

The Effect of HAART and HCV Infection on the Development of Diabetes Mellitus

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ABSTRACT

Background: Hyperglycemia has been reported frequently both among HIV-infected patients receiving protease inhibitors (PIs) and HCV-infected persons. However, little is known about the relationship of HCV and diabetes mellitus (DM) in HIV-infected persons receiving highly active antiretroviral therapy (HAART).

Methods: We examined these relationships among 513 persons on their first HAART regimen for at least 6 months with at least 2 nonfasting glucose measurements before and during treatment in a university-based, urban HIV clinic. We compared the prevalence of DM at baseline among persons with and without HCV infection and the incidence of DM while on HAART among those who were free of DM at baseline. Incident and prevalent DM were defined as nonfasting glucose ≥ 200 mg/dl. Cox proportional hazards regression was used to identify risk factors of diabetes.

Results: The prevalence of DM was higher in HCV-infected persons (8.9%) than HCV-uninfected persons (4.1%, $p=0.03$) even after adjustment for age, gender, race and weight (odds ratio, 2.3; 95% confidence interval [CI], 1.1-4.9). Among HAART recipients, the incidence of DM per 100 person-years was 4.0 (95% CI, 2.8-5.6) overall, 4.6 (95% CI, 2.8-7.5) for HCV-infected persons and 4.1 (95% CI, 2.4-6.9) for HCV-uninfected persons. The incidence of diabetes per 100 person-years was higher among persons receiving PIs (4.7; 95% CI, 3.2-6.8) than those receiving non-nucleoside reverse transcriptase inhibitors (NNRTIs) (2.6; 95% CI, 0.9-8.2), but this difference was not statistically significant ($p>0.05$). There were no significant differences between individual drugs. Older age, race, baseline glucose level and failure to increase weight during treatment were independent risk factors for DM. Of note, 25% of DM cases occurred in young persons (< 40 years) weighing <150 pounds.

Conclusion: DM is marginally more common in HCV/HIV co-infected patients, but HCV did not substantially increase the risk of incident DM in persons receiving HAART. In addition, although incident DM appears to be common during HAART, particularly among patients without traditional risk factors for diabetes (e.g., older age and obesity), the incidence rate of DM was similar for PIs and efavirenz, suggesting that factors other than PI use may contribute to the pathogenesis of DM in HIV-infected persons.

BACKGROUND

The use of highly active antiretroviral therapy (HAART) has substantially reduced the morbidity and mortality associated with HIV infection by decreasing plasma HIV RNA levels, increasing CD4 cell counts and reducing rates of opportunistic infections. However, recent reports have indicated that these drugs and specifically, protease inhibitors, may also cause metabolic disturbances including hyperlipidemia, hyperglycemia and insulin resistance. Additionally, some studies have noted the occurrence of overt diabetes mellitus among persons receiving protease inhibitors.

Nearly 30% of all HIV-infected persons, 60% of HIV-infected hemophiliacs and 80% of HIV-infected injection drug users are co-infected with the hepatitis C virus (HCV). HCV infection has also been associated with the development of diabetes. Studies have suggested that the prevalence of diabetes among persons with HCV infection ranges from 25% to 50%. Given this, it is possible that some of the diabetes that has been associated with protease inhibitors may actually have been attributable to HCV infection. Alternatively, it is possible that HCV infection and protease inhibitors together could have a synergistic effect on diabetes, increasing the risk to a higher than expected level.

Few investigations into the relationship between HAART and diabetes have examined the effect of HCV as a cofactor and consequently, little is known about the relationship of HCV and diabetes mellitus (DM) in HIV-infected persons receiving highly active antiretroviral therapy (HAART).

Objective

To examine the relationship between HCV infection, HAART and diabetes in a cohort of HIV-infected persons receiving treatment in an urban HIV clinic.

