

# Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010

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## ABSTRACT

**Background:** Nationally representative estimates of diabetes mellitus (DM) prevalence among HIV-infected adults in the USA are lacking, and whether HIV-infected adults are at increased risk of DM compared with the general adult population remains controversial.

**Methods:** We used nationally representative survey (2009–2010) data from the Medical Monitoring Project (n=8610 HIV-infected adults) and the National Health and Nutrition Examination Survey (n=5604 general population adults) and fit logistic regression models to determine and compare weighted prevalences of DM between the two populations, and examine factors associated with DM among HIV-infected adults.

**Results:** DM prevalence among HIV-infected adults was 10.3% (95% CI 9.2% to 11.5%). DM prevalence was 3.8% (CI 1.8% to 5.8%) higher in HIV-infected adults compared with general population adults. HIV-infected subgroups, including women (prevalence difference 5.0%, CI 2.3% to 7.7%), individuals aged 20–44 (4.1%, CI 2.7% to 5.5%), and non-obese individuals (3.5%, CI 1.4% to 5.6%), had increased DM prevalence compared with general population adults. Factors associated with DM among HIV-infected adults included age, duration of HIV infection, geometric mean CD4 cell count, and obesity.

**Conclusions:** 1 in 10 HIV-infected adults receiving medical care had DM. Although obesity contributes to DM risk among HIV-infected adults, comparisons to the general adult population suggest that DM among HIV-infected persons may develop at earlier ages and in the absence of obesity.

## INTRODUCTION

Diabetes mellitus (DM) is an important cause of morbidity and mortality in the USA. In 2014, there were an estimated 29.1 million persons with DM, of whom 27.8% were undiagnosed.<sup>1</sup> Uncontrolled DM can result in significant disability due to complications such as blindness and end-stage renal disease, and is associated with premature mortality due to cancer and vascular disease.<sup>2–3</sup> Furthermore, the medical and societal costs of DM are substantial. In 2012,

## Key messages

- Among a nationally representative US sample of HIV-infected adults receiving medical care, the prevalence of diagnosed diabetes mellitus (DM) was 10.3%.
- HIV-infected adults may be likely to have DM at younger ages and in the absence of obesity compared with the general US adult population.
- The prevalence of DM among HIV-infected adults is high and HIV-care providers should follow existing screening guidelines, which recommend FBG and HbA1c be obtained prior to and after starting antiretroviral therapy.

in the USA alone, DM accounted for \$176 billion US in direct medical costs and \$69 billion US in reduced productivity.<sup>4</sup>

In the USA, advances in treatment of HIV infection have led to decreased mortality and increased life expectancy among HIV-infected persons.<sup>5–6</sup> Consequently, chronic metabolic and cardiovascular diseases such as DM are gaining importance as causes of morbidity and mortality among HIV-infected persons.<sup>7</sup> While the burden of DM among the general US adult population has been well described, nationally representative estimates of DM prevalence among HIV-infected adults are lacking. In addition, whether HIV-infected adults are at increased risk of developing DM compared with the general adult population remains controversial.<sup>8–11</sup>

We analyzed nationally representative data from the Medical Monitoring Project (MMP) with the following objectives: (1) estimate DM prevalence among a nationally representative sample of HIV-infected adults; (2) compare the prevalence of DM in HIV-infected adults versus the general US adult population; and (3) identify factors associated with prevalent DM among HIV-infected adults.

## METHODS

### Data sources and study design

We used 2009–2010 data from MMP and the National Health and Nutrition Examination Survey (NHANES) to estimate DM prevalence among HIV-infected adults and the general US adult population, respectively. Our analyses were restricted to adults aged  $\geq 20$  years, and excluded pregnant women.

MMP is a surveillance system that produces nationally representative estimates of behavioral and clinical characteristics of HIV-infected adults who receive HIV medical care in the USA. MMP is a cross-sectional survey with a multistage probability design. Detailed descriptions of the sampling methodology and data collection procedures have been published elsewhere.<sup>12</sup> Briefly, sampling was conducted in three consecutive stages: (1) USA and dependent areas, (2) outpatient HIV care facilities, and (3) HIV-infected adults aged  $\geq 18$  years who made at least one medical care visit to a sampled facility between January and April of 2009 and 2010. Data were collected during June 2009 through May 2011. Facility response rates were 76% (461/603) in 2009 and 81% (474/582) in 2010. Approximately 50% of persons sampled from these facilities completed an interview and had their medical records abstracted. After excluding 81 individuals who were either  $< 20$  years of age or pregnant, our MMP sample included 8610 participants, representing an estimated average of 427 928 HIV-infected adults. The Centers for Disease Control and Prevention (CDC) National Center for HIV, Viral Hepatitis, STD, and TB Prevention has determined MMP to be a non-research public health surveillance activity, and thus, it was not reviewed by a federal institutional review board (IRB). Participating states or territories and facilities obtained local IRB approval to conduct MMP if required locally. Informed consent was obtained from all interviewed participants.

NHANES is a cross-sectional health examination survey with a stratified multistage probability design representative of the general non-institutionalized US population. Descriptions of the sampling plan, and examination and interview protocol are published elsewhere.<sup>13</sup> In the 2009–2010 cycle of NHANES, the unweighted response rate for the interviewed and examined persons was 77.3%, resulting in a final sample of 10 253 persons. After excluding individuals  $< 20$  years and pregnant women, 5604 (54.6%) adults remained in the sample, representing an estimated 2.1 million non-institutionalized adults living in the USA in 2009–2010. NHANES was approved by CDC's National Center for Health Statistics Institutional Research Ethics Review Board.

Survey sample weights in NHANES and MMP account for the differential probabilities of selection, non-response to survey instruments, and differences between the final sample and the total population.

### Measures

The primary outcome variable was DM. In MMP, DM was defined using the following criteria documented in

the medical record: (1) physician-diagnosed DM listed on a problem list or in the assessment/plan portion of a progress note; or (2) prescription of insulin or oral hypoglycemic medications (excluding metformin monotherapy). In NHANES, DM was defined using the following criteria: (1) answered 'Yes' to the question: 'Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?'; or (2) answered 'Yes' to any of the following questions: (a) 'Are you now taking insulin?'; or (b) 'Are you now taking diabetic pills to lower your blood sugar? These are sometimes called oral agents and oral hypoglycemic agents'. Prescription medication data available in NHANES were used to exclude individuals treated with metformin monotherapy who had responded 'Yes' to question 2b. Exclusion of patients on metformin monotherapy who were not classified as having DM in MMP or answered 'No' to question 1 in NHANES were excluded due to the use of this medication for pre-diabetes and polycystic ovarian syndrome. Laboratory criteria to establish the diagnosis of DM were available for MMP and NHANES; however, they were not used because the fasting nature of blood glucose measurements from laboratory data abstracted from medical charts was unknown, and HbA1c measurements have not been validated for the diagnosis of DM among HIV-infected individuals.<sup>10 14 15</sup> Our analyses of DM prevalence were therefore restricted to comparisons of diagnosed DM, as described above.

Sociodemographic variables collected for MMP and NHANES included age, sex at birth, race/ethnicity, education, and poverty level. The number and percentage of participants meeting current poverty guidelines for MMP and NHANES were determined using the US Department of Health and Human Services poverty guidelines. In MMP, body mass index (BMI) measurements were abstracted from medical records for the year prior to the interview. If height was missing ( $n=1534$  (17.7%) in MMP), BMI category was inferred from recorded weight using previously published methods.<sup>16</sup> In NHANES, BMI was measured using standardized techniques and equipment. BMI  $\geq 30$  kg/m<sup>2</sup> was considered indicative of obesity. Clinical MMP variables included time since HIV diagnosis, geometric mean CD4+ T-lymphocyte (CD4) count, documented prescription of antiretroviral therapy (ART), and disease stage per CDC criteria.<sup>17</sup>

CD4 were described using geometric means, calculated by back transforming the logarithm of CD4; geometric means instead of arithmetic means were used because of the skewed distribution of CD4. MMP participants were classified as being infected with hepatitis C virus (HCV) if any of the following were documented in their medical record: (1) a positive anti-HCV enzyme immunoassay (EIA) or strip immunoblot assay (RIBA); (2) an HCV genotype or (3) HCV-RNA identified through reverse transcriptase-PCR (RT-PCR).<sup>18</sup> Indeterminate results of EIA/RIBA, HCV genotype, or

HCV-RNA were considered negative. All NHANES participants received a screening HCV antibody test by EIA with confirmation of positive test results using RIBA. Samples with an indeterminate RIBA were tested for HCV-RNA to confirm HCV infection status.

## Data analyses

### Prevalence of and factors associated with DM among HIV-infected adults

Among HIV-infected adults, we calculated the weighted prevalence and 95% CIs of DM overall and by each of the following characteristics: age (20–44, 45–60, and  $\geq 60$  years), sex at birth, race/ethnicity (non-Hispanic White and Black, Hispanic, and Other), education (less than high school, high school or equivalent, and more than high school), poverty level (living at or below the poverty line and living above the poverty line), obesity, time since HIV diagnosis (<5, 5–9, and  $\geq 10$  years), geometric mean CD4 count (0–199, 200–349, 350–499, and  $\geq 500$  cells/mm<sup>3</sup>), use of ART during the surveillance period, CDC HIV disease stage (AIDS or nadir CD4 0–199, no AIDS and nadir CD4 200–500, and no AIDS and nadir CD4 >500), and HCV coinfection. All characteristics were analyzed as categorical variables.

To identify factors associated with DM in HIV-infected persons, we used multivariable logistic regression models with DM as the dependent variable, and all previously mentioned characteristics as independent variables. We computed model-adjusted prevalences for all levels of each of the selected characteristics with predicted marginal means, and estimated crude and adjusted prevalence ratios (PR) for each characteristic.<sup>19 20</sup> We calculated CIs for adjusted-prevalence estimates and PRs.

### Comparisons between HIV-infected adults receiving medical care and general US population adults

Weighted percentages and CIs were determined for DM among HIV-infected adults and the general US adult population stratified by age group, sex at birth, race/ethnicity, education, poverty level, obesity, and HCV infection.

We used marginal standardization methods with predicted marginal probabilities to compare the prevalence of DM between MMP and NHANES. In marginal standardization, the predicted probability of the outcome of interest is adjusted to a weighted average reflecting the distribution of covariates in the target population; the marginal effect obtained is the proportion of subjects with the outcome that would have been observed were the study population forced to the exposure level (ie, HIV infection). In other words, given the demographic and clinical characteristics of the populations in MMP and NHANES, what would the predicted probability of DM be were they to be infected with HIV and vice-versa.<sup>20</sup>

Under the assumption that MMP and NHANES were two independent samples, with independent design variables and weights, we combined the two data sets and

constructed a multivariable logistic model using predicted marginal probabilities with DM as the outcome variable and the following independent variables: an indicator variable for survey type (1=MMP; 0=NHANES), all characteristics listed above, and interaction terms between the indicator variable and all characteristics.<sup>21 22</sup>

Using the predicted marginal prevalence of DM, we computed prevalence differences (PD) comparing the two populations, adjusting for all characteristics in MMP and NHANES included in the model.<sup>19</sup> Linear contrasts were used to test for heterogeneity among subgroups between the adjusted estimates of diagnosed DM in the HIV-infected and general US adult populations. To assess whether differences in care-seeking could account for differences in DM prevalence between the two populations, we performed a second analysis restricting our comparison of HIV-infected adults receiving medical care to the general US adult population who had received medical care in the previous year.

All analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA) and SAS-callable SUDAAN 10.0.1 (RTI International, Research Triangle Park, North Carolina, USA) and accounted for clustering, unequal selection probabilities, and non-response.

## RESULTS

MMP participants had the following characteristics: male (73.6%), non-Hispanic black (41.3%), aged 45 or more years (59.9%), with greater than a high school education (52.2%), and living above the federal poverty level (56.5%) (table 1). A quarter of MMP participants had a BMI  $\geq 30$  kg/m<sup>2</sup>, 20.6% were HCV-positive, 90.0% had been prescribed ART in the previous year, and 73.0% had their most recent HIV viral load reported <200 copies/mL. NHANES participants had the following characteristics: male (49.3%), non-Hispanic black (11.7%), aged 45 or more years (51.4%), with greater than a high school education (58.7%), and living above the federal poverty level (91.5%). More than a third (36.0%) of the general US adult population had a BMI  $\geq 30$  kg/m<sup>2</sup>, and 1.7% had HCV infection.

The unadjusted prevalence of DM (CI) among HIV-infected adults was 10.3% (9.1% to 11.5%), and was higher compared with the general US adult population (8.3% (7.2% to 9.4%)) as well as the general US adult population having received care in the previous 12 months (9.7% (8.4% to 11.1%)) (data not shown). Among HIV-infected adults with diagnosed DM, 3.9% (95% CI 2.9% to 5.2%) had DM type 1, 52.3% (CI 46.7% to 57.8%) had DM type 2, and 43.9% (CI 38.1% to 49.8%) had unspecified DM. After adjusting for differences in distributions of sex, age, race/ethnicity, education, poverty, obesity, and HCV infection prevalence, the adjusted PD (aPD) of DM in HIV-infected adults versus the general US adult population was 3.8% (table 2). The largest difference in DM prevalence among HIV-infected adults relative to their counterparts

**Table 1** Characteristics of HIV-infected adults and general US population adults, MMP and NHANES 2009–2010

	HIV-infected adults*		General population adults*	
	Sample n	Weighted % (95% CI)	Sample n	Weighted % (95% CI)
Total	8610	–	5604	–
Sex at birth				
Male	6349	73.6 (70.3 to 76.7)	2745	49.3 (48.1 to 50.6)
Female	2261	26.4 (23.3 to 29.7)	2859	50.7 (49.4 to 51.9)
Race/ethnicity				
White (non-Hispanic)	2869	34.6 (27.6 to 42.3)	2584	67.3 (59.8 to 74.0)
Black (non-Hispanic)	3512	41.3 (32.4 to 50.8)	1051	11.7 (10.0 to 13.7)
Hispanic or Latino	1827	19.3 (14.2 to 25.7)	1656	14.0 (8.8 to 21.3)
Other	402	4.9 (3.9 to 6.0)	313	7.1 (5.1 to 9.9)
Age in years				
20–44	3412	40.1 (38.7 to 41.5)	2518	48.6 (46.2 to 51.1)
45–60	4366	50.3 (48.9 to 51.6)	1473	29.8 (28.5 to 31.1)
≥60	832	9.6 (8.8 to 10.6)	1613	21.6 (20.1 to 23.2)
Education				
Less than high school	1937	21.5 (19.1 to 24.1)	1570	18.4 (16.5 to 20.5)
High school or equivalent	2314	26.3 (24.1 to 28.7)	1289	22.9 (20.7 to 25.2)
More than high school	4356	52.2 (47.7 to 56.6)	2722	58.7 (55.7 to 61.7)
Living at or below poverty line†				
Yes	3790	43.5 (39.6 to 47.5)	713	8.5 (7.0 to 10.3)
No	4565	56.5 (52.5 to 60.4)	4608	91.5 (89.7 to 93.0)
Obese (BMI ≥30 kg/m <sup>2</sup> )				
Yes	2071	25.5 (23.9 to 27.2)	2073	36.0 (34.0 to 38.2)
No	6208	74.5 (72.8 to 76.2)	3291	64.0 (61.9 to 66.0)
Hepatitis C virus‡				
Positive	1556	20.6 (18.7 to 22.7)	106	1.7 (1.2 to 2.4)
Negative	5590	79.4 (77.3 to 81.3)	5190	98.3 (97.6 to 98.8)
Time since HIV diagnosis				
Less than 5 years	1866	22.4 (20.7 to 24.1)	–	–
5–9 years	1932	22.6 (21.6 to 23.6)	–	–
10 or more years	4806	55.0 (52.8 to 57.3)	–	–
AIDS/nadir CD4 count in cells/mm <sup>3</sup>				
AIDS or nadir CD4 0–199	5952	68.5 (67.2 to 69.7)	–	–
No AIDS and nadir CD4 200–500	2098	24.8 (23.4 to 26.2)	–	–
No AIDS and nadir CD4 >500	540	6.8 (6.0 to 7.6)	–	–
Geometric mean CD4 past 12 months				
0–199 cells/mm <sup>3</sup>	1118	13.0 (12.1 to 13.9)	–	–
200–349 cells/mm <sup>3</sup>	1486	17.9 (16.9 to 19.1)	–	–
350–499 cells/mm <sup>3</sup>	1949	23.6 (22.6 to 24.7)	–	–
≥500 cells/mm <sup>3</sup>	3739	45.5 (44.0 to 47.0)	–	–
Prescribed ART				
Yes	7751	90.0 (89.2 to 90.7)	–	–
No	828	10.1 (9.3 to 10.8)	–	–
Most recent viral load undetectable or <200 copies/mL				
Yes	6287	73.0 (71.0 to 75.0)	–	–
No	2323	27.0 (25.1 to 29.1)	–	–

\*Includes adults ≥20 years of age and excludes pregnant women.

†Calculated using the ratio of annual household income to number of people in the household.

‡A total of n=7146 and n=5295 were screened for hepatitis C (HCV) in MMP and NHANES, respectively. HCV positivity was defined as having a documented positive anti-HCV enzyme immunoassay or strip immunoblot assay RIBA, HCV genotype, or HCV RNA through reverse transcriptase-PCR (RT-PCR).

ART, antiretroviral therapy; BMI, body mass index; MMP, Medical Monitoring Project; NHANES, National Health and Nutrition Examination Survey.

in the general US adult population occurred among those with HCV infection (6.3%), those with a high school or equivalent education (5.1%), women (5.0%), non-Hispanics whites (4.9%), individuals living at or below the poverty line (4.6%), obese individuals (4.4%)

and ages 20–44 years (4.1%). After restricting the NHANES population to adults who had received care in the previous 12 months, associations were similar to those described above with a slight decrease in the magnitude of DM PD (table 3).

**Table 2** Predicted marginal prevalence and prevalence comparisons of diagnosed diabetes among HIV-infected adults and general US population adults, MMP and NHANES 2009, 2010

	HIV-infected adults Adjusted prevalence (95% CI)	General population adults Adjusted prevalence (95% CI)	aPR (95% CI)*	aPD (95% CI)†	p Value
Total	11.8 (10.1 to 13.7)	8.0 (7.1 to 9.1)	1.47 (1.21 to 1.78)	3.8 (1.8 to 5.8)	0.0002
Sex at birth					
Male	11.2 (9.9 to 12.7)	8.9 (7.2 to 10.7)	1.28 (1.02 to 1.60)	2.4 (0.3 to 4.6)	0.03
Female	12.4 (10.1 to 15.2)	7.4 (6.4 to 8.5)	1.68 (1.31 to 2.15)	5.0 (2.3 to 7.7)	0.0003
Race/ethnicity					
White (non-Hispanic)	11.4 (9.6 to 13.5)	6.5 (5.3 to 7.9)	1.76 (1.37 to 2.28)	4.9 (2.7 to 7.2)	<0.0001
Black (non-Hispanic)	13.1 (11.1 to 15.4)	11.8 (9.7 to 14.3)	1.11 (0.87 to 1.42)	1.3 (−1.7 to 4.3)	0.4
Hispanic or Latino	13.1 (10.3 to 16.4)	11.4 (9.4 to 13.8)	1.14 (0.85 to 1.54)	1.6 (−2.1 to 5.4)	0.4
Other	11.7 (8.5 to 15.9)	14.8 (11.4 to 18.9)	0.79 (0.53 to 1.17)	−3.1 (−8.3 to 2.1)	0.2
Age in years					
20–44	6.4 (5.3 to 7.6)	2.3 (1.7 to 3.2)	2.77 (1.91 to 4.02)	4.1 (2.7 to 5.5)	<0.0001
45–60	13.0 (11.0 to 15.2)	9.1 (7.5 to 10.9)	1.43 (1.12 to 1.81)	3.9 (1.3 to 6.5)	0.004
≥60	21.9 (17.9 to 26.6)	19.5 (16.8 to 22.6)	1.12 (0.88 to 1.44)	2.4 (−2.8 to 7.6)	0.4
Education					
Less than high school	13.0 (10.3 to 16.2)	10.6 (9.3 to 12.1)	1.22 (0.94 to 1.59)	2.3 (−0.9 to 5.6)	0.2
High school or equivalent	11.4 (9.9 to 13.6)	6.3 (5.3 to 7.5)	1.81 (1.39 to 2.35)	5.1 (2.6 to 7.5)	0.0001
More than high school	11.6 (9.9 to 13.6)	7.8 (6.5 to 9.4)	1.48 (1.17 to 1.87)	3.8 (1.5 to 6.1)	0.001
Living at or below poverty line‡					
No	11.8 (10.1 to 13.8)	8.1 (7.2 to 9.1)	1.46 (1.20 to 1.77)	3.7 (1.6 to 5.8)	0.0005
Yes	11.8 (9.8 to 14.1)	7.2 (5.4 to 9.7)	1.63 (1.17 to 2.27)	4.6 (1.7 to 7.4)	0.002
Obesity (BMI ≥30 kg/m <sup>2</sup> )					
No	7.8 (6.2 to 9.9)	4.3 (3.5 to 5.4)	1.81 (1.32 to 2.49)	3.5 (1.4 to 5.6)	0.0009
Yes	18.1 (15.8 to 20.7)	13.7 (12.1 to 15.6)	1.32 (1.10 to 1.58)	4.4 (1.5 to 7.4)	0.003
Hepatitis C virus§					
Positive	13.4 (11.0 to 16.2)	7.1 (3.8 to 13.1)	1.88 (0.98 to 3.61)	6.3 (1.1 to 11.4)	0.02
Negative	11.8 (10.1 to 13.7)	8.1 (7.1 to 9.1)	1.46 (1.21 to 1.77)	3.7 (1.7 to 5.7)	0.0003

\*Prevalence ratio using NHANES as the referent category.

†Prevalence difference calculated as prevalence(MMP)–prevalence(NHANES).

‡Calculated using the ratio of annual household income to number of people in the household.

§A total of n=7146 and n=5295 were screened for hepatitis C (HCV) in MMP and NHANES, respectively. HCV positivity was defined as having a documented positive anti-HCV enzyme immunoassay or strip immunoblot assay RIBA, HCV genotype, or HCV RNA through reverse transcriptase–PCR (RT–PCR).

aPD, adjusted prevalence difference; aPR, adjusted prevalence ratio; BMI, body mass index; MMP, Medical Monitoring Project; NHANES, National Health and Nutrition Examination Survey.

**Table 3** Predicted marginal prevalence and prevalence comparisons of diagnosed diabetes among HIV-infected adults and general US population adults having received medical care in the previous 12 months, MMP and NHANES 2009–2010

	HIV-infected adults Adjusted prevalence (95% CI)	General population adults Adjusted prevalence (95% CI)	aPR (95% CI)*	aPD (95% CI)†	p Value
Total	12.4 (10.6 to 14.4)	9.38 (8.2 to 10.7)	1.32 (1.09 to 1.61)	3.0 (0.8 to 5.2)	0.007
Sex at birth					
Male	11.7 (10.3 to 13.3)	10.6 (8.6 to 13)	1.11 (0.88 to 1.4)	1.1 (–1.4 to 3.7)	0.4
Female	13.0 (10.5 to 15.9)	8.36 (7.3 to 9.6)	1.55 (1.22 to 1.97)	4.6 (1.7 to 7.5)	0.002
Race/ethnicity					
White (non-Hispanic)	12.0 (10.1 to 14.2)	7.58 (6.2 to 9.2)	1.58 (1.23 to 2.04)	4.4 (1.9 to 6.9)	0.0005
Black (non-Hispanic)	13.8 (11.7 to 16.2)	13.47 (11.3 to 15.9)	1.02 (0.81 to 1.29)	0.3 (–2.8 to 3.4)	0.8
Hispanic or Latino	13.8 (10.9 to 17.3)	14 (11.6 to 16.7)	0.98 (0.73 to 1.31)	–0.3 (–4.3 to 3.8)	0.9
Other	12.3 (8.9 to 16.7)	17.22 (13.3 to 22)	0.71 (0.48 to 1.06)	–4.9 (–11.0 to 0.8)	0.09
Age in years					
20–44	6.5 (5.4 to 7.8)	2.72 (1.9 to 3.9)	2.37 (1.59 to 3.54)	3.7 (2.2 to 5.3)	<0.0001
45–60	13.1 (11.1 to 15.4)	10.35 (8.6 to 12.4)	1.27 (1.00 to 1.61)	2.8 (–0.0 to 5.6)	0.05
≥60	22.2 (18.1 to 26.9)	20.54 (17.8 to 23.6)	1.08 (0.85 to 1.37)	1.6 (–3.6 to 6.9)	0.5
Education					
Less than high school	13.6 (10.8 to 17)	13.12 (11.3 to 15.1)	1.04 (0.79 to 1.36)	0.5 (–3.2 to 4.2)	0.8
High school or equivalent	11.9 (9.9 to 14.4)	7.32 (6 to 8.9)	1.63 (1.23 to 2.15)	4.6 (1.9 to 7.3)	0.001
More than high school	12.2 (10.3 to 14.4)	8.94 (7.4 to 10.8)	1.36 (1.07 to 1.74)	3.3 (0.7 to 5.8)	0.01
Living at or below poverty line‡					
No	12.4 (10.6 to 14.5)	9.43 (8.3 to 10.6)	1.31 (1.08 to 1.60)	3.0 (0.7 to 5.2)	0.01
Yes	12.4 (10.3 to 14.8)	8.72 (6.6 to 11.5)	1.42 (1.03 to 1.95)	3.6 (0.5 to 6.8)	0.02
Obesity (BMI ≥30 kg/m <sup>2</sup> )					
No	8.1 (6.4 to 10.3)	5.14 (4.1 to 6.5)	1.58 (1.13 to 2.21)	3.0 (0.7 to 5.3)	0.01
Yes	18.7 (16.2 to 21.4)	15.35 (13.5 to 17.4)	1.22 (1.01 to 1.46)	3.3 (0.2 to 6.5)	0.04
Hepatitis C virus§					
Positive	14.0 (11.5 to 17)	8.22 (4.4 to 14.8)	1.71 (0.90 to 3.23)	5.8 (0.1 to 11.5)	0.04
Negative	12.4 (10.6 to 14.4)	9.4 (8.3 to 10.7)	1.32 (1.08 to 1.60)	3.0 (0.8 to 5.2)	0.009

\*Prevalence ratio using NHANES as the referent category.

†Prevalence difference calculated as prevalence(MMP)–prevalence(NHANES).

‡Calculated using the ratio of annual household income to number of people in the household.

§A total of n=7146 and n=5295 were screened for hepatitis C (HCV) in MMP and NHANES, respectively. HCV positivity was defined as having a documented positive anti-HCV enzyme immunoassay or strip immunoblot assay RIBA, HCV genotype, or HCV RNA through reverse transcriptase–PCR (RT–PCR).

aPD, adjusted prevalence difference; aPR, adjusted prevalence ratio; BMI, body mass index; MMP, Medical Monitoring Project; NHANES, National Health and Nutrition Examination Survey.

Among HIV-infected adults, DM prevalence varied by selected characteristics (table 4). The adjusted DM prevalence was lowest among those aged 20–44 years (6.7%) and highest among those aged  $\geq 60$  years (19.6%), and obese (18.9%) (table 4). Factors independently associated with total DM among HIV-infected adults included increasing age, obesity, increasing time since HIV diagnosis, and geometric mean CD4.

## DISCUSSION

Among a nationally representative US sample of HIV-infected adults receiving medical care in 2009 and 2010, the DM prevalence was 10.3%; increasing age, obesity, longer duration of HIV infection, and geometric mean CD4 were independently associated with a higher DM prevalence. When compared with the general US adult population, HIV-infected individuals had a 3.8% higher prevalence of DM after adjusting for age, sex, race/ethnicity, education, poverty-level, obesity, and HCV infection. This analysis provides the first nationally representative estimate of DM burden among HIV-infected adults and suggests that HIV-infected persons may be more likely to have DM at younger ages and in the absence of obesity compared with the general US adult population.

Our estimates of DM prevalence among HIV-infected adults are lower compared with previous US studies. The Multicenter AIDS Cohort Study reported 14% DM prevalence among 411 men who have sex with men recruited from 1999 to 2003.<sup>8</sup> The Veterans Aging Cohort Study Virtual Cohort observed a similar baseline prevalence (14%) in a cohort of 27 350 HIV-infected veterans recruited from 2003 to 2009.<sup>23</sup> These differences may reflect the burden of undiagnosed diabetes measured with fasting blood glucose and HbA1c. The HIV Outpatient Study (HOPS) reported a higher DM prevalence among HIV-infected women (19%) compared with HIV-infected men (12%), a finding that although not statistically significant was observed in our sample.<sup>24</sup> Conversely, DM prevalence among HIV-infected individuals in non-US cohorts is significantly lower than our estimate, ranging from 2.7% to 3.3%.<sup>9 25 26</sup>

Similar to previous studies, we observed a strong association between both increasing age and obesity and prevalent DM among HIV-infected individuals,<sup>8 10 11 24 26 27</sup> suggesting that these traditional risk factors play a major role in the development of DM among HIV-infected adults. Despite evidence suggesting a link between ART and DM, ART prescription in the past year was not associated with prevalent DM in our study.<sup>9 24 26</sup> This may be due to our inability to assess cumulative exposure to ART in MMP. The ARTs indinavir, zidovudine, saquinavir, stavudine, and didanosine have been associated with a higher prevalence of DM;<sup>9 24 25</sup> only a small percentage of HIV-infected adults in MMP were currently prescribed these agents (0.4% indinavir, 11.2% zidovudine, 1.0% saquinavir, 1.2% stavudine, and 2.4% didanosine),

which may also account for the null association between ART exposure and DM. Time since HIV diagnosis was significantly associated with a higher DM prevalence. Although the exact mechanistic pathways measured by this variable are hard to elucidate, it may serve as a proxy for older age, exposure to chronic inflammation due to HIV infection, as well as cumulative exposure to ART, all of which have been linked to insulin resistance.<sup>24 26–30</sup> Another surrogate marker for systemic inflammation, CD4 count nadir, was not associated with increased prevalence of DM after adjusting for other covariates. This is contrary to previous studies which have linked CD4+ nadir  $< 200$  cells/ $\mu\text{L}$  with increased levels of interleukin 6, high-sensitivity C reactive protein, and soluble tumor necrosis receptors.<sup>26 31 32</sup> In addition, geometric mean CD4 count was associated with a higher prevalence of DM in our sample; however, the lack of clear directionality makes it hard to interpret. Taken together, our results highlight the need for more nuanced measures of chronic inflammation present in HIV infection and their interaction with traditional risk factors such as obesity.

The aPD of DM between HIV-infected adults and the general US adult population was heterogeneous by sub-population. HIV-infected women had a 5% higher prevalence than their counterparts in the general population, an effect that was independent of obesity. There is evidence that the use of ART may increase conversion to DM among women with high-risk genetic polymorphisms;<sup>33</sup> however, sex-specific differences in insulin resistance, particularly the role of sex hormones in the setting of HIV infection, remain understudied. Beyond the effect of ART on insulin resistance and development of DM, chronic inflammation during HIV infection may accelerate the development of comorbid conditions such as DM.<sup>32</sup> Although this chronic inflammatory state may explain the development of DM among HIV-infected adults at younger ages and among the non-obese, there is a continued need for research assessing other important risk factors for DM among HIV-infected individuals, including diet and exercise, as well as a deeper understanding of insulin and glucose homeostasis in the setting of HIV infection.

Finally, although HCV has been described as a risk factor for DM in the general population, our findings indicate that HIV may compound the deleterious effects of HCV, putting HIV/HCV coinfecting individuals at even higher risk of DM.<sup>34</sup> Observed differences could be due to a lower engagement in medical care by HCV-infected adults in the general population and sub-optimal screening practices.<sup>35</sup> Nevertheless, this finding is particularly relevant, given the availability of directly acting antiviral agents as curative HCV therapy and highlights a potential additional benefit of HCV treatment for coinfecting patients.<sup>36</sup>

Based on our findings, as well as current literature regarding DM among HIV-infected individuals, there are several important implications. First, HIV-care

**Table 4** Prevalence of and factors associated with diagnosed diabetes mellitus among HIV-infected adults, MMP 2009–2010

	Sample n*	Weighted prevalence % (95% CI)	Adjusted weighted prevalence % (95% CI)	cPR (95% CI)	aPR (95%CI)	p Value†
Total	8610	10.2 (9.1 to 11.4)	10.7 (9.6 to 11.8)	–	–	–
Sex at birth						0.2
Male	6349	9.5 (8.3 to 10.7)	10.3 (9.2 to 11.5)	Ref	Ref	
Female	2261	12.4 (10.7 to 14.0)	11.5 (9.7 to 13.6)	1.30 (1.14 to 1.49)	1.12 (0.94 to 1.33)	
Race/ethnicity						0.1
White (non-Hispanic)	2869	8.9 (7.4 to 10.5)	9.4 (8.0 to 10.9)	ref	ref	
Black (non-Hispanic)	3512	11.3 (9.9 to 12.7)	11.5 (10.0 to 13.2)	1.26 (1.07 to 1.50)	1.23 (1.02 to 1.48)	
Hispanic or Latino	1827	10.4 (8.7 to 12.1)	11.2 (9.3 to 13.6)	1.17 (0.93 to 1.46)	1.20 (0.96 to 1.50)	
Other	402	10.3 (6.7 to 13.9)	10.7 (7.8 to 14.7)	1.16 (0.87 to 1.53)	1.15 (0.87 to 1.52)	
Age in years						<0.0001
20–44	3412	5.8 (4.9 to 6.7)	6.7 (5.8 to 7.7)	ref	ref	
45–60	4366	12.0 (10.7 to 13.4)	11.9 (10.5 to 13.6)	2.07 (1.82 to 2.36)	1.79 (1.53 to 2.08)	
≥60	832	19.3 (16.1 to 22.6)	19.6 (16.3 to 23.5)	3.33 (2.83 to 3.91)	2.94 (2.36 to 3.67)	
Education						0.6
Less than high school	1937	12.1 (10.1 to 14.1)	11.5 (9.7 to 13.6)	1.24 (1.00 to 1.55)	1.09 (0.89 to 1.34)	
High school or equivalent	2314	9.7 (8.0 to 11.5)	10.3 (8.6 to 12.2)	1.00 (0.84 to 1.18)	0.97 (0.80 to 1.18)	
More than high school	4356	9.7 (8.3 to 11.2)	10.5 (9.3 to 12)	ref	ref	
Living at or below poverty line‡						0.9
No	4565	10.4 (8.8 to 11.3)	10.6 (9.2 to 12.2)	ref	ref	
Yes	3790	10.7 (9.1 to 12.2)	10.8 (9.3 to 12.5)	1.06 (0.92 to 1.23)	1.02 (0.83 to 1.25)	
Obesity (BMI ≥30 kg/m <sup>2</sup> )						<0.0001
No	6208	7.8 (6.4 to 9.1)	7.9 (6.7 to 9.4)	ref	ref	
Yes	2071	17.7 (16.4 to 19.1)	18.9 (17 to 20.9)	2.29 (1.88 to 2.79)	2.38 (1.91 to 2.95)	
Hepatitis C virus§						0.3
Positive	1556	12.9 (10.9 to 14.9)	11.6 (9.8 to 13.6)	1.31 (1.10 to 1.58)	1.11 (0.92 to 1.35)	
Negative	5590	9.8 (8.7 to 11.0)	10.4 (9.2 to 11.8)	ref	ref	
Time since HIV diagnosis						<0.0001
Less than 5 years	1866	5.4 (3.9 to 6.9)	7.0 (5.3 to 9.1)	ref	ref	
5–9 years	1932	8.6 (7.0 to 10.2)	9.8 (8.1 to 11.8)	1.59 (1.22 to 2.08)	1.41 (1.06 to 1.87)	
10 or more years	4806	12.9 (11.6 to 14.2)	12.3 (11.1 to 13.5)	2.40 (1.88 to 3.05)	1.77 (1.38 to 2.27)	
AIDS/nadir CD4 count in cells/mm <sup>3</sup>						0.3
AIDS or nadir CD4 0–199	5952	10.8 (9.7 to 11.8)	10.5 (9.5 to 11.6)	1.27 (1.08 to 1.52)	1.01 (0.83 to 1.22)	
No AIDS and nadir CD4 200–500	2098	8.5 (6.5 to 10.4)	10.4 (8.6 to 12.6)	ref	ref	
No AIDS and nadir CD4 >500	540	11.2 (8.0 to 14.3)	13.5 (9.6 to 18.6)	1.32 (0.97 to 1.79)	1.29 (0.94 to 1.78)	
Geometric mean CD4 past 12 months						0.0007
0–199 cells/mm <sup>3</sup>	1118	9.8 (7.8 to 11.8)	10.1 (7.9 to 12.7)	1.11 (0.87 to 1.40)	1.14 (0.88 to 1.47)	
200–349 cells/mm <sup>3</sup>	1486	9.8 (7.9 to 11.7)	11.4 (9.5 to 13.7)	1.11 (0.89 to 1.37)	1.29 (1.05 to 1.59)	
350–499 cells/mm <sup>3</sup>	1949	8.9 (7.8 to 10.0)	8.8 (7.7 to 10.1)	ref	ref	
≥500 cells/mm <sup>3</sup>	3739	11.3 (9.8 to 12.8)	11.5 (10.1 to 13.2)	1.27 (1.13 to 1.90)	1.30 (1.14 to 1.50)	
Prescribed ART						0.054
No	828	7.2 (5.1 to 9.4)	8.3 (6.2 to 10.9)	Ref	Ref	
Yes	7751	10.6 (9.5 to 11.7)	10.9 (9.8 to 12.1)	1.47 (1.13 to 1.90)	1.32 (0.99 to 1.76)	

\*Includes adults aged ≥ 20 years.

†p Value of association for the multivariable model.

‡Calculated using the ratio of annual household income to number of people in the household.

§A total of n=7146 were screened for hepatitis C (HCV) in MMP. HCV positivity was defined as having a documented positive anti-HCV enzyme immunoassay or strip immunoblot assay RIBA, HCV genotype, or HCV RNA through reverse transcriptase–PCR (RT–PCR).

aPR, adjusted prevalence ratio; ART, antiretroviral therapy; BMI, body mass index; cPR, crude prevalence ratio; MMP, Medical Monitoring Project.



providers should follow existing DM screening guidelines, which recommend FBG and HbA1c be obtained prior to and after starting ART.<sup>37</sup> Second, existing data from prospective studies should be examined to determine if screening guidelines should be modified, given the increased prevalence of DM among younger and non-obese HIV-infected persons. Third, improved tests for DM diagnosis and monitoring among HIV-infected persons should be explored, given studies that have demonstrated the diagnostic limitations of HbA1c in this population.<sup>10 14 15</sup> Finally, additional research will be important to identify optimal DM management strategies among HIV-infected persons as traditional strategies to improve insulin sensitivity such as weight loss and diabetic medical therapy have been shown to be less effective among HIV-infected individuals.<sup>38 39</sup>

This analysis is subject to several limitations. First, the definition of diagnosed DM was different between MMP (medical record abstraction) and NHANES (self-reported) and may be a source of bias. A recent cohort-based validation of prevalence of DM based on self-report showed a specificity and negative predictive value >95%, with a sensitivity and positive predictive value between 60% and 70%.<sup>40</sup> This indicates that were there a bias introduced by self-reporting of DM, it would be towards and increased prevalence of DM with self-report. Furthermore, comparisons between self-reported and medical record-based estimates of DM have shown substantial agreement between both measures, and in some cases, an underestimation of DM prevalence in medical records relative to self-report.<sup>41–43</sup> Second, there is a risk of observer bias in our sample, given differences in engagement in care between our samples. We addressed this by performing a sensitivity analysis restricting the NHANES sample to adults having received care in the previous 12 months. Although we observed only slight changes in the magnitude of the associations, there is a possibility of overestimation of the PD between MMP and NHANES. Third, risk factors for DM, such as family history/genetics, diet, and exercise, were not included in this analysis and could explain some of the excess prevalence observed among HIV-infected adults. However, the inclusion of patients with type 1 diabetes is unlikely to have resulted in the excess diabetes prevalence observed in our study as the prevalence of type 1 diabetes in NHANES has been estimated to range between 3.6% and 4.8%.<sup>44</sup> Fourth, the measurement of BMI and HCV were standardized for the NHANES population and not for MMP participants resulting in a biased association between these variables and DM when comparing NHANES and MMP participants. Fifth, MMP data are representative of HIV-infected persons receiving medical care and do not necessarily reflect DM prevalence among HIV-infected persons not diagnosed or not receiving care. Sixth, the increased prevalence of DM among HIV-infected women relative to the general US adult population may be due to misclassification bias; although we excluded pregnant women and diagnoses labeled

gestational diabetes in the medical record of MMP participants, female patients with gestational diabetes may have been mislabeled and included in our sample. Finally, the NHANES population included HIV-infected adults who may or may not have received medical care. However, the prevalence of HIV-infected individuals in the NHANES population is negligible (0.21%).<sup>45</sup> Although diabetes rates were standardized to the combined population of MMP and NHANES, given the very small percentage represented by MMP in the general US adult population, the bias introduced should be minimal.

## CONCLUSION

We presented the first nationally representative estimate of DM prevalence among HIV-infected adults receiving medical care in the USA in 2009–2010 where 1 in 10 HIV-infected adults had a diagnosis of DM. Although obesity is a risk factor for prevalent DM among HIV-infected adults, when compared with the general US adult population, HIV-infected adults may have higher DM prevalence at younger ages and in the absence of obesity. Healthcare providers caring for HIV-infected patients should follow existing DM screening guidelines. Given the large burden of DM among HIV-infected adults, additional research would help to determine whether DM screening guidelines should be modified to include HIV infection as a risk factor for DM and to identify optimal management strategies in this population.

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**Data sharing statement** NHANES additional data include biometric, social, and demographic characteristics, and data sets are available to the general public through the Centers for Disease Control and Prevention website. MMP additional data include biometric, social, behavioral, and demographic data and are only available to Centers for Disease Control and Prevention employed in the Clinical and Behavioral Branches of domestic HIV surveillance.

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