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Risk for Incident Diabetes is Greater in Pre-Diabetic Men with HIV than Without HIV

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Abstract

Background: Diabetes mellitus (DM) is a major comorbidity in people living with HIV (PWH). Hyperglycemia below diabetic range defines pre-diabetes (pre-DM). We compared the progression from pre-DM to DM in PWH and people without HIV (PWOH).

Methods: Fasting glucose (FG) was measured semi-annually in the MACS since 1999. Men with pre-DM (FG between 100–125 mg/dL, confirmed within a year by FG in the pre-DM range or HbA1c between 5.7–6.4%) were included. The first visit with pre-DM was the baseline visit. Incident DM was defined as FG ≥126 mg/dL, confirmed at a subsequent visit, or self-reported DM, or use of anti-DM medication. We used binomial transition models to compare the progression from pre-DM to DM by HIV serostatus, adjusted for age, number of previous pre-DM to DM transitions, ethnicity, body mass index (BMI), family history of DM, and hepatitis C virus (HCV) infection.

Results: Between 1999 and 2019, 1584 men (793 PWH; 791 PWOH) with pre-DM were included. At baseline, PWH were younger (48 vs 51 years, $p<0.01$), had lower BMI (26 vs 27), were more frequently non-white (47% vs 30%), and HCV-infected as per last measure (8% vs 4%) than PWOH (all $p<0.01$). Over a median 12-year follow-up, 23% of participants developed DM. In adjusted analyses, the risk for incident DM was 40% [95% CI: 0% to 80%] higher among PWH than PWOH ($p=0.04$).

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Conflicts of Interest

LS has served as a consultant to Gilead Sciences, Merck, ViiV. TTB has served as a consultant to ViiV Healthcare, Gilead Sciences, Merck, Theratechnologies, and Janssen. FJP has served on Advisory Boards and has done speaker programs for Gilead Sciences, Janssen, ViiV, Merck. JL has served as a consultant for Merck and Theratechnologies. JPV, JEL, AGA and BWB declared no conflict of interest.

Conclusion: Among men with pre-DM, PWH had an increased risk of incident DM adjusted for competing risk factors, warranting the evaluation of DM prevention strategies.

Keywords

Pre diabetes; Incident diabetes; HIV infected patients; MACS cohort study

Introduction

Use of combination antiretroviral therapy (cART) has dramatically improved survival and life expectancy among people living with HIV (PWH). However, in the context of life-long cART use, the management of chronic non-infectious comorbidities, including diabetes mellitus (DM), has become a major issue in the care of aging PWH. The incidence of DM is increasing among PWH and has been linked to the effects of cART, as well as to the effects of chronic HIV infection[1–3]. There is also conflicting evidence on whether HIV infection is an independent risk factor for DM[4]. Similar to the general population, DM in PWH has been associated with hypertension, dyslipidemia, and overall increased risk for cardiovascular disease and renal impairment[5].

Both fasting glucose (FG) and hemoglobin A1c (HbA1c) are now widely used for the diagnosis of DM, supported by current guidelines[6]. The Expert Committee on the Diagnosis and Classification of DM[6] recognizes a group of persons whose glucose levels do not meet the criteria for DM but are not within the normal range. They termed this condition pre-diabetes (pre-DM), defined as a FG level between 100 and 125 mg/dL (5.6 and 6.9 mmol/L), or a HbA1c level between 5.7 and 6.4%. In the MESA study, individuals with pre-DM had an increased incidence of DM during the seven years of follow-up (HR: 10.5 [95% CI: 8.4–13.1], $p<0.0001$) compared to those with normal FG[7].

As cART-treated PWH age, the prevalence of DM is expected to increase. In a modelling study, Smit et al.[8] predicted a marked increase in the prevalence of DM (from 4% to 17%) between 2010 and 2030 within the ATHENA cohort in the Netherlands. Among PWH, specific factors have been clearly associated with DM, including certain antiretroviral therapies[9], systemic levels of inflammation[10], aging, and genetic factors. However, the clinical significance of pre-DM in PWH has not been established.