METHODS

The study population included persons receiving HAART from April 1995 through August 2001 in the Johns Hopkins Hospital HIV clinic. At enrollment and six-month intervals, data on patient demographics, social practices, clinical and laboratory parameters, including glucose measurements, and prescribed medications were abstracted from patient charts and the Johns Hopkins Hospital laboratory database by trained personnel. These charts were updated at each clinical encounter, including those by telephone and mail.

Patients were classified as receiving HAART if a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) was prescribed. The standard clinic schedule for patients receiving antiretroviral therapy was four weeks after the initiation of therapy and every 12 weeks thereafter. At each visit, patients had a clinical exam and laboratory evaluation that included a complete blood count, serum chemistries, and determination of CD4 cell count and plasma HIV RNA level (RT-PCR). HCV testing is routinely performed on all cohort members using a second or third generation enzyme immunoassay (EIA). Persons with repeatedly reactive HCV antibody by EIA were considered to have HCV infection.

Persons were categorized into the PI, NNRTI and PI & NNRTI groups according to the first regimen prescribed. Incident and prevalent diabetes were defined as nonfasting glucose ≥ 200 mg/dl. Persons were considered to have prevalent diabetes if any of two pretreatment glucose levels were ≥ 200 mg/dl. Those with prevalent diabetes were excluded from the analysis of incident diabetes. Persons were considered to have incident diabetes if any glucose level during treatment was ≥ 200 mg/dl.

Statistical analysis

Correlates of diabetes and HCV infection at baseline were determined using chi-square tests for categorical variables and Mann-Whitney tests for continuous variables. The prevalence of diabetes among persons with and without HCV infection was compared using logistic regression analysis. For the incidence analysis, persons were analyzed in three groups, PI alone, NNRTI alone, and PI and NNRTI, according to the first regimen prescribed after enrollment. The incidence of diabetes was calculated by dividing the number of cases per 100 person-years exposed. Individuals were censored at either their last follow-up visit or when a change in regimen was noted. Independent risk factors of type 2 diabetes were determined using Cox proportional hazards regression. All analysis was performed using STATA software, version 7.0 (College Station, Texas).

RESULTS

Prevalent Diabetes and HCV Infection

Of the 1002 persons receiving HAART, 513 were on their first HAART regimen for at least 6 months and had at least 2 pretreatment glucose measurements and 2 glucose measurements during treatment. Of the 513 persons studied, 244 (48%) were HCV negative and 269 (52%) were HCV positive. Persons with HCV infection were older and more often African-American than those without HCV infection (table 1). Persons with HCV infection were more likely to report injection drug use (IDU) than those without HCV infection. There were no differences in prevalence of hepatitis B virus infection, baseline CD4 cell counts, HIV RNA viral load or nonfasting glucose levels.

The prevalence of diabetes was significantly higher among persons with HCV infection (24 of 269, 8.9%) compared to those without HCV infection (24 of 269, 4.1%, $p=0.03$). This relationship persisted in multivariate analysis that considered other risk factors of diabetes including age, gender, race and weight. We also considered hepatitis B virus infection, baseline cholesterol levels and parameters of HIV infection including CD4 cell count and HIV RNA viral load. Only age greater than 50 years, weight between 137 and 154 pounds and HCV infection (odds ratio, 2.12; 95% confidence interval [CI], 1.08-4.19) were significantly associated with prevalent diabetes at baseline (table 2).

Incident Diabetes, HCV and Antiretroviral therapy

Of the 513 persons, 479 did not have prevalent diabetes at baseline and were thus included in the analysis of incident diabetes. Characteristics of the study population at baseline by type of therapy received are shown in table 1. Persons prescribed PIs were more often male and less frequently African-American than those on other regimens. Those prescribed PIs also tended to weigh more and have lower glucose levels at baseline compared to persons on other regimens.

