HIV Infection and the Risk of Diabetes Mellitus

Adeel A. Butt, MD, MS[1,2], Kathleen McGinnis, MS[2], Maria C. Rodriguez-Barradas, MD[3], Stephen Crystal, PhD[4], Michael Simberkoff, MD[5], Matthew Bidwell Goetz, MD[6], David Leaf, MD[6], Amy C. Justice, MD, PhD[7], For the Veterans Aging Cohort Study

[1] University of Pittsburgh School of Medicine, [2] Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, PA; [3] Baylor College of Medicine and Michael E. DeBakey VA Medical Center, Houston, TX; [4] Center on Pharmacotherapy (Dr. Crystal), Chronic Disease Management, and Outcomes, Rutgers University, New Brunswick, NJ; [5] New York VA Medical Center, New York, NY; [6] VA Greater Los Angeles Healthcare System and the David Geffen School of Medicine at UCLA, Los Angeles, CA; [7] VA Connecticut Healthcare System, West Haven and Yale University School of Medicine and Public Health

Abstract

Background: The role of HIV upon the risk of DM after adjusting for traditional and novel risk factors is unclear. We determined the association of HIV infection itself with DM, and predictors of DM in HIV infected and uninfected groups.

Methods: We determined the baseline prevalence and risk factors for diabetes among HIV infected and uninfected subjects in the Veterans Aging Cohort Study (VACS), a prospective, multicenter, observational cohort. 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) compared with HIV uninfected controls. In addition, HIV infected subjects had less alcohol use but more drug use. In multivariable analysis, HIV was still associated with a lower risk of DM (OR 0.84, 95% CI 0.72-0.97). Increasing age, male gender, minority race, and BMI were associated with an increased risk, while incremental alcohol use and a history of drug use were associated with a lower risk of DM. The effects of increasing age, minority race and BMI were more pronounced in the HIV infected group. HCV coinfection was associated with a higher risk of DM in the HIV infected, but not in the HIV uninfected group.

Conclusion: HIV infection does not increase the risk of diabetes. After adjusting for traditional and novel risk factors, HIV infected persons have a lower risk of diabetes.

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 the 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 and do not clearly demonstrate the true association between HIV and DM.[5,6]

The role of HCV coinfection is similarly unclear and controversial.

In the FIRST study, HCV coinfection was associated with a higher risk of DM in the antiretroviral-naive HIV infected population who were < 50 years old,[7] while no increased risk was found in the Swiss HIV Cohort Study[8] or an urban cohort of HIV infected persons in New York city.[9]

And 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.[9,10]

Methods

The Veterans Aging Cohort Study (VACS) has been described in detail in previous publications.[1,11-14]

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).

HIV infected subjects are recruited from the Infectious Diseases clinics at the participating sites.

HIV uninfected controls are recruited from the General Internal Medicine clinics at the same site, and are matched 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, HIV-related symptom inventory, comorbidities, height, weight, adherence, sexual history, homelessness, health services utilization, and measures of depression and quality of life. It includes the 3-item AUDIT C, [15,16] the Short Inventory of Problems (SIP), and the Alcohol Dependence Scale (ADS). Complete electronic medical records data (including data prior to enrollment in VACS) is 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.

Subjects were considered to have diabetes at baseline if they met any of the following criteria:
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.

Discussion

- We founnd 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.
- 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.
- 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).
- We found that use of CART was assocaited with a significantly higher risk of DM in the HIV infected group.
- 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 afford protection from 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 protective effect of alcohol is due to the alcohol consuming population being younger, there are other likely mechanisms that modulate this effect.

Results

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)
CART use (per year of use)	*		---
NNRTI		1.09 (1.02-1.17)	
NRTI		1.06 (1.02-1.10)	
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;

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)
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 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 (%)	14.9	21.4	<0.001
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	
≥ 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;

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