (data not shown) Whether HCV and HIV act synergistically at a cellular level or through other factors to increase the risk of DM is not known. Insulin resistance and higher levels of inflammatory cytokines are also seen in patients with chronic HCV (but not with HCV/HIV coinfection as referenced in the previous paragraph), and may be one common pathway leading to a higher risk of DM.²²⁻²⁵

We found that use of CART was associated with a significantly higher risk of DM in the HIV infected group. This is essentially a confirmation of multiple previous studies that have demonstrated induction of insulin resistance and a higher risk of DM with the use of CART. The precise role of each class, or each drug in the CART regimens is extremely difficult to determine since such therapy is always used in combination, and often changes in individual subjects. We studied the role of CART in several different ways, including cumulative exposure, current exposure and past exposure for each class (as a part of CART) as well as CART itself. The results were generally consistent indicating a higher risk of DM with use of NRTI and NNRTI. However, the association with PI use was not significant in the multivariable model. Mitochondrial toxicity associated with nucleoside reverse transcriptase inhibitors (e.g. stavudine, zidovudine and didanosine),²⁶⁻²⁹ likely plays a role in the risk associated with NRTI class of drugs. Since PIs are almost never used alone, it is possible that the risk being attributed to NRTIs is at least partly due to the use of PIs. It is notable that the mean duration of NRTI use was nearly twice that of PI use, and duration of NNRTI use was significantly less than duration of NRTI or PI use. In addition, it is also possible that patients with higher risk for DM or with existent DM are more likely to be treated with a NNRTI containing regimen instead of a PI containing regimen. The risk of DM due to each class of drugs may be related to a cumulative dose effect, and individual class exposure cannot currently be separated from concurrent use of a second or third class of the CART regimen.

Our finding of a lower risk of DM associated with increasing alcohol use and drug use is intriguing. Increasing quantity/frequency of alcohol use was associated with increasing protection except in HIV infected persons who consumed > 60 drinks per month. Increasing

alcohol use is associated with increasing liver damage, and may be expected to increase the risk of diabetes. We conducted separate analyses including liver damage (defined as alanine or aspartate aminotransferase levels > 5 times upper limit of normal) with and without HCV in the models and found no significant association with liver damage. It is also plausible that increased alcohol consumption and drug abuse or dependence may lead to poor nutrition and lower BMI which may indirectly dilute the association with DM. However, we found no significant association between quantity and frequency of alcohol use and BMI. Another possibility is that people with alcohol and drug abuse may not seek medical care and the opportunity to diagnose DM may have been missed. We did find that non-drinkers were older, while moderate to heavy drinkers were more likely to be younger. These data suggest that while some of the decreased association with alcohol is due to the alcohol consuming population being younger, there are other likely mechanisms that modulate this effect.

There are many strengths of our study. This study was conducted in a large, prospective cohort of HIV infected persons and appropriate controls. VACS has validated measures of alcohol and drug abuse, as well as well defined algorithms for identifying comorbidities. We use multiple sources of data (surveys, electronic medical records, national data) to ensure as complete and accurate data collection as possible. However, certain limitations should also be noted. Most important, we analyzed prevalent diabetes, not incident diabetes. While we find a negative association between HIV infection and diabetes at baseline, it is entirely possible that incidence rates may be very different. Data on BMI and laboratory data were gathered in the course of routine clinical care. There are few women included in this analysis. Little is known about alcohol consumption patterns among women infected with HIV. Family history of DM is an important risk factor and was not determined in our study. Most of our study subjects were enrolled between 2002-2004. With the approval of newer antiretrovirals and updated recommendations about initial regimens, it is possible that the risk associated with CART may have changes. Finally, it has been argued that the veterans in care are a non-representative sample for the US population in general. However, with the exception of this gender difference, HIV infected veterans are similar to many other HIV infected persons, being more likely to be people of color, having contracted HIV via injection drug use or heterosexual exposure, and to be of lower socioeconomic status.² According to the National Institutes of Health, the estimated prevalence of diagnosed and undiagnosed DM among people age 20 or older is 11.2% in men and 10.2% in women. (<http://diabetes.niddk.nih.gov/DM/PUBS/statistics/>, accessed February 20, 2009) Prevalence of DM is 9.8% among non-Hispanic whites and 14.7% among non-Hispanic blacks. Since only 2.5% of the HIV infected and 7.9% of the HIV uninfected subjects in our study were women, readers are cautioned to interpret any gender differences in our study with caution.

In conclusion, we found that HIV itself is not associated with a higher risk of DM. In fact, after adjusting for traditional risk factors, HIV is actually associated with a lower risk. A return to a more healthy state with increasing BMI and CD4+ lymphocyte counts was associated with a higher risk of diabetes. However, the magnitude of association with the traditional risk factors varies between HIV infected and uninfected persons. Further studies are warranted to understand the mechanisms behind our observations.