The overall incidence of diabetes per 100 person-years was 4.0 (2.8-5.6). The incidence of diabetes per 100 persons years was higher among PI users (4.7; 95% CI, 3.2-6.8) than both NNRTI users (2.6; 95% CI, 0.9-8.2) and those on both a PI and NNRTI (1.8; 95% CI, 0.45-7.26), but these differences were not statistically significant (figure 1). The incidence of diabetes per 100 person-years was also not different in HCV positive persons (4.6; 95% CI, 2.8-7.5) compared to HCV negative persons (4.1; 95% CI, 2.4-6.9) (figure 2). Moreover, there were no differences in the incidence of diabetes with respect to specific PIs and NNRTIs overall or stratified by HCV status (figure 3).

In univariate Cox regression analysis, older age, African-American race, baseline CD4 cell count between 50-200 cells/mm³, baseline glucose level and failure to gain weight during therapy were associated with the development of diabetes. Neither HCV infection nor PI use was associated with the development of diabetes (table 4). In multivariate Cox regression analysis, older age, African-American race, baseline glucose levels and failure to gain weight during therapy were independent predictors of diabetes (table 5).

Interestingly, nearly 25% of cases occurred among persons who were both younger than 40 years of age and weighed less than 150 pounds and only 19% of cases occurred among persons who were both 40 years of age and older and weighed 150 pounds or more.

Table 3. Characteristics of persons receiving HAART by type of antiretroviral therapy

	NNRTI* (n=95)	PI* (n=324)	NNRTI & PI (n=60)	P value
Median age (IQR)*	38 (32-43)	37 (32-42)	38 (30-44)	0.73
Male gender (%)	57 (60)	243 (75)†	38 (63)	<0.01
African-American race	77 (81)	240 (75)	53 (88)‡	0.05
Median weight (IQR)	148 (134-164)	157 (139-184)†	153 (133-176)	0.02
Injection drug use (%)	55 (58)	151 (47)	28 (47)	0.14
Hepatitis C virus positive (%)	50 (53)	165 (51)	30 (50)	0.94
Hepatitis B surface antigen positive (%)	3 (3)	26 (8)	8 (13)	0.07
Baseline CD4 cell count/mm ³ (IQR)	166 (47-322)	152 (36-362)	126 (26-256)	0.44
Baseline Log ₁₀ HIV RNA (IQR)	4.8 (4.2-5.3)	4.7 (4.0-5.3)	4.9 (4.5-5.3)	0.13
Baseline glucose in mg/dl (IQR)	89 (80-96)	82 (74-92)†	85 (74-95)	0.02
Concurrent NRTI exposure (%)				
D4T	49 (49)	232 (71)†	48 (72)†	<0.001
DDI	31 (31)	127 (37)	36 (54)†‡	<0.01
DDC	1 (1)	4 (1)	1 (2)	0.96
3TC	2 (2)	1 (1)	1 (2)	0.18
AZT	16 (16)	151 (44)†	13 (19)‡	<0.001

Table 1. Characteristics of study population at baseline by hepatitis C virus (HCV) status *

	Total (n=513)	HCV negative (n=244)	HCV positive (n=269)	P value†
Median age (IQR)‡	37 (32-43)	35 (30-42)	39 (34-43)	<0.0001
Male gender (%)	361 (70)	173 (71)	188 (70)	0.80
African-American race (%)	400 (78)	170 (70)	230 (86)	<0.00001
Median weight (IQR)	155 (137-178)	156 (136-179)	153 (138-178)	0.68
Injection drug use (%)	259 (51)	26 (11)	233 (87)	<0.0001
HBSAg positive (%)	40 (8)	22 (9)	18 (7)	0.33
Median CD4 cell count/mm ³ (IQR)	147 (35-332)	141 (32-325)	152 (43-339)	0.36
Median log ₁₀ copies HIV RNA (IQR)	4.8 (4.1-5.3)	4.8 (4.0-5.3)	4.7 (4.2-5.3)	0.66
Median cholesterol (mg/dl) (IQR)	168 (139-201)	170 (148-183)	162 (134-208)	0.66
Median glucose (mg/dl) (IQR)	84 (75-95)	84 (75-93)	84 (75-96)	0.66