In previous Multicenter AIDS Cohort Study (MACS) analyses, we found that PWH have a higher incidence of DM and a higher prevalence of pre-DM, defined by FG criteria[11, 12], compared to people without HIV (PWOH). Using data from the MACS, we sought to determine whether the progression to DM among pre-DM PWH differs from the pre-DM PWOH, and to identify factors associated with the transition from pre-DM to DM.

Methods

Study population

The MACS is an ongoing prospective cohort study of HIV infection among men who have sex with men (MSM) at four centers in the USA (Baltimore, MD/Washington DC; Pittsburgh, PA/Columbus, OH; Chicago, IL; and Los Angeles, CA). Institutional

review boards at each site approved the MACS protocol and forms, and each participant gave written informed consent. Details of the study design and follow-up methods have been published[13]. Briefly, participants attend semi-annual study visits, which include a detailed interview featuring longitudinal data capture of all medications received (such as antiretroviral therapy), physical examination, and collection of biological specimens. For the present study, we included all MACS participants with confirmed pre-DM by study definitions. The study baseline was defined as the first visit with pre-DM. Men with prevalent DM at baseline were excluded from our analysis.

Laboratory methods

Since April 1999, glucose and HbA1c were measured from participant serum samples from each semi-annual visit. Glucose levels were measured by the combined hexokinase/glucose-6-phosphate dehydrogenase method at a central laboratory (Heinz Laboratory, Pittsburgh, PA; coefficient of variation 1.8%). HbA1c was measured by Quest Diagnostics (Baltimore, MD) using standard immunoassay assays (Roche Cobas Integra 800 analytical system, Indianapolis, IN; coefficient of variation < 3.3%). Standardized protocols were used to measure T lymphocyte subsets. Plasma HIV-RNA levels were assessed using either, the Roche standard assay, the Roche ultrasensitive assay, the Roche COBAS TaqMan, or the Roche COBAS 6800/8800.

Diabetes and pre-diabetes assessment

We restricted the glucose measures to serum samples that were taken while the participant was fasting (self-reported ≥6 hours without food). Pre-DM was defined as a FG between 100–125 mg/dL (i.e baseline visit), confirmed within a year by either a FG in the pre-DM range (between 100–125 mg/dL) or HbA1c between 5.7–6.4%.

Incident DM was defined as: FG ≥126 mg/dL confirmed with self-reported use of anti-DM medication or a second FG ≥126 mg/dL at a subsequent visit, self-reported DM confirmed with self-reported use of anti-DM medication or FG ≥126 mg/dL confirmed at a subsequent visit(s) or self-reported anti-DM medication use.

Statistical analysis

Baseline characteristics were compared by HIV serostatus using Wilcoxon rank sum and chi-squared tests. Binomial transition models were used to determine whether the progression from pre-DM to DM at the next observed MACS visit differed by HIV serostatus. Briefly, transition models estimate the odds of moving from one health state to another at a future point in time. Individuals can move between any two states unless the probability is assumed to be zero. In the present study, we were focused on the odds that an individual had DM at a MACS visit, given that they were classified as pre-DM at their previous MACS visit. Owing to the time-varying nature of pre-DM and DM, we allowed for an individual to transition from pre-DM to DM multiple times over follow-up, and also examined the odds of transition from DM back to pre-DM.

Our multivariate transition models were adjusted for age (years), number of previous pre-DM to DM transitions, race/ethnicity (non-Latino white and non-white), body mass

index (BMI; kg/m^2), family history of diabetes, and hepatitis C virus (HCV) infection (last measured negative, and last measured positive antibody or HCV RNA). HCV infection was based on a summary measure that accounted for HCV RNA and antibody status. HCV RNA and antibodies were not measured at every MACS visit – among men who were classified as HCV positive at study baseline, the median (IQR) year of their last HCV RNA measure over follow-up was 2008 (2006–2009), and the median (IQR) year of their last HCV antibody measure over follow-up was 2011 (2009–2013). In between (and after the latest) HCV RNA and antibody measurements, HCV status was assumed to be constant and carried forward. As a sensitivity analysis, we added waist-hip circumference ratio (waist and hip circumferences were recorded to the nearest centimeter by tape measure as previously described[14]) to the multivariate model (including BMI), in order to evaluate the contribution of regional fat distribution to DM transition.

We also performed analysis stratified by HIV serostatus to better estimate differences in the association between DM risk factors and the odds of transition from pre-DM to DM. Models including only PWH adjusted for the variables listed above, plus examiner-assessed lipoatrophy at a visit (moderate/severe vs mild/none measured in the buttocks, legs and face: yes/no), years of known HIV exposure, history of clinical AIDS (yes/no), cumulative HIV viral copy-years after baseline, cumulative years of stavudine use, cumulative years of nucleoside reverse transcriptase inhibitor (NRTI) use, cumulative years of protease inhibitor (PI) use, and thymidine analogue use at a visit.

Finally, we performed several supplemental analyses. Although our main focus was on the transition from a pre-DM state to a DM state, we also modelled the odds of transition from DM to pre-DM, and the probability of transition from pre-DM to normal. The multivariate model for the transition from DM to pre-DM was adjusted for HIV serostatus, age, number of previous DM to pre-DM transitions, race/ethnicity, BMI, weight change between visits (kg), family history of diabetes, HCV infection, and smoking status (never smoked, former smoker, and current smoker). The multivariate model for the transition from pre-DM to normal was adjusted for HIV serostatus, age, number of previous pre-DM to normal transitions, race/ethnicity, BMI, weight change between visits, HCV infection, and smoking status.

Results

Baseline characteristics

Of the 3572 men with a visit between 1 April 1999 and 30 September 2019, 1584 participants (791 PWOH (22%) and 793 (22%) PWH) had observed confirmed pre-DM at baseline (Table 1). The median (IQR) year of the baseline visit was 2005 (2004, 2008).

When comparing baseline characteristics of our selected pre-DM population (n=1584) to the overall MACS population (n=3572), pre-DM participants were older, had a lower percentage of non-white participants, a smaller rate of current smokers, a higher average BMI and waist-hip ratio, a lower prevalence of lipoatrophy and a greater proportion of individuals with a family history of DM (all $p \leq 0.02$). Further, pre-DM PWH had a longer duration of known HIV exposure, had a higher prevalence of HIV virologic control (HIV viral load < 50

copies/mL), a longer use of NRTIs and PIs medications, and less thymidine analog use (all p<0.01) compared to MACS PWH with normal FG (Table 1).

Comparing pre-DM PWOH (n=791) and pre-DM PWH (n=793), PWH were younger, more likely to be non-white, had a lower BMI (all p<0.01), and were more likely to be current smokers (p=0.048) and co-infected with HCV, as per last measure (p<0.01). As expected, lipoatrophy was more common among PWH compared to PWOH (p<0.01) (Table 1).

Among both pre-DM PWOH and PWH groups, 23% of each group of participants had at least one visit with incident DM over a median of 12 years of follow-up. Men with incident DM during follow-up were more likely to have a family history of DM (p<0.01), and at baseline to have a higher average BMI and waist-hip ratio (both p<0.01), compared to those who did not have incident DM during follow-up. In addition, PWH who had an incident DM were more likely to have a history of AIDS (p=0.04), a shorter duration of known HIV infection (p=0.01), and longer use of NRTIs (p=0.02) – stavudine in particular (p=0.03) – compared to PWH who did not have incident DM over follow-up (Table 2).

Multivariate transition models: pre-DM to DM

In multivariate transition models adjusted for age, number of previous pre-DM to DM transition, race/ethnicity, HCV infection (ie. last visit measurement), BMI and family history of DM the odds of transition from pre-DM to DM were 40% [95% CI: 0% to 80%] higher among PWH than PWOH (p=0.04; model A, Table 3) whereas it was not significant in univariate models (additionally controlling for age and number of previous transition from pre-DM to DM, Table 3 supplementary file). The greater risk among PWH of transitioning from pre-DM to DM can be observed in Figure 1a, where PWH had a significