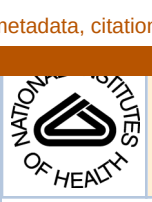

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The Effects of Opiate Use and Hepatitis C Virus Infection on Risk of Diabetes Mellitus in the Women's Interagency HIV Study

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Abstract

Background—Opiate use is common in HIV- and hepatitis C virus (HCV)-infected individuals, however its contribution to the risk of diabetes mellitus is not well understood.

Methods—Prospective study of 1,713 HIV-infected and 652 uninfected participants from the Women's Interagency HIV Study between October 2000 and March 2006. Diabetes defined as fasting glucose ≥126 mg/dl, or self-report of diabetes medication use or confirmed diabetes diagnosis. Opiate use determined using an interviewer-administered questionnaire. Detectable plasma HCV RNA confirmed HCV infection.

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Results—Current opiate users had a higher prevalence of diabetes (15%) than non-users (10%, p=.03), as well as a higher risk of incident diabetes (adjusted relative hazard [RH_{adj}] 1.58, 95% CI 1.01, 2.46), after controlling for HCV infection, HIV/antiretroviral therapy status and diabetes risk factors including age, race/ethnicity, family history of diabetes and body mass index. HCV infection was also an independent risk factor for diabetes (RH_{adj} 1.61, 95% CI 1.02, 2.52). HCV-infected women reporting current opiate use had the highest diabetes incidence (4.83 cases/100 person-years).

Conclusions—Among women with or at-risk for HIV, opiate use is associated with increased diabetes risk independently of HCV infection. Diabetic screening should be part of care for opiate users, and those infected with HCV.

Keywords

opiate use; diabetes mellitus; fasting glucose; Hepatitis C virus; HIV; women

Introduction

Rates of diabetes mellitus are high in HIV-infected women and men, a relationship that has been reported to be due, in part, to use of antiretroviral therapy (ART) and hepatitis C virus (HCV) infection.[1-4] Opiate use is often common in such patients,[5,6] and has been linked to perturbations in glucose metabolism in limited studies of animals and humans.[7-11] Little is known about the contribution of opiate use to the risk of diabetes among individuals with or at-risk for HIV infection. We examined the associations of opiate use and HCV infection with the prevalence and incidence of diabetes in a well-characterized cohort of HIV-infected and at-risk uninfected women.

Methods

Study participants

The Women's Interagency HIV Study (WIHS) is a prospective cohort study that enrolled 2,793 HIV-seropositive and 975 seronegative women at risk for HIV infection from six inner-city sites in 1994-95 or 2001-02. Recruitment methods and data collection procedures for the WIHS have been previously described.[12,13] Briefly, participants were followed at semi-annual research visits, during which blood was obtained for laboratory tests, a physical exam was conducted, and an interviewer-administered questionnaire was completed to ascertain sociodemographic characteristics, medical and family history, medication use, and substance use behaviors. The protocol was approved by the Institutional Review Boards for the protection of human subjects at each study site, and all participants provided written informed consent.

Beginning in October 2000, plasma glucose levels were obtained at the study visit after fasting for ≥8 hours. Of 2,859 WIHS participants with a study visit between October 2000 and March 2006, 2,554 had at least one fasting glucose measurement; the first visit with fasting glucose data available was defined as the index visit. We excluded women who were pregnant (n=60) or did not have pregnancy data (n=7) at the index visit, and those without HCV data (n=122), resulting in 2,365 included women.

Laboratory measures

HCV serology was performed at WIHS enrollment using the Abbott HCV EIA 2.0 or 3.0 (Abbott Laboratories, Abbott Park, IL). As previously described,[14] HCV RNA was measured on frozen specimens from HCV-seropositive women using either the COBAS Amplicor Monitor 2.0 assay (Roche Diagnostics, Branchburg, NJ) which has a linear range

of 600 – 5×10^5 IU/ml, or the COBAS Taqman assay (Roche Diagnostics, Branchburg, NJ), which has a linear range of 10 - 2.0×10^8 IU/ml. Extensive testing demonstrated concordance in results between the two assay systems (data not shown). Fasting specimens for glucose determination were collected in tubes with glycolytic inhibitors and stored at −70° C. Plasma glucose was measured at a central laboratory using the hexokinase method. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by standard methodology in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.

Assessment of predictor variables

The primary predictor variables evaluated were opiate use and HCV infection. *Past opiate use* was defined as self-reported use of heroin or methadone (licit or illicit) at any visit between baseline and that prior to the index visit. *Current opiate use* at each visit was defined as self-reported opiate use since the previous visit. HCV infection was defined as being HCV seropositive and having detectable plasma HCV RNA. Other covariates considered included age, race/ethnicity, body mass index (BMI), family history of diabetes, AST, ALT, and HIV/ART status. BMI was categorized based on National Heart, Lung, and Blood Institute guidelines: <25 kg/m^2 (normal), 25-29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).[15] ART regimens were classified as no therapy, monotherapy or combination therapy, PI-based HAART, and non-PI-based HAART. The WIHS uses a standard definition of HAART16 adapted from the Department of Health and Human Services/Kaiser Panel guidelines.17

Diabetes Mellitus Ascertainment

Prevalent diabetes was defined as a fasting plasma glucose ≥126 mg/dl at the index visit, or a self-report of either diabetes medication use or a diabetes diagnosis at or prior to the index visit. For those who did not have prevalent diabetes at the index visit, incident diabetes was defined as having at a study visit subsequent to the index visit either 1) a fasting plasma glucose ≥126 mg/dl; 2) a self-report of diabetes medication use; or 3) a self-report of a diabetes diagnosis with subsequent corroboration by either a fasting glucose ≥126 mg/dl or reported diabetes medication use.

Statistical Analysis

Prevalent Diabetes—Univariate associations of participant characteristics were determined with the chi-square or Wilcoxon tests, as appropriate. Multivariate logistic regression analysis was used to identify independent predictors of prevalent diabetes. Corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were computed. All models adjusted for the potentially confounding effects of variables measured at the index visit. Specifically, adjustment was made for HIV/ART status and classic diabetes risk factors, including age, race/ethnicity, family history of diabetes, and BMI. Analyses were performed in 3 steps. In addition to the covariates listed above, model 1 included past opiate use; model 2 included HCV infection; and model 3 included both past opiate use and HCV infection.

Incident Diabetes—Proportional hazard regression analysis was performed to determine predictors of diabetes incidence. Time at risk began at the index visit and terminated at the end of the study period, report of pregnancy, or new onset diabetes, whichever occurred first. Analyses were performed in 3 steps. In addition to HIV/ART status and the diabetes risk factors listed above, model 1 included current opiate use as a time-dependent variable; model 2 included HCV infection; and model 3 included current opiate use and HCV infection.

To assess for potential bias associated with misclassification of diabetes, we repeated the prevalent diabetes multivariate logistic regression models excluding women with prevalent diabetes defined only by a self-reported diagnosis of diabetes. We also repeated all models (prevalent and incident diabetes) excluding 1) HCV seropositive women with an undetectable HCV RNA, because without an HCV RNA level at a second point in time, it was not possible to determine with certainty whether these women did or did not have persistent HCV infection;18 and 2) women who reported use of interferon and/or ribavirin for hepatitis C, because HCV treatment has been associated with changes in glucose tolerance.19,20 Due to the skewness of HCV RNA level that could not be corrected by other transformations, in models that assessed the association of HCV RNA level with diabetes risk, a continuous variable with numerical values of 0, 1, 2, and 3 was created indicating the quartile of HCV RNA. Analyses were performed using SAS software version 9.1 (Cary, NC).

Results

Study Participants

Participant characteristics are listed in Table 1. Of 2,365 WIHS women with an index visit, 464 (20%) women reported a history of opiate use at any visit prior to the index, of whom 130 (5%) reported heroin or illicit methadone use only, 129 (5%) reported methadone maintenance therapy only, and 205 (9%) reported both illicit opiate use and methadone maintenance therapy. Two-thirds of the past opiate users also reported a history of crack and/or cocaine use, and 42% (n=197) reported current opiate use. Compared to women who did not use opiates, opiate users were older and more often HCV-infected, but had a similar HIV seroprevalence.

A total of 612 (26%) women were HCV seropositive and 470 (20%) had active HCV infection, as determined by a detectable HCV RNA level. Compared with HCV-uninfected women, HCV-infected women were older, more often African American and HIV-infected, and less likely to be obese. HCV-infected women had higher ALT and AST levels and lower albumin levels compared with HCV-uninfected women, but regardless of HCV status, the majority of participants had transaminase and albumin levels within the normal range. A small minority of women (n=70) reported use of interferon and/or ribavirin for hepatitis C.

Prevalent Diabetes

A total of 259 (11%) women had prevalent diabetes at the index visit, of whom 115 (44%) had a fasting glucose ≥126 mg/dl, 49 (19%) reported diabetes medication use and 95 (37%) reported a diabetes diagnosis at or prior to the index visit. The prevalence of diabetes was higher among past opiate users compared to nonusers (18% vs. 9%, p<.001) (Table 2). Prevalent diabetes was more common among women who reported a history of either opiate use alone (36 of 155, 23%) or both opiate and crack/cocaine use (49 of 309, 16%) compared with women who reported only crack/cocaine use (31 of 304, 10%) or no drug use (143 of 1597, 9%). Because the association between past opiate use and diabetes was not modified by crack/cocaine use, opiate users who did and did not use crack/cocaine were combined for all subsequent analyses. The prevalence of diabetes was also greater among current opiate users compared to nonusers (15% vs. 10%, p=.03), and women with HCV infection compared with those without (16% vs. 10%, p=.0004). When current prescription narcotic use was included as a covariate, we found an association with prevalent diabetes (OR 1.72, 95% CI 1.14, 2.61), and when combined with illicit opiate use/methadone, strengthened the association of current opiate use with prevalent diabetes (OR 2.58, 95% CI 1.10, 6.07). Among HCV-infected women, there was no association between levels of AST (OR 1.00 per 5 U/L, 95% CI 0.97, 1.03) or ALT (OR 1.00 per 5 U/L, 95% 0.97, 1.03) and prevalent

diabetes. There was no pattern in diabetes prevalence or statistically significant associations by HIV infection or ART use at index visit.

Table 2 shows the results of three models for the association between past opiate use, HCV infection, and prevalent diabetes. After adjusting for age, race/ethnicity, family history of diabetes, BMI, and HIV/ART status (Model 1), past opiate use remained associated with prevalent diabetes (OR_{adj} 1.69, 95% CI 1.24, 2.31). In a separate model (Model 2) adjusting for the same covariates, the association between HCV infection and prevalent diabetes was no longer significant (OR_{adj} 1.27, 95% CI 0.92, 1.75). When both past opiate use and HCV infection were included in the same model (Model 3), the association between HCV and prevalent diabetes was further attenuated (OR_{adj} 0.97, 95% CI 0.67, 1.41), while the association between past opiate use and prevalent diabetes remained the same (OR_{adj} 1.71, 95% CI 1.20, 2.45). Other factors associated with prevalent diabetes in this model included older age (OR_{adj} 1.06 per year, 95% CI 1.04, 1.08), family history of diabetes (OR_{adj} 1.77, 95% CI 1.34, 2.34), and BMI ≥ 30 kg/m^2 (OR_{adj} 3.21, 95% CI 2.28, 4.50; reference <25.0 kg/m^2). The point estimates for the multivariate models were essentially unchanged when we excluded women in whom diabetes was defined by self-report only, those who were HCV seropositive and had an undetectable HCV RNA level, or those who reported use of interferon and/or ribavirin for hepatitis C (data not shown).

Incident Diabetes

Among the 2,365 women analyzed above, 2,106 did not have prevalent diabetes at the index visit, and of these 2,016 (96%) had a fasting glucose level measured at a subsequent study visit and were thus included in the analysis of incident diabetes. The median duration of follow-up of 3.47 years (IQR 2.22, 4.41) did not differ by HCV status (p=.60). New-onset diabetes was observed in 145 women, of whom 94 (65%) were defined by a fasting plasma glucose ≥126 mg/dl at a study visit, 44 (30%) by self-report of diabetes medication use, and 7 (5%) by self-report of diabetes diagnosis with subsequent corroboration with either a fasting glucose ≥126 mg/dl or reported diabetes medication use.

Incidence rates of diabetes stratified by past opiate use, current opiate use, and HCV infection status are shown in Table 3. Women with a history of opiate use (past or current) had a higher diabetes incidence (3.68/100 person-years, 95% CI 2.66, 4.96 and 3.57/100 person-years, 95% CI 2.21, 5.45, respectively) than did non-users (1.89/100 person-years, 95% CI 1.54, 2.29 and 2.07/100 person-years, 95% CI 1.72, 2.47, respectively). Similarly HCV-infected women had a higher diabetes incidence (3.68/100 person-years, 95% CI 2.70, 4.91) than did HCV-uninfected women (1.86/100 person-years, 95% CI 1.51, 2.26). HCV-infected women who reported current opiate use had the highest diabetes incidence (4.83/100 person-years, 95% CI 2.81, 7.73).

Table 4 shows the results of three proportional hazards regression models for the association between HCV infection, current opiate use, and incident diabetes. In models controlling for classic diabetes risk factors and HIV/ART status, current opiate use and HCV infection were associated with the development of diabetes: for current opiate use (Model 1) RH_{adj} 1.89 (95% CI 1.27, 2.80); and for HCV infection (Model 2), RH_{adj} 1.78 (95% CI 1.22, 2.61). Due to the positive association between current opiate use and HCV infection, both of these hazard ratios were attenuated when current opiate use and HCV infection were entered into the same model (Model 3). Factors remaining associated with incident diabetes in this final model included current opiate use (RH_{adj} 1.58, 95% CI 1.01, 2.46), age (RH_{adj} 1.04 per year, 95% CI 1.02, 1.06), family history of diabetes (RH_{adj} 1.64, 95% CI 1.16, 2.32) and BMI ≥30 kg/m^2 (RH_{adj} 3.06, 95% CI 1.96, 4.78; reference BMI <25 kg/m^2). These point estimates were essentially unchanged when we excluded HCV seropositive women with an undetectable HCV RNA level from the fully adjusted model. When women who reported

use of interferon and/or ribavirin for hepatitis C were excluded from the fully adjusted model, the association between HCV and incident diabetes reached statistical significance (RH_{adj} 1.61, 95% CI 1.02, 2.52). HIV/ART status was not associated with incident diabetes in any model.

Among HCV-infected women, increasing HCV RNA quartiles appeared to be associated with new-onset diabetes (HR 1.30 per quartile, 95% CI 0.97, 1.73), however this association may be due to chance. Among HCV-infected women, there was no association between AST and ALT levels and incident diabetes (data not shown).

Discussion

In this large ethnically-diverse cohort of women with or at-risk for HIV infection, past opiate use was associated with increased diabetes prevalence independent of HCV infection, HIV status, or antiretroviral use. In addition, current opiate use was independently associated with an increased risk of incident diabetes. Among current opiate users, women infected with HCV had a higher diabetes incidence than did women who were uninfected. While classic diabetes risk factors, including older age, obesity and a family history of diabetes were also predictive of diabetes, the association of recent ART use with diabetes was not statistically significant.

To our knowledge, this is the first study to use prospectively collected data to investigate the possible opiate-diabetes relationship. Prior cross-sectional studies have reported associations between opiate use and disordered glucose metabolism, however they did not control for HCV status, which may have confounded the observed relationship. In the Menopause Study, a cohort of mid-life women with or at-risk for HIV infection, methadone use was found to be associated with prevalent diabetes, with an increased odds of diabetes for each quartile of current methadone dose.[21] This study also found that current opiate use (heroin or methadone) was associated with lower insulin secretion, estimated using the 30-minute incremental ratio of insulin to glucose. A similar study in CHAMPS, a comparable cohort of men with or at-risk for HIV infection, also found an independent association between methadone use and prevalent diabetes.[22] Furthermore in this cohort, a history of heroin use was associated with greater insulin resistance. Several small studies of HIV-uninfected patients have also demonstrated an association between opiate use and abnormal glucose metabolism. One study suggested that opiate use may induce insulin resistance, as higher insulin levels while fasting and after an oral glucose load were observed in heroin users compared to healthy controls.9 Other studies have reported a lower acute insulin response after an intravenous glucose load in heroin users compared to control subjects, suggesting impaired beta cell function.10,11 Abnormal glucose tolerance has also been observed in experimental studies of methadone-addicted rats.[7]

While these data provide further evidence that opiate use may affect glucose metabolism, the fact that certain studies point to beta cell dysfunction, and other studies to effects on insulin sensitivity, leaves the mechanisms uncertain. In animal models, morphine administration was found to induce glucagon release, suggesting that opiates may exert a direct effect on the pancreas, resulting in hepatic glucose output.[8] Another animal study found that opiate-induced glucose intolerance was accompanied by both a reduction in the activity of specific glycolytic enzymes, and an elevation in the activity of gluconeogenic enzymes in the liver of exposed animals.[7] Further experimental data suggest that opiates can inhibit insulin signaling through direct cross talk between downstream signaling pathways of the μ-opioid receptor and the insulin receptor.[23]

Prior studies have found that HCV infection is associated with disorders of glucose metabolism, particularly among individuals at increased risk of diabetes due to greater age and/or BMI.[24,25] We found that HCV infection, as well as greater HCV RNA levels, appeared to be positively associated with incident diabetes, although the associations were not statistically significant in all models. One retrospective cohort analysis of 1149 HIV-infected persons on HAART over a median follow-up of 8.9 months found a two-fold increase in hyperglycemia incidence among HCV-infected persons (4.9 cases/100 person-years) compared with uninfected persons (2.3 cases/100 person-years).[3] Unlike the present study, that study did not adjust for family history of diabetes, a key diabetes risk factor, and did not obtain glucose levels systematically for all cohort members, which may have resulted in selection bias. Biological evidence to support an association between HCV and diabetes include several studies demonstrating that HCV proteins interfere with insulin signaling.[26-28] In addition HCV RNA has been identified in pancreatic tissue of HIV/HCV co-infected patients, suggesting that HCV may have a direct influence on islet cell function.[29]

We did not find a strong association between ART status and incident diabetes when compared to HIV-uninfected women, in contrast to another study in men, which did not control for several key factors associated with diabetes including family history of diabetes and HCV status.1 Our findings may also be partially attributable to changing patterns of antiretroviral use, as newer PIs have less of an effect on insulin sensitivity than indinavir,[30-32] which was commonly used early in the HAART era. Among HIV-infected individuals, cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with risk of diabetes incidence and insulin resistance,[2,33] which may be attributable to NRTI-induced mitochrondrial dysfunction.34

The strengths of our study include the prospective design, the availability of fasting glucose levels to define diabetes, and the use of HCV RNA levels as an indicator of persistent HCV infection. Inclusion of data on family history of diabetes also allowed us to adjust for this important risk factor. Furthermore, our analysis was strengthened by inclusion of an HIV-uninfected comparison group with a similar demographic and behavioral profile.

Our study also has certain limitations. First, as in other analyses of diabetes in HIV cohorts,[1] we defined diabetes based on a single fasting glucose measurement, rather than after confirmation on a subsequent day as recommended by the American Diabetes Association.[35] Second, we were not able to distinguish whether diabetes medications were used to treat diabetes or for other reasons such as to treat insulin resistance or changes in fat distribution associated with HIV infection. In addition, we only measured plasma HCV RNA in HCV seropositive women. Recent data suggest that some HCV seronegative HIV-infected individuals may have detectable HCV RNA, particularly in the setting of a low CD4+ count.[36] Therefore, some HCV-infected women may have been misclassified. Finally, the findings in our cohort of predominantly African American and Hispanic women may not apply to HIV-infected populations with different sociodemographic characteristics. However given that drug use, HCV infection and diabetes all disproportionately affect these racial and ethnic groups,[37,38] understanding the association of these disorders in this population is of great importance.

In summary, we observed that opiate use was associated with increased diabetes prevalence and incidence among HIV-infected and at-risk-uninfected women, independent of HCV infection or antiretroviral use. HCV infection also appeared to increase the risk of incident diabetes. Based on our findings, routine monitoring of fasting glucose levels in women with or at-risk for HIV infection who use opiates or have persistent HCV infection may be warranted.

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Table 1

Characteristics of 2,365 participants in the Women's Interagency HIV Study at index visit by history of opiate use[a] and Hepatitis C virus status

Characteristic	History of opiate use (N = 464)	No history of opiate use (N = 1901)	*P* value[b]	HCV-infected[c] (N = 470)	HCV-uninfected[d] (N = 1895)	*P* value[b]
Age (y), median (IQR)	45 (40, 49)	37 (31, 43)	<.0001	46 (41, 49)	37 (31, 43)	<.0001
Race/ethnicity, % (N)						
African American	58% (271)	57% (1081)		64% (303)	55% (1049)	
Hispanic	27% (124)	28% (528)	0.52	20% (94)	29% (558)	<.0001
Caucasian	12% (58)	12% (223)		13% (63)	12% (218)	
Other	2% (11)	4% (69)		2% (10)	4% (70)	
Family history of diabetes, % (N)	32% (147)	28% (539)	0.16	31% (146)	28% (540)	0.27
Body mass index, % (N) [e]						
Normal (<25.0 kg/m^2)	40% (178)	34% (625)		43% (198)	33% (605)	
Overweight (25.0-29.9 kg/m^2)	28% (127)	30% (546)	0.06	27% (126)	30% (547)	0.0002
Obese (≥ 30 kg/m^2)	32% (143)	36% (670)		29% (135)	37% (678)	
Ever injected drugs, % (N)	80% (373)	12% (234)	<.0001	86% (406)	11% (201)	<.0001
Past drug use, % (N)						
None	0% (0)	84% (1597)		25% (118)	78% (1479)	
Opiates only	33% (155)	0% (0)	<.0001	18% (84)	4% (71)	<.0001
Crack or cocaine only	0% (0)	16% (304)		14% (65)	13% (239)	
Opiates and crack/cocaine	66% (309)	0% (0)		43% (203)	6% (106)	
Current opiate use, % (N)	42% (197)	1% (18)	<.0001	29% (135)	4% (80)	<.0001
Current prescription narcotic use, % (N)	14% (64)	6% (115)	<.0001	14% (68)	6% (111)	<.0001
HCV infected, % (N)	62% (287)	10% (183)	<.0001	100% (470)	0% (1895)	
HIV/ART since last visit, % (N)						
HIV-uninfected	27% (125)	28% (527)		18% (84)	30% (568)	
HIV-infected (overall)	73% (339)	72% (1374)		82% (386)	70% (1327)	
No therapy	27% (124)	24% (467)	0.18	27% (128)	24% (463)	<.0001
Mono/combination therapy	5% (23)	4% (79)		7% (34)	4% (68)	
Non-PI HAART	16% (76)	21% (399)		19% (89)	20% (386)	

Characteristic	History of opiate use (N = 464)	No history of opiate use (N = 1901)	*P* value[b]	HCV-infected[c] (N = 470)	HCV-uninfected[d] (N = 1895)	*P* value[b]
PI-HAART	25% (116)	22% (428)		29% (135)	22% (409)	
CD4 count (/mm^3), median(IQR) [f]	349 (218, 572)	443 (274, 636)	<.0001	374 (220, 574)	443 (274, 639)	0.0002
AST (U/L), median (IQR) [e]	34 (22, 55)	22 (17, 28)	<.0001	43 (30, 65)	21 (17, 27)	<.0001
ALT (U/L), median (IQR) [e]	26 (16, 44)	22 (14, 33)	<.0001	36 (24, 57)	21 (14, 31)	<.0001
Albumin (g/dL), median (IQR)	4.0 (3.7, 4.2)	4.1 (3.8, 4.3)	<.0001	3.9 (3.6, 4.2)	4.1 (3.8, 4.3)	<.0001

[a] HIV human immunodeficiency virus, HCV hepatitis C virus, AST aspartate aminotransferase, ALT alanine aminotransferase

[b] P value from chi-square test when discrete variables are compared, and from Wilcoxon rank sum test when continuous variables are compared

[c] Includes HCV seropositive women with a detectable plasma HCV RNA level

[d] Includes HCV seronegative women and HCV seropositive women with an undetectable plasma HCV RNA level

[e] Missing data for body mass index (n=76), AST (n=17) and ALT (n=21)

[f] Among HIV-infected women only

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Table 2

Unadjusted and adjusted odds of prevalent diabetes among 2,365 women[a]

	Diabetes Prevalence, % (N)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)		
			Model 1	Model 2	Model 3
Past opiate use				----[b]	
No	9 (174/1901)	1 (reference)	1 (reference)		1 (reference)
Yes	18 (85/464)	2.23 (1.68, 2.95)[c]	1.69 (1.24, 2.31)[d]		1.71 (1.20, 2.45)[e]
			----[b]	----[b]	----[b]
Current opiate use	10 (226/2150)	1 (reference)			
No	15 (33/215)	1.54 (1.04, 2.29)[f]			
Yes					
HCV infection			----[b]		
No	10 (185/1895)	1 (reference)		1 (reference)	1 (reference)
Yes	16 (74/470)	1.73 (1.29, 2.31)[d]		1.27 (0.92, 1.75)	0.97 (0.67, 1.41)
Age (per year)	--	1.07 (1.05, 1.08)[c]	1.06 (1.04, 1.08)[c]	1.07 (1.05, 1.08)[c]	1.06 (1.04, 1.08)[c]
Race/ethnicity					
African American	11 (151/1352)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Hispanic	11 (73/652)	1.00 (0.75, 1.35)	1.08 (0.79, 1.49)	1.11 (0.81, 1.52)	1.08 (0.78, 1.49)
Caucasian	11 (30/281)	0.95 (0.63, 1.44)	1.15 (0.74, 1.78)	1.15 (0.74, 1.79)	1.14 (0.74, 1.78)
Other	6 (5/80)	0.53 (0.21, 1.33)	0.78 (0.30, 2.02)	0.76 (0.29, 1.97)	0.78 (0.30, 2.02)
Family history of diabetes					
No	9 (148/1679)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	16 (111/686)	2.00 (1.53, 2.60)[c]	1.77 (1.34, 2.34)[c]	1.76 (1.33, 2.33)[c]	1.77 (1.34, 2.34)[c]
Body mass index (kg/m^2)					
Normal (<25.0)	7 (58/803)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Overweight (25.0-29.9)	7 (46/673)	0.94 (0.63, 1.41)	0.96 (0.63, 1.44)	0.95 (0.63, 1.43)	0.95 (0.63, 1.44)
Obese (≥ 30)	18 (150/813)	2.91 (2.11, 4.00)[c]	3.21 (2.29, 4.51)[c]	3.17 (2.26, 4.44)[c]	3.21 (2.28, 4.50)[c]
HIV/ART since last visit					
HIV uninfected	11 (73/652)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HIV infected					

	Diabetes Prevalence, % (N)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)		
			Model 1	Model 2	Model 3
No therapy	9 (54/591)	0.80 (0.55, 1.16)	0.78 (0.53, 1.15)	0.76 (0.52, 1.12)	0.78 (0.53, 1.16)
Mono/combination therapy	9 (9/102)	0.77 (0.37, 1.59)	0.62 (0.28, 1.37)	0.55 (0.25, 1.23)	0.62 (0.28, 1.38)
Non-PI HAART	11 (54/475)	1.02 (0.70, 1.48)	0.97 (0.65, 1.46)	0.92 (0.61, 1.37)	0.97 (0.65, 1.46)
PI-HAART	13 (69/544)	1.15 (0.81, 1.64)	1.08 (0.74, 1.59)	1.03 (0.70, 1.51)	1.09 (0.74, 1.60)

[a] OR odds ratio, CI confidence interval, HCV hepatitis C virus, HIV human immunodeficiency virus

[b] Variable not included in the model

[c] p <.0001

[d] p <.001

[e] p < .01

[f] p<.05

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Table 3

Incidence of diabetes among 2,016 women by HCV infection status and opiate use[a]

Group	N	Person years of follow-up[a]	No. incident diabetes cases	Incidence [cases/100 py] (95% CI)	Incidence [cases/100 py], (95% CI)	
					HCV infected	HCV uninfected
Overall	2,016	6,578	145	2.20 (1.86, 2.59)	3.68 (2.70, 4.91)	1.86 (1.51, 2.26)
Past opiate use						
Yes	367	1,168	43	3.68 (2.66, 4.96)	4.17 (2.81, 5.95)	2.90 (1.54, 4.95)
No	1,649	5,409	102	1.89 (1.54, 2.29)	3.02 (1.73, 4.91)	1.76 (1.41, 2.18)
Current Opiate use (time dependent) [b]						
Yes	236	589	21	3.57 (2.21, 5.45)	4.83 (2.81, 7.73)	1.69 (0.46, 4.32)
No	1,892	5,988	124	2.07 (1.72, 2.47)	3.23 (2.17, 4.64)	1.87 (1.51, 2.28)

[a] py person-years, HCV Hepatitis C virus

[b] numbers in subgroups do not always add to total due to rounding error

[c] Some participants contributed to both “used” and “did not use” opiates since last visit as their opiate use behavior was different for different visits; hence 236 + 1,892 > 2,016.

Table 4

Unadjusted and adjusted relative hazards of incident diabetes among 2,016 women[a]

Variable	Unadjusted RH (95% CI)	Adjusted RH (95% CI)		
		Model 1	Model 2	Model 3
Current opiate use	2.04 (1.41, 2.96)[b]	1.89 (1.27, 2.80)[c]	--- [c]	1.58 (1.01, 2.46)[d]
HCV infected	2.02 (1.43, 2.87)[b]	--- [d]	1.78 (1.22, 2.61)[c]	1.48 (0.96, 2.28)
Age (per year)	1.05 (1.03, 1.07)[f]	1.04 (1.02, 1.07)[f]	1.04 (1.02, 1.06)[f]	1.04 (1.02, 1.06)[b]
Race/ethnicity				
African American	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Hispanic	0.79 (0.53, 1.17)	0.87 (0.57, 1.31)	0.94 (0.62, 1.43)	0.90 (0.59, 1.37)
Caucasian	1.09 (0.68, 1.76)	1.24 (0.74, 2.06)	1.28 (0.77, 2.13)	1.26 (0.76, 2.10)
Other	0.17 (0.02, 1.24)	0.27 (0.04, 1.92)	0.28 (0.04, 2.02)	0.27 (0.04, 1.96)
Family history of diabetes	1.91 (1.37, 2.66)[c]	1.65 (1.17, 2.33)[d]	1.68(1.19, 2.36)[d]	1.64 (1.16, 2.32)[d]
Body mass index (kg/m^2)				
Normal (<25.0)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Overweight (25.0-29.9)	0.89 (0.56, 1.41)	1.58 (0.96, 2.58)	1.64 (1.00, 2.68)	1.64 (1.00, 2.68)
Obese (≥ 30)	1.70 (1.15, 2.51)[d]	2.93 (1.88, 4.56)[e]	3.01 (1.92, 4.71)[e]	3.06 (1.96, 4.78)[e]
HIV/ART status				
HIV uninfected	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HIV infected				
No therapy	0.89 (0.54, 1.47)	0.94 (0.56, 1.58)	0.89 (0.53, 1.49)	0.91 (0.54, 1.53)
Mono/combination therapy	1.17 (0.52, 2.64)	1.19 (0.52, 2.74)	1.06 (0.46, 2.43)	1.14 (0.49, 2.63)
Non-PI HAART	1.55 (0.98, 2.45)	1.67 (1.02, 2.73)[d]	1.52 (0.93, 2.47)	1.61 (0.98, 2.64)
PI-HAART	1.32 (0.83, 2.10)	1.19 (0.71, 1.97)	1.11 (0.67, 1.84)	1.15 (0.69, 1.92)

[a] RH relative hazard, CI confidence interval, HCV hepatitis C, HIV human immunodeficiency virus

[b] p<.001

[c] p<.01

[d] Variable not included in the model

[e] p<.05

[f] p<.0001