*Study population included persons on first HAART regimen for at least 6 months with at least 2 pretreatment glucose measurements and 2 glucose measurements during treatment.
 †p value from chi-square test for categorical variables and Mann-Whitney test for continuous variables
 ‡IQR, interquartile range

Table 2. Relative odds of diabetes for 513 persons prior to starting HAART*

	Odds ratio (95% confidence interval)*
HCV antibody status	2.3 (1.1-4.9)
Age > 50 years	2.8 (1.1-7.3)
Weight quartiles (pounds)	
<137	1.0
137-154	3.4 (1.2-9.8)
155-177	1.7 (0.5-5.4)
>177	1.2 (0.4-4.0)

*Results from multivariate logistic regression

Figure 1. Probability of developing diabetes by type of therapy

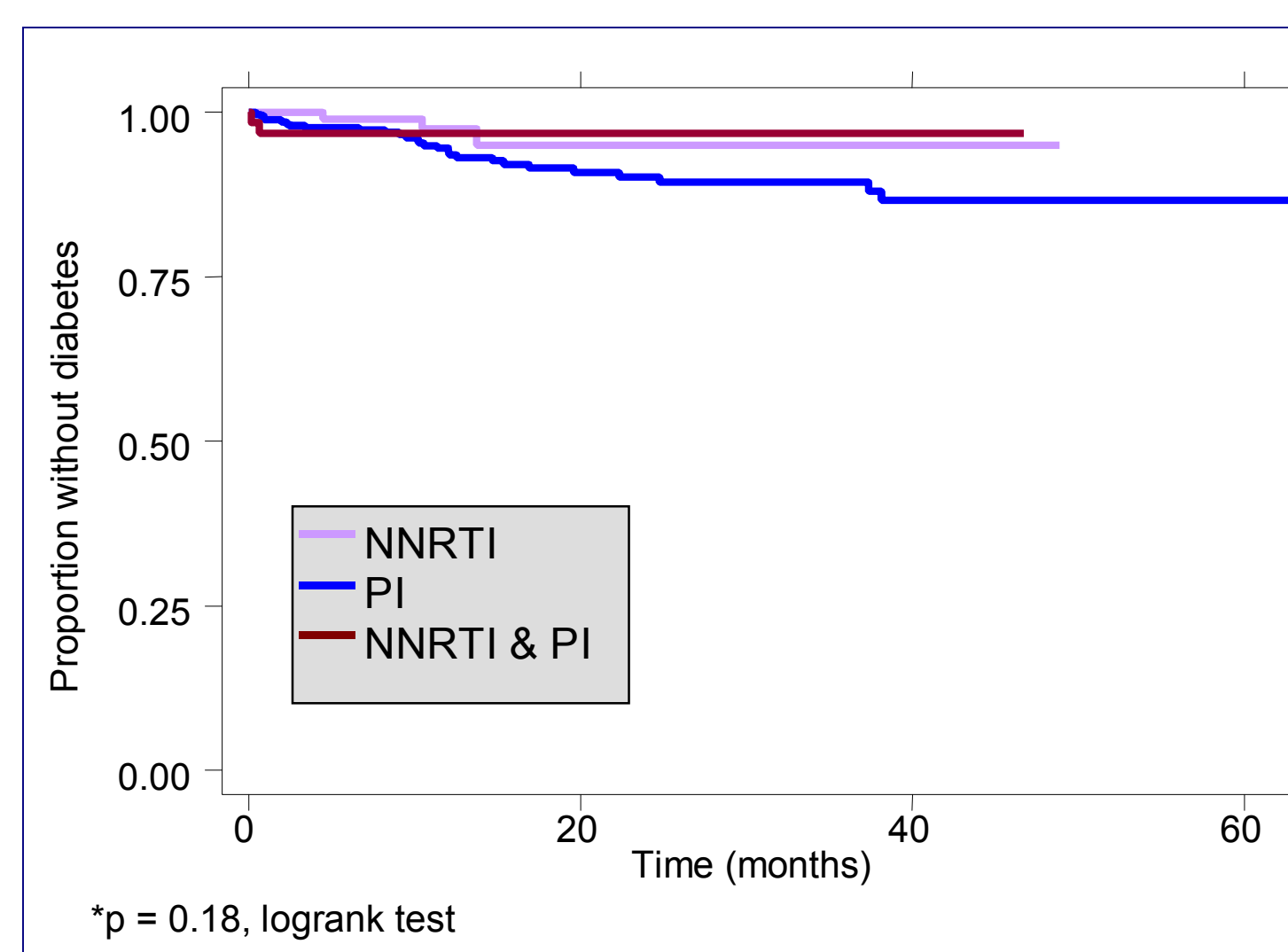


Figure 2. Probability of developing diabetes by HCV infection

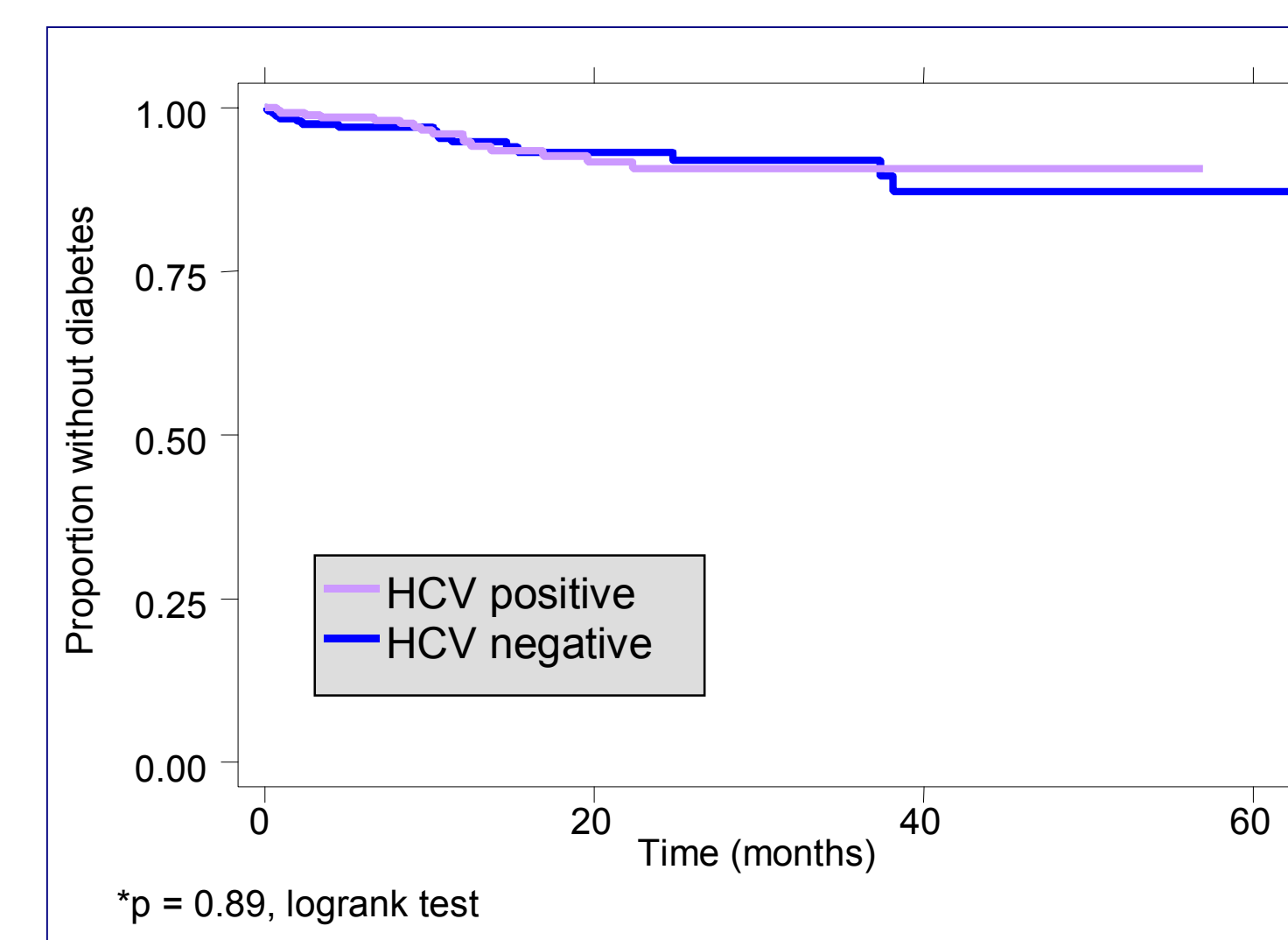


Figure 3. Incidence of diabetes per 100 person-years by type of antiretroviral therapy and hepatitis C virus (HCV) antibody status

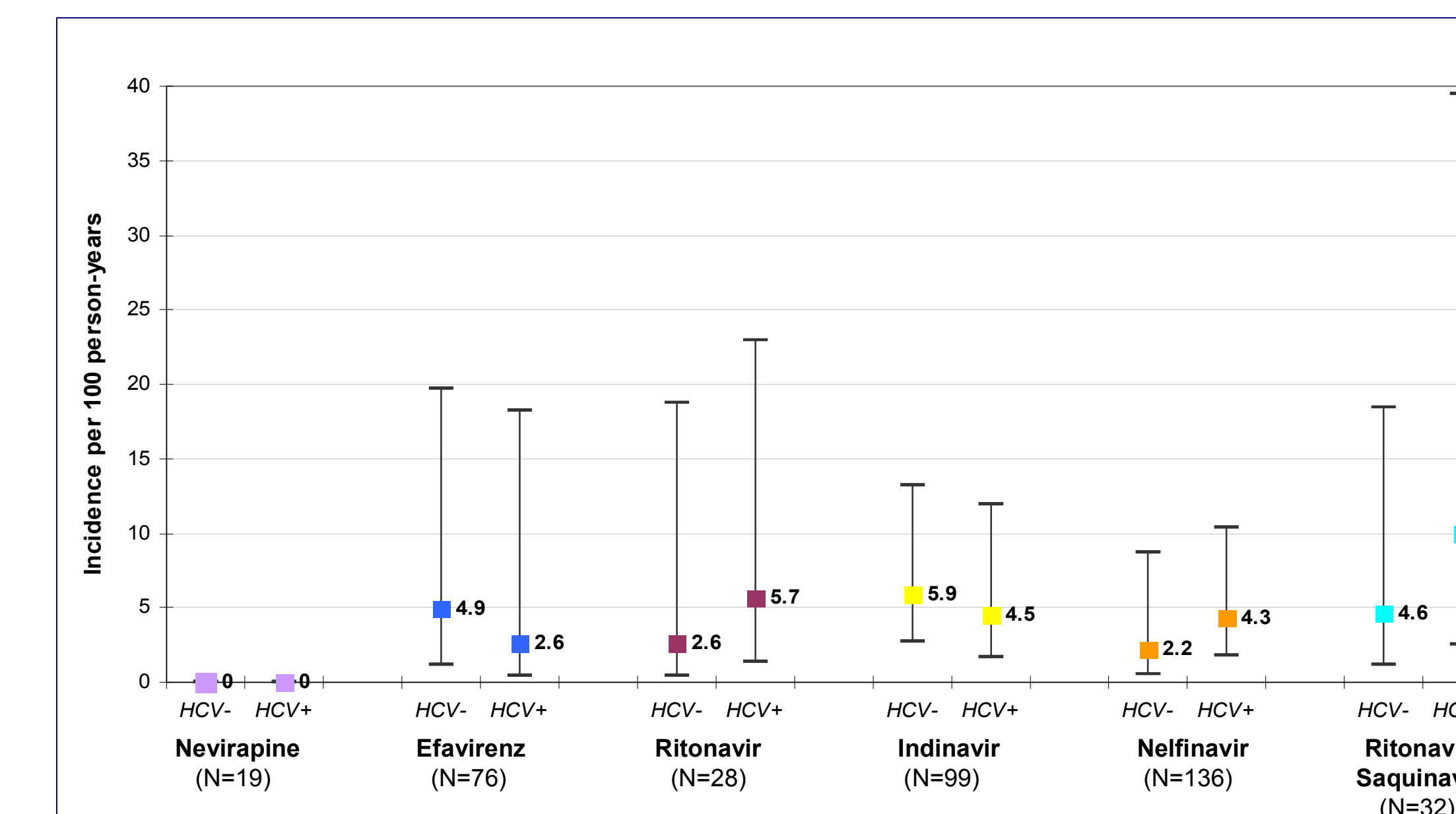


Table 4. Unadjusted relative hazards of diabetes among 479 persons receiving HAART

	Relative Hazard (95% confidence interval)*
Age (years)	1.04 (1.00-1.08)
Male gender	0.64 (0.31-1.31)
African-American race	3.06 (0.93-10.04)
Baseline weight	0.99 (0.99-1.01)
Injection drug use	1.29 (0.64-2.58)
Hepatitis C virus positive	0.98 (0.49-1.95)
Hepatitis B surface antigen positive	0.33 (0.05-2.44)
Baseline CD4 cell count (cells/mm ³)	
>200	1.0
50-200	2.49 (1.08-5.78)
>200	1.65 (0.65-4.15)
Baseline HIV RNA (copies/ml)	
>10,000	1.0
400-10,000	0.81 (0.28-2.35)
<400	1.42 (0.42-4.74)
Baseline glucose (mg/dl)	1.02 (1.01-1.03)
Concurrent D4T use	1.41 (0.65-3.05)
Concurrent DDI use	1.01 (0.50-2.04)
Concurrent AZT use	1.36 (0.68-2.74)
Change in weight during therapy (pounds)	
> 0	1.0
≤ 0	3.14 (1.54-6.41)

Table 5. Adjusted relative hazards of diabetes among 479 persons receiving HAART

	Relative Hazard (95% confidence interval)*
Age (years)	1.03 (1.0-1.07)
African-American race	3.36 (1.02-11.12)
Baseline glucose (mg/dl)	1.02 (1.01-1.03)
Change in weight during therapy (pounds)	
> 0	1.0
≤ 0	3.29 (1.60-6.76)

*Results from Cox proportional hazards regression

CONCLUSIONS

Among HIV-infected patients receiving care in an urban clinic, prevalent diabetes mellitus is more common in HCV/HIV co-infected patients (8.9%) compared to HIV-infected patients (4.1%). However, HCV co-infection did not substantially increase the risk of incident diabetes in persons receiving an initial highly active antiretroviral regimen, which included NNRTIs, PIs, or both.

Nonetheless, incident diabetes appears to be common during HAART, particularly among patients without traditional risk factors for diabetes (e.g., obesity). In multivariate analysis, the development of diabetes was associated with older age, African-American ethnicity, and the failure to gain weight during HAART. Interestingly, the incidence rate of diabetes was similar for all PIs and efavirenz (but not nevirapine), suggesting that factors other than PI use may contribute to the development of diabetes in HIV-infected persons. Further research is needed to define the pathogenesis of diabetes among HIV-infected patients receiving HAART.