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Hepatitis C virus infection is associated with insulin resistance among older adults with or at risk of HIV infection

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Abstract

Objectives—To determine the associations of hepatitis C virus (HCV) infection with insulin resistance and abnormal glucose tolerance in a cohort of older adults with or at risk of HIV infection.

Design—A cross-sectional study of 267 HIV-infected and 179 at-risk-uninfected adults without a history of diabetes mellitus.

Methods—HCV antibody assays and RNA levels were performed to assess HCV status. Antiretroviral use, family history of diabetes, sedentary behavior, and sociodemographic data were obtained using standardized interviews. Fasting insulin levels and oral glucose tolerance tests were performed to assess two outcomes, the homeostasis model assessment of insulin resistance and abnormal glucose tolerance [impaired glucose tolerance (IGT) or diabetes].

Results—Of 446 participants, 265 (59%) were HCV seropositive; of these, 199 (75%) had detectable HCV-RNA levels. Insulin resistance was greater among HCV-seropositive compared with seronegative participants, adjusting for body mass index, Hispanic ethnicity, age greater than 55 years, sedentary behavior (watching television > 4 h/day), HIV status, HAART, and protease inhibitor (PI) use. Ninety-eight participants (22%) had abnormal glucose tolerance (69 with IGT and 29 with diabetes). Among HIV-infected participants, 25% were on non-PI HAART and 52% were on PI HAART, but HAART and PI use were not associated with insulin resistance or abnormal glucose tolerance. Among obese participants, abnormal glucose tolerance was more common in HCV-seropositive than seronegative individuals, whereas among non-obese participants there was no association.

Conclusion—The potential impact of HCV co-infection and obesity on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected individuals.

Keywords

Hepatitis C virus; HIV; impaired glucose tolerance; insulin resistance; obesity; type 2 diabetes

Introduction

With the widespread use of HAART, increased frequencies of insulin resistance and its clinical correlates, impaired glucose tolerance (IGT) and type 2 diabetes, have been reported among HIV-infected individuals [1–3]. Some epidemiological studies have demonstrated an increased

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risk of these disorders associated with the receipt of HAART, particularly protease inhibitors (PI) [4–7]. The association between HAART and abnormal glucose metabolism has been attributed to a direct effect on insulin sensitivity by PIs [8], as well as HAART-associated changes in fat distribution [9]. Other studies have, however, found that classic diabetes risk factors, rather than HIV infection or HAART use, predict insulin resistance and abnormal glucose tolerance in individuals with or at risk of HIV infection [10–12]. Investigation of other factors that may influence the risk of diabetes in the HIV-infected population is therefore important.

Chronic infection with hepatitis C virus (HCV) has been associated with an increased risk of developing type 2 diabetes in the general population, particularly among older, overweight individuals [13,14]. HCV infection is common among HIV-infected individuals, occurring in 85−93% of HIV-infected drug users and in 10−14% of individuals with other HIV transmission risk behaviors [15–17]. Studies of the effect of HCV infection on glucose metabolism among HIV-infected patients are beginning to emerge. We previously reported that HCV infection was associated with self-reported diabetes in a cohort of drug users with or at risk of HIV infection [18]. Among HIV-infected patients on HAART, HCV infection has also been associated with insulin resistance [19], and the development of hyperglycemia [20].

In the present study we performed oral glucose tolerance tests (OGTT) and measured fasting insulin levels in a cohort of older adults with or at risk of HIV infection, to determine the associations of HCV infection with insulin resistance and abnormal glucose tolerance. Previous studies examining these relationships have not used a sensitive screening blood test to detect diabetes [18,20], have not controlled for classic diabetes risk factors, including a family history of diabetes or sedentary behavior [18–20], or have not included an HIV-negative comparison group [19,20].

Methods

Study participants

Participant recruitment and study design have been described in detail elsewhere [11,12]. Briefly, between July 2002 and January 2005, participants were recruited from two ongoing cohorts of middle-aged and older adults with or at risk of HIV infection, the Menopause Study, and the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS). As previously reported, Menopause Study and CHAMPS enrolled adults who either had documented HIV infection, or were at risk of acquiring HIV through self-reported illicit drug use or high-risk sexual behavior [21,22]. Menopause Study and CHAMPS participants were followed with semi-annual research visits, during which a structured interview was administered, blood was obtained for HIV serology and T-lymphocyte studies, and physical measures were obtained according to a standardized protocol. Screening and enrollment of consecutive eligible participants for the present study took place during these research visits. To be enrolled, participants had to meet criteria for one of the following enrollment groups: (i) HIV uninfected; (ii) HIV infected and antiretroviral naive; (iii) HIV infected, currently receiving HAART, and PI naive (‘non-PI HAART’); or (iv) HIV infected and currently receiving HAART including a PI (‘PI HAART’). Participants were ineligible if they reported a history of diabetes, were taking antidiabetic medications, were pregnant, or had poor venous access. The studies were approved by the Institutional Review Boards for the protection of human subjects of Montefiore Medical Center and Albert Einstein College of Medicine. All participants provided written informed consent to participate in the present study, in addition to that provided at the time of enrollment in the Menopause Study or CHAMPS.

Interview data

A standardized face-to-face interview was administered by trained research staff, and elicited information on sociodemographic characteristics, medical and family history, and antiretroviral use, with the aid of pill chart prompts. Additional information on physical activity and substance abuse behaviors was assessed using the audio computer-assisted self-interviewing technique.

Physical measurements

Participants were weighed on a calibrated scale, and height was measured using a stadiometer with participants in stockinged feet.

Oral glucose tolerance test

Participants underwent an OGTT according to World Health Organization procedures [23] at the Einstein General Clinical Research Center. Participants were instructed to report to the medical center after a 10−16 h overnight fast, and to take their morning dose of medications with water. Seventy-five grams of dextrose in water was administered orally over less than 5 min. Blood samples were drawn immediately before and 120 min after the ingestion of dextrose.

Assays

Fasting specimens for insulin determination were collected in iced, heparinized tubes. Plasma was separated within 20 min of collection and stored at −70°C until the day of the assay. Plasma insulin was measured by double antibody radioimmunoassay in the hormone assay core of the Einstein Diabetes Research and Training Center [intrassay coefficient of variance (CV) 7.2%, interassay CV 9.4%; cross-reactivity with proinsulin 36.8%]. Specimens for glucose determination were collected at 0 and 120 min in tubes with glycolytic inhibitors. Plasma glucose was measured using the hexokinase method.

HCV antibody testing was performed by enzyme immunoassay (ELISA 3.0; Ortho-Clinical Diagnostics, Raritan, New Jersey, USA) using blood samples obtained at the OGTT visit. For HCV-seropositive participants, HCV-RNA quantification was performed using the Versant HCV-RNA assay (Bayer Corporation, Tarrytown, New York, USA), which has a lower limit of detection of 615 IU/ml.

Exposure variables

The primary exposure variable was HCV infection, defined by a positive HCV antibody assay. Enrollment group (HIV uninfected; HIV infected and antiretroviral naive; HIV infected, on non-PI HAART; or HIV infected, on PI HAART) was included as a covariate in all analyses. Non-PI HAART was defined as three or more antiretroviral medications including at least one non-nucleoside reverse transcriptase inhibitor or abacavir, whereas PI-based HAART was defined as three or more antiretroviral medications including at least one PI [24]. Body mass index (BMI) was categorized on the basis of National Heart, Lung and Blood Institute guidelines: less than 25 kg/m^2 (lean/normal), 25−29.9 kg/m^2 (over-weight), and 30 kg/m^2 or greater (obese) [25]. Sedentary behavior was defined as watching television more than 4 h per day [26]. Other covariates considered included age, race/ethnicity, family history of diabetes, drug use, and among HIV-infected participants, CD4 cell count.

Outcome variables

Insulin resistance was calculated using the homeostasis model assessment: [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5 [27]. Abnormal glucose tolerance included both IGT and diabetes, and was determined using American Diabetes Association criteria, which define

IGT as a 120-min glucose level of 140 mg/dl or greater and less than 200 mg/dl in the absence of diabetes; and diabetes as a fasting glucose level of 126 mg/dl or greater, or a 120-min glucose level of 200 mg/dl or greater during an OGTT [28].

Data analysis

Univariate associations of sociodemographic, behavioral, and clinical characteristics with insulin resistance were determined using the Mann–Whitney test. Analysis of covariance was performed to adjust the effect of possible confounding factors on the observed mean differences. These analyses were based on the ranks of the dependent variable, as insulin resistance was not normally distributed. Multivariate logistic regression analysis was performed to assess the predictors of abnormal glucose tolerance (i.e. IGT or diabetes). Corresponding odds ratios (OR) and 95% confidence intervals (CI) were computed. Covariates included in multivariate analyses included HCV serostatus and enrollment group (HIV uninfected; HIV infected, antiretroviral naive; HIV infected, receiving non-PI HAART; or HIV infected, receiving PI HAART), as well as those factors with a *P* value of 0.2 or less on univariate analysis. Interaction terms were tested and the model fit examined. Analyses were performed using SPSS software version 10.0 (SPSS Inc., Chicago, Illinois, USA) and SAS software version 8.1 (SAS Institute Inc., Cary, North Carolina, USA). Statistical significance was determined using two-tailed tests with alpha equal to 0.05.

Results

Study participants

Of 1077 Menopause Study and CHAMPS participants screened, 528 (49%) were eligible, and 446 out of 528 (84%) enrolled. Participant characteristics are listed in Table 1. Of the 446 participants, 265 (59%) were seropositive for HCV; of these, 199 (75%) had detectable plasma HCV-RNA levels. Compared with the remainder of the study sample, HCV-seropositive participants were older, more often male and unemployed, and more likely to use or have used illicit drugs. Among 209 out of 265 (79%) HCV-seropositive participants with an injection drug use history, we estimated the median duration of HCV infection to be 33 years [interquartile range (IQR) 24−37], using age at first injection as a surrogate for age at HCV acquisition. Sixteen (6%) HCV-seropositive participants reported that they had received interferon for a median of 8.5 months (IQR 5.8−9.8); of these, four (25%) had an undetectable HCV-RNA level.

Sixty percent ($n = 267$) of the participants were HIV seropositive, with no difference by HCV serostatus ($P = 0.64$). Compared with HIV-mono-infected individuals, HIV/HCV-co-infected participants were more likely to have been diagnosed with HIV for over 10 years ($P = 0.001$). Among the 139 participants receiving PI-based HAART, the most commonly used PIs were lopinavir/ritonavir ($n = 52$), nelfinavir ($n = 48$) and indinavir ($n = 21$). The median duration of PI use was 50.0 months (IQR 25.0−72.0), with no difference by HCV status ($P = 0.36$).

Risk factors for diabetes were common; 174 (39%) reported a family history of diabetes, 281 (63%) had a BMI of 25 kg/m^2 or greater, and 230 (52%) reported watching television more than 4 h per day. Compared with HCV-seronegative individuals, HCV-seropositive individuals were less likely to be obese, but were more likely to report watching television more than 4 h per day (Table 1).

Oral glucose tolerance test results

OGTT results are shown in Table 1. Fasting insulin levels were higher in HCV-seropositive participants compared with seronegative participants ($P = 0.02$). There were no significant differences in fasting or 120-min plasma glucose levels by HCV status.

Insulin resistance

In univariate analysis, factors associated with greater insulin resistance were greater BMI ($P < 0.0005$), Hispanic ethnicity ($P = 0.01$), and having a family history of diabetes ($P = 0.01$). There was no difference in insulin resistance by HIV status, receipt of HAART, or PI use. Individuals with a history of ever injecting drugs had greater insulin resistance than those with other HIV transmission risk behaviors ($P = 0.02$); however, there was no difference in insulin resistance when comparing those who reported using heroin or cocaine in the past 6 months by any route ($P = 0.21$) or by injecting ($P = 0.14$) with those who did not.

Factors associated with greater insulin resistance on multivariate analysis are shown in Table 2. After adjusting for enrollment group and risk factors for insulin resistance including BMI ($P < 0.0001$), Hispanic ethnicity ($P = 0.009$), age 55 years or greater ($P = 0.002$), and watching television more than 4 h per day ($P = 0.09$), HCV seropositivity was independently associated with greater insulin resistance ($P = 0.004$). Ever injecting drugs was not included as a covariate in this model as it was highly correlated with HCV seropositivity (Table 1). When recent (past 6 months) injection drug use was included in the model, however, HCV seropositivity remained associated with insulin resistance, whereas injection drug use did not.

Because a single undetectable HCV-RNA level does not exclude chronic infection, it is not possible to determine with certainty whether an HCV-seropositive individual without detectable plasma HCV RNA at one point in time does or does not have persistent HCV infection [29]. Therefore, to assess the association between persistent HCV infection and insulin resistance, we repeated the multivariate analysis including only individuals with detectable HCV-RNA levels and those uninfected (i.e. negative for HCV antibody). In this model, after adjusting for the same covariates, persistent HCV infection was independently associated with greater insulin resistance ($P = 0.004$). There was no difference in insulin resistance between HCV-seropositive/HCV-RNA undetectable participants and HCV-seronegative participants ($P = 0.16$).

Among HIV-infected participants, on univariate analysis, insulin resistance (μU/ml·mmol/l) was greatest in those with a higher CD4 cell count (mean ± SEM 4.17 ± 0.30 for CD4 cell counts > 500 cells/μl versus 4.03 ± 0.34 for CD4 cell counts 201−500 cells/μl, versus 3.21 ± 0.47 for CD4 cell counts < 200 cells/μl; $P = 0.04$), and in those with a higher BMI ($P < 0.0005$). There was no difference in insulin resistance by receipt of HAART or PI use. Factors associated with greater insulin resistance among HIV-infected participants on multivariate analysis are shown in Table 2. In a model adjusting for age, receipt of HAART, and PI use, a higher BMI ($P < 0.0001$) was independently associated with greater insulin resistance. In addition, there was a significant interaction between HCV infection and CD4 cell count ($P = 0.04$); the effect of HCV infection was modified by the CD4 cell count. Among participants with a CD4 cell count of 500 cells/μl or less, HCV infection was associated with greater insulin resistance, whereas among participants with a CD4 cell count greater than 500 cells/μl, there was no association. In a model including only participants either with a detectable plasma HCV-RNA level or negative for HCV antibody, and controlling for the same covariates, BMI ($P < 0.0001$) and the persistent HCV infection × CD4 cell count interaction ($P = 0.03$) were significantly associated with insulin resistance.

Abnormal glucose tolerance

Ninety-eight (22%) participants had an OGTT consistent with abnormal glucose tolerance, of whom 69 (16%) had IGT, and 29 (6%) had diabetes. As shown in Table 3, abnormal glucose tolerance (IGT or diabetes) was more common among individuals aged 55 years or older ($P < 0.0005$), and among those who watched television more than 4 h per day ($P = 0.009$). The effect of HCV infection on abnormal glucose tolerance appeared to be modified by BMI.

Among obese participants (BMI ≥ 30 kg/m^2), abnormal glucose tolerance was more common among HCV-seropositive individuals than among seronegative individuals (30 versus 14%, $P = 0.04$), whereas among non-obese participants, there was no association (20 versus 25%, $P = 0.31$). The interaction between HCV infection and obesity remained significant ($P = 0.03$) on multivariate analysis after adjusting for enrollment group and family history of diabetes. Other factors associated with abnormal glucose tolerance in this model included age 55 years of older (OR_{adj} 3.2, 95% CI 1.9, 5.5), watching television more than 4 h per day (OR_{adj} 2.1, 95% CI 1.3, 3.4), and Hispanic ethnicity (OR_{adj} 2.5, 95% CI 1.03, 6.1).

Discussion

In this cohort of older adults with or at risk of HIV infection, we found that HCV infection was strongly associated with greater insulin resistance. Furthermore, among obese individuals, we observed an increased prevalence of abnormal glucose tolerance among those with HCV infection compared with those without HCV infection. These associations were independent of classic diabetes risk factors including a family history of diabetes and sedentary behavior, as well as HIV infection and HAART use.

Our finding that HCV infection was associated with greater insulin resistance is consistent with other reports that have demonstrated decreased insulin sensitivity in individuals with HCV mono-infection [30,31]. Konrad *et al*. [30] performed frequently sampled intravenous glucose tolerance tests and found lower insulin sensitivity in non-cirrhotic HCV-infected patients with normal glucose tolerance compared with healthy controls. Hui *et al*. [31] found greater homeostasis model assessment insulin resistance levels in HCV-infected subjects with no or minimal hepatic fibrosis compared with healthy volunteers matched by sex, BMI, and waist–hip ratio. Our study extends these findings by detecting a similar association between HCV infection and insulin resistance in older adults with or at risk of HIV infection.

The mechanisms underlying the association between HCV infection and insulin resistance have not been determined. Several human and experimental studies lend evidence to the hypothesis that HCV may induce insulin resistance by interfering with insulin signalling. In a study of liver tissue from HCV-infected patients, tyrosine phosphorylation of insulin receptor substrate (IRS)-1 was found to be reduced in comparison with controls with non-viral liver disease, and was accompanied by a marked decrease in insulin-stimulated phosphatidylinositol 3-kinase activity and Akt phosphorylation [32]. Furthermore *in vitro*, HCV core protein has been shown to reduce IRS-1 and IRS-2 expression with the resulting inhibition of insulin signaling through the phosphatidylinositol 3-kinase pathway and reduced Akt-dependent metabolic effects [33]. There is also evidence to suggest that an excessive tumor necrosis factor alpha response may mediate the induction of insulin resistance in HCV-infected patients [34]. Other potential mechanisms that have been proposed include the development of insulin resistance as a consequence of elevated iron stores [35] or fatty liver disease [36], both of which are associated with HCV infection.

Despite the strong association between hepatitis C and insulin resistance, we found that HCV infection was only associated with abnormal glucose tolerance (i.e. IGT or diabetes) in participants with a BMI in the obese range. Similarly, in a community-based cohort of HIV-uninfected individuals, Mehta *et al*. [14] found that HCV infection increased the risk of developing diabetes only among overweight individuals over the age of 50 years. Other epidemiological studies have not found that BMI modifies the association between hepatitis C and diabetes [13,18]. In experiments involving transgenic mice, however, Shintani *et al*. [37] demonstrated that whereas HCV core protein alone induced insulin resistance, the development of overt diabetes required the concomitant administration of a high-fat diet. Taken together, these results suggest that HCV *per se* can induce insulin resistance; however, the presence of

additional host factors, such as obesity, may be necessary for the occurrence of IGT or overt diabetes.

In earlier studies of HIV-infected patients, the receipt of HAART has been associated with insulin resistance and diabetes mellitus [4–7]. Evidence for a direct effect on insulin sensitivity by PIs comes from in-vitro studies demonstrating the inhibition of glucose movement through the GLUT4 transporter in the presence of PIs [8], as well as clinical studies in which the acute administration of indinavir to HIV-uninfected individuals resulted in decreased insulin sensitivity [38]. In similar clinical studies of other PI, including nelfinavir, atazanavir and amprenavir, a direct effect on insulin sensitivity has not been observed [39–41]. In our study, PI use was not associated with greater insulin resistance, perhaps because only a minority of PI-treated participants received indinavir. In HAART-experienced patients, lipodystrophy may also contribute to the risk of diabetes, as both increased visceral adiposity and reduced subcutaneous fat are associated with insulin resistance [9,42,43]. Among urban ethnic and racial minority populations with HIV infection, however, in which obesity has reached epidemic proportions, increased BMI may be a more potent risk factor for insulin resistance and diabetes than lipodystrophy [10,44,45].

Our findings highlight the important and under-recognized problems of obesity and physical inactivity among HIV and HCV-infected populations. In our cohort consisting predominantly of inner city, unemployed individuals of minority race or ethnicity, 34% of participants were overweight and 28% were obese. Furthermore, over half of the participants reported watching television for more than 4 h per day, a marker of sedentary behavior [26]. Although overweight has been associated with delayed HIV progression in the HAART era [46,47], as HIV-infected individuals age, obesity is likely to result in increased morbidity from type 2 diabetes and cardiovascular disease. Among HCV-infected individuals, obesity has also been associated with hepatic fibrosis progression [48], and a poor response to interferon-based therapy [49].

This study had several strengths, including the use of a sensitive screening test to diagnose diabetes, and the availability of plasma HCV-RNA levels as an indicator of persistent HCV infection. The inclusion of data on family history of diabetes and sedentary behavior also allowed us to adjust for these important correlates of insulin resistance. Furthermore, our study was strengthened by the inclusion of an HIV-uninfected comparison group with a similar demographic and behavioral profile.

Despite these strengths, our study has limitations. Because of the cross-sectional design, we were unable to infer a possible causal relationship between HCV infection and insulin resistance. In addition, our findings were limited by a lack of information on the severity of liver disease, because liver biopsy specimens and markers of hepatic function were not available. Finally, the findings in our cohort of predominantly older African American and Hispanic adults may not apply to other HIV-infected populations with different sociodemographic characteristics. Given that both HCV infection and type 2 diabetes disproportionately affect these racial and ethnic minority groups [50,51], understanding the association of these common disorders in this population is of great importance.

In conclusion, we have demonstrated that in older adults with or at risk of HIV infection, hepatitis C is associated with insulin resistance, and among obese individuals, with abnormal glucose tolerance. The potential impact of HCV co-infection and obesity on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected individuals.

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Table 1

Participant characteristics by hepatitis C serostatus (N = 446).

	HCV seronegative N = 181	HCV seropositive N = 265	P value[a]
Median age, years (range)	46 (35−73)	51 (37−75)	< 0.0005
Male sex, N (%)	56 (31)	159 (60)	< 0.0005
Race/ethnicity, N (%)			0.22
White	14 (8)	35 (13)	
African American	108 (60)	145 (55)	
Hispanic	52 (29)	79 (30)	
Other	7 (4)	6 (2)	
Unemployed, N (%)[b]	139 (77)	229 (86)	0.01
Family history of diabetes, N (%)[b]	73 (40)	101 (38)	0.62
Body mass index, N (%)[b]			0.01
Lean/normal (< 25.0 kg/m^2)	53 (29)	111 (42)	
Overweight (25.0−29.9 kg/m^2)	64 (35)	90 (34)	
Obese (≥ 30.0 kg/m^2)	63 (35)	64 (24)	0.01
Watch television > 4 h/day, N (%)	83 (46)	147 (56)	0.046
Ever injected drugs, N (%)	19 (10)	209 (79)	< 0.0005
Heroin use past 5 years, N (%)[b]	31 (17)	101 (38)	< 0.0005
Heroin use past 6 months, N (%)[b]	10 (6)	48 (18)	< 0.0005
Cocaine use past 5 years, N (%)	84 (46)	153 (58)	0.02
Cocaine use past 6 months, N (%)[b]	38 (21)	75 (28)	0.08
Injected drugs past 6 months, N (%)[b]	1 (1)	16 (6)	0.003
Currently on methadone maintenance, N (%)[b]	13 (7)	43 (16)	0.004
HIV infected, N (%)	106 (59)	161 (61)	0.64
Duration of HIV diagnosis, N (%)[c]			0.001
< 5 years	30 (28)	20 (12)	
5−10 years	42 (40)	57 (35)	
> 10 years	34 (32)	84 (52)	
CD4 cell count, cells/μl[b,c]			0.08
≤ 200	11 (10)	30 (19)	
201−500	47 (44)	75 (46)	
> 500	46 (43)	52 (32)	
Antiretroviral use, N (%)[c]			0.13
Naive	21 (20)	41 (26)	
HAART, PI naive	33 (31)	33 (20)	
HAART, with PI	52 (49)	87 (54)	
Fasting glucose (mg/dl), mean (SEM)	95.8 (1.2)	94.5 (1.4)	0.05
120-Min glucose (mg/dl), mean (SEM)	116.9 (3.0)	116.4 (2.9)	0.63
Fasting insulin (μU/ml), mean (SEM)	15.3 (0.9)	17.8 (0.9)	0.02

HCV, Hepatitis C virus; PI, protease inhibitor.

[a] P value for Mann—Whitney test (for age, glucose and insulin) or chi-square test (for all other variables) comparing HCV-seronegative and HCV-seropositive participants.

[b] Missing data for unemployed (n = 5), family history of diabetes (n = 4), body mass index (n = 1), heroin past 5 years (n = 1), heroin past 6 months (n = 4), cocaine use past 6 months (n = 4), injected drugs past 6 months (n = 4), current methadone maintenance (n = 1), CD4 cell count (n = 6).

[c] Among HIV-infected participants.

Table 2

Non-parametric analysis of covariance of factors independently associated with insulin resistance.

Variable	Entire cohort (*N* = 446)		HIV-infected participants (*N* = 267)	
	Unadjusted mean (SEM) HOMA—IR (μU/ml mmol/l)	*P* value (multivariate analysis)	Unadjusted mean (SEM) HOMA—IR (μU/ml mmol/l)	*P* value (multivariate analysis)
Enrollment group		0.70		0.78
HIV uninfected	4.45 (0.39)		—	
HIV infected, HAART naive	3.77 (0.35)		3.77 (0.35)	
HIV infected, receiving non-PI HAART	4.51 (0.56)		3.77 (0.25)	
HIV infected, receiving PI HAART	3.77 (0.25)		4.51 (0.56)	
HCV serostatus		0.004		
HCV seronegative	3.84 (0.30)			
HCV seropositive	4.37 (0.26)			
HCV serostatus × CD4 cell count		—[a]		0.04[b]
CD4 cell count ≤ 200 cells/μl				
HCV seronegative			1.99 (0.32)	
HCV seropositive			3.66 (0.62)	
CD4 cell count 201−500 cells/μl				
HCV seronegative			3.52 (0.52)	
HCV seropositive			4.35 (0.45)	
CD4 cell count > 500 cells/μl				
HCV seronegative			4.41 (0.41)	
HCV seropositive			3.95 (0.43)	
Body mass index (kg/m^2)		< 0.0001		< 0.0001
< 25.0 (lean/normal)	2.69 (0.17)		2.86 (0.24)	
25.0−29.9 (overweight)	4.39 (0.36)		4.07 (0.33)	
≥ 30.0 (obese)	5.72 (0.46)		5.70 (0.51)	
Age (years)		0.002		0.14
< 55	3.95 (0.19)		3.96 (0.24)	
≥ 55	4.86 (0.59)		3.92 (0.36)	
Sex		—[a]		—[a]
Male	4.26 (0.32)		3.91 (0.29)	
Female	4.06 (0.24)		3.99 (0.29)	
Race/ethnicity		0.009		—[a]
White/other	4.42 (0.85)		3.24 (0.49)	
African American	3.85 (0.22)		3.87 (0.26)	
Hispanic	4.62 (0.35)		4.43 (0.44)	
Watch television > 4 h/day		0.09		—[a]
No	3.98 (0.27)		3.91 (0.33)	
Yes	4.32 (0.29)		3.99 (0.25)	
Family history of diabetes		—[a]		—[a]
No	3.76 (0.20)		3.89 (0.24)	
Yes	4.80 (0.40)		4.12 (0.38)	
Ever injected drugs		—[a]		—[a]
No	3.65 (0.25)		3.52 (0.25)	
Yes	4.63 (0.31)		4.37 (0.32)	
Injected drugs past 6 months		—[a]		—[a]
No	4.20 (0.21)		3.99 (0.21)	
Yes	3.07 (0.68)		3.34 (0.88)	
Heroin use past 6 months		—[a]		—[a]
No	4.22 (0.21)		4.06 (0.22)	
Yes	3.75 (0.65)		3.02 (0.39)	
Cocaine use past 6 months		—[a]		—[a]
No	4.38 (0.26)		4.13 (0.25)	
Yes	3.51 (0.25)		3.49 (0.33)	

HCV, Hepatitis C virus; HOMA—IR, homeostasis model assessment of insulin resistance; PI, protease inhibitor.

[a] Variable not retained in the final multivariate model.

[b] The model is adjusted for an interaction between HCV serostatus and CD4 cell count, such that the effect of HCV seropositivity on insulin resistance depends on the CD4 cell count.

Table 3

Univariate and multivariate analyses of factors associated with abnormal glucose tolerance (impaired glucose tolerance or diabetes)[a,b].

	Abnormal glucose tolerance (*N* = 98)	Normal glucose tolerance (*N* = 348)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Enrollment group						
HIV uninfected	40 (22)	139 (78)	1.00		1.00	
HIV infected, HAART naive	14 (23)	48 (77)	1.01 (0.51, 2.02)	0.97	1.03 (0.50, 2.15)	0.93
HIV infected, receiving non-PI HAART	16 (24)	50 (76)	1.11 (0.57, 2.16)	0.75	1.24 (0.60, 2.54)	0.56
HIV infected, receiving PI HAART	28 (20)	111 (80)	0.88 (0.51, 1.51)	0.64	0.88 (0.49, 1.57)	0.66
HCV serostatus						
HCV seronegative	39 (22)	142 (78)	1.00		—[c]	
HCV seropositive	59 (22)	206 (78)	1.04 (0.66, 1.65)	0.86		
Body mass index (kg/m^2)						
< 30.0 (normal/overweight)	69 (22)	249 (78)	1.00		—[c]	
≥ 30.0 (obese)	28 (22)	99 (78)	1.02 (0.62, 1.68)	0.94		
HCV seropositive × obese[c]					0.03	
Not obese						
HCV seronegative	29 (25)	88 (75)	1.00		1.00	
HCV seropositive	40 (20)	161 (80)	0.75 (0.44, 1.30)	0.31	0.62 (0.35, 1.10)	
Obese						
HCV seronegative	9 (14)	54 (86)	1.00		1.00	
HCV seropositive	19 (30)	45 (70)	2.53 (1.04, 6.15)	0.04	2.11 (0.84, 5.28)	
Age, years						
< 55	61 (18)	285 (82)	1.00		1.00	
≥ 55	37 (37)	63 (63)	2.74 (1.68, 4.48)	< 0.0005	3.23 (1.89, 5.53)	< 0.0005
Sex						
Male	55 (26)	160 (74)	1.00		—[d]	
Female	43 (19)	188 (81)	0.66 (0.42, 1.04)	0.08		
Race/ethnicity						
White/other	8 (13)	54 (87)	1.00		1.00	
African American	58 (23)	195 (77)	2.00 (0.90, 4.45)	0.09	1.81 (0.78, 4.18)	0.17
Hispanic	32 (24)	99 (76)	2.18 (0.94, 5.06)	0.07	2.51 (1.04, 6.10)	0.04
Watch television > 4 h/day						
No	36 (17)	180 (83)	1.00		1.00	
Yes	62 (27)	168 (73)	1.84 (1.16, 2.93)	0.009	2.10 (1.28, 3.44)	0.004
Family history of diabetes						
No	56 (21)	212 (79)	1.00		1.00	
Yes	42 (24)	132 (76)	1.20 (0.76, 1.90)	0.42	1.21 (0.74, 1.97)	0.45
Ever injected drugs						
No	43 (20)	175 (80)	1.00		—[d]	
Yes	55 (24)	173 (76)	1.29 (0.82, 2.03)	0.26		
Injected drugs past 6 months						
No	91 (21)	334 (79)	1.00		—[d]	
Yes	4 (24)	13 (77)	1.13 (0.36, 3.55)	1.00		
Heroin use past 6 months						
No	83 (22)	301 (78)	1.00		—[d]	
Yes	12 (21)	46 (79)	0.95 (0.48, 1.87)	0.87		
Cocaine use past 6 months						
No	73 (22)	256 (78)	1.00		—[d]	
Yes	22 (20)	91 (80)	0.85 (0.50, 1.44)	0.54		

CI, Confidence interval; HCV, hepatitis C virus; OR, odds ratio.

[a] Data are *N* (%) of participants, unless otherwise indicated.

[b] Values may not total to 446 for some variables because of missing data.

[c] The model is adjusted for an interaction between HCV serostatus and obesity, such that the effect of HCV seropositivity on abnormal glucose tolerance depends on the presence or absence of obesity.

[d] Variable not retained in the final multivariate model.