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Table 1
Baseline characteristics of HIV infected and uninfected persons in the Veterans Aging Cohort Study

	HIV + (n=3,227)	HIV – (n=3,240)	p-value
Age at study entry, mean (SD) years	49.6 (8.8)	50.8 (10.0)	<0.001
Age at study entry (years)			<.001
<35	4.6	5.1	
35-39	7.4	6.7	
40-44	14.9	12.9	
45-49	23.5	21.6	
50-54	22.3	22.1	
55-59	16.4	16.3	
60-64	5.4	6.0	
65-69	2.9	4.3	
≥ 70	2.5	5.0	
Gender (% male)	97.5	92.1	<0.001
Race			<0.001
White	19.9	24.3	
Black	66.7	62.1	
Hispanic	9.5	10.0	
Other/Unknown	3.9	3.6	
Hepatitis C infection (%)	31.2	15.4	<0.001
Diabetes (%) overall	14.9	21.4	<0.001
By BMI category:			
BMI < 20	8.5	14.6	0.08
BMI 20-24.9	11.7	13.7	0.2
BMI 25-29.9	15.8	18.8	0.06
BMI ≥ 30	27.7	29.2	0.6
Height (SD) (meters)	1.77 (0.07)	1.77 (0.08)	0.6
Weight (SD) (kilograms)	79.1 (15.4)	90.6 (19.4)	<0.001
Body mass index, mean (SD)	25.2 (4.5)	28.9 (5.6)	<0.001
Body mass index			<.001
<20	9.2	3.2	
20-24.9	41.2	20.2	
25-29.9	37.3	39.2	

	HIV + (n=3,227)	HIV – (n=3,240)	p-value
≥ 30	12.3	37.4	
Alcohol use (average number of drinks per month)			.01
0	23.7	20.9	
1-4	25.3	25.1	
5-10	13.3	12.7	
11-30	17.1	17.2	
31-60	7.1	8.0	
>60	13.5	16.2	
Drug use (%)	50.7	38.3	<0.001
HIV+			
CD4+ lymphocyte count/mm ³ , N (%)			
≤ 200	695 (23.9)	*	
201-500	1,331 (45.7)	*	
>500	886 (30.4)	*	
Median (SD) CD4+ lymphocyte count	366 (264)	*	
Median HIV RNA (SD), Log ₁₀ copies/ml	3.08 (1.87)	*	

ALT=serum alkaline aminotransferase; AST=serum aspartate aminotransferase;

Table 2
Predictors of diabetes in the HIV infected and uninfected subjects (univariable logistic regression)

	Odds Ratio (95% CI) Overall	Odds Ratio (95% CI) HIV+	Odds Ratio (95% CI) HIV-
HIV	0.64 (0.56-0.73)	---	---
Age at study entry (years)			
<35			
35-39	1.83 (0.97-3.45)	5.21 (1.18-23.01)	1.30 (0.62-2.74)
40-44	2.52 (1.42-4.49)	7.15 (1.71-29.88)	1.82 (0.94-3.50)
45-49	3.56 (2.04-6.20)	10.33 (2.52-42.41)	2.48 (1.34-4.62)
50-54	5.61 (3.23-9.73)	16.97 (4.15-69.35)	3.75 (2.03-6.92)
55-59	6.82 (3.92-11.86)	18.47 (4.50-75.74)	5.01 (2.70-9.29)
60-64	8.41 (4.70-15.06)	20.55 (4.86-86.81)	6.52 (3.38-12.60)
65-69	11.96 (6.57-21.77)	26.45 (6.09-114.85)	9.29 (4.72-18.27)
≥ 70	10.42 (5.72-18.96)	23.93 (5.43-105.55)	7.43 (3.81-14.49)
Male gender	1.90 (1.34-2.71)	2.71 (1.09-6.73)	2.07 (1.41-3.04)
Race			
White			
Black	1.05 (0.90-1.23)	1.39 (1.06-1.82)	0.93 (0.76-1.14)
Hispanic	1.26 (1.00-1.60)	1.64 (1.12-2.39)	1.12 (0.83-1.53)
Other/Unknown	1.36 (0.98-1.91)	1.64 (0.97-2.75)	1.32 (0.85-2.07)
Body mass index			
<20			
20-24.9	1.25 (0.88-1.79)	1.42 (0.91-2.21)	0.93 (0.61-.94)
25-29.9	1.87 (1.32-2.63)	2.02 (1.30-3.13)	1.35 (0.77-2.38)
≥ 30	3.60 (2.55-5.08)	4.10 (2.57-6.53)	2.42 (1.38-4.24)
Hepatitis C infection	1.13 (.98-1.31)	1.51 (1.24-1.84)	1.00 (0.79-1.26)
Alcohol use (average number of drinks per month)			
0	1.00	1.00	1.00
1-4	0.77 (0.65-.91)	0.75 (0.57-.97)	0.77 (0.60-.97)
5-10	0.59 (0.47-.74)	0.53 (0.37-.74)	0.63 (0.50-.85)
11-30	0.57 (0.46-.70)	0.51 (0.37-.70)	0.60 (0.45-.78)
31-60	0.53 (0.40-.71)	0.37 (0.22-.61)	0.62 (0.44-.88)
60	0.69 (0.56-.85)	0.81 (0.59-1.10)	0.58 (0.44-.77)
Drug use	0.60 (0.52-0.68)	0.70 (0.57-.85)	0.56 (0.50-.68)

	Odds Ratio (95% CI) Overall	Odds Ratio (95% CI) HIV+	Odds Ratio (95% CI) HIV-
CART use (per year of use)	*		---
NRTI		1.08 (1.06-1.11)	
NNRTI		1.18 (1.12-1.24)	
PI		1.06 (1.02-1.10)	
CD4 lymphocyte count at study entry	*		---
≤ 200 (comparator)		1.00	
201-500		1.15 (0.88-1.49)	
>500		1.38 (1.05-1.82)	

CART=combination antiretroviral therapy; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; ULN=upper limit of normal;

Table 3
Predictors of diabetes in the HIV infected and uninfected subjects (multivariate logistic regression)

	Odds Ratio (95% CI) Overall	Odds Ratio (95% CI) HIV+	Odds Ratio (95% CI) HIV-
HIV	0.84 (0.72-0.97)	---	---
Age at study entry (years)			
<35	1.00	1.00	1.00
35-39	1.86 (0.98-3.54)	4.54 (1.01-20.34)	1.25 (0.58-2.68)
40-44	2.69 (1.50-4.83)	6.80 (1.61-28.71)	1.97 (1.01-3.84)
45-49	3.65 (2.08-6.42)	8.43 (2.03-35.06)	2.72 (1.44-5.12)
50-54	5.57 (3.18-9.77)	13.52 (3.26-56.07)	3.88 (2.07-7.27)
55-59	6.94 (3.95-12.19)	13.75 (3.30-57.23)	5.31 (2.82-9.97)
60-64	8.85 (4.89-16.02)	18.38 (4.27-79.13)	6.81 (3.47-13.39)
65-69	12.15 (6.58-22.41)	22.53 (5.08-99.93)	9.59 (4.79-19.22)
≥ 70	10.68 (5.78-19.71)	17.04 (3.70-78.62)	8.03 (4.04-15.97)
Male gender	1.79 (1.23-2.59)	2.51 (0.96-6.52)	1.65 (1.09-2.49)
Race			
White	1.00	1.00	1.00
Black	1.35 (1.13-1.60)	1.65 (1.22-2.22)	1.24 (1.00-1.55)
Hispanic	1.49 (1.15-1.92)	1.55 (1.01-2.37)	1.42 (1.02-1.97)
Other/Unknown	1.55 (1.08-2.22)	1.55 (0.86-2.79)	1.61 (0.99-2.60)
Body mass index			
<20	1.00	1.00	1.00
20-24.9	1.40 (0.97-2.02)	1.68 (1.04-2.70)	1.20 (0.64-2.24)
25-29.9	1.99 (1.39-2.84)	2.30 (1.43-3.69)	1.70 (0.93-3.11)
≥ 30	4.00 (2.77-5.77)	5.35 (3.20-8.93)	3.25 (1.78-5.94)
Hepatitis C infection	1.34 (1.12-1.59)	1.36 (1.06-1.73)	1.28 (0.98-1.66)
Alcohol use (average number of drinks per month)			
0	1.00	1.00	1.00
1-4	0.90 (0.75-1.09)	0.84 (0.63-1.13)	0.95 (0.74-1.23)
5-10	0.67 (0.53-0.85)	0.58 (0.40-0.85)	0.72 (0.52-0.98)
11-30	0.62 (0.50-0.77)	0.56 (0.39-0.80)	0.66 (0.49-0.88)
31-60	0.58 (0.43-0.78)	0.40 (0.22-0.72)	0.71 (0.48-1.03)
>60	0.71 (0.57-0.89)	0.79 (0.56-1.11)	0.68 (0.50-0.92)
Drug use	0.72 (0.62-0.83)	0.89 (0.71-1.11)	0.67 (0.54-0.83)

	Odds Ratio (95% CI) Overall	Odds Ratio (95% CI) HIV+	Odds Ratio (95% CI) HIV-
CART use (per year of use)	*		---
NRTI		1.06 (1.02-1.10)	
NNRTI		1.09 (1.02-1.17)	
PI		0.99 (0.94-1.04)	
CD4 lymphocyte count at study entry	*		---
≤ 200 (comparator)		1.00	
201-500		0.89 (0.67-1.19)	
>500		1.03 (0.76-1.40)	

* not included in the model, since HIV uninfected subjects were included

CART=combination antiretroviral therapy; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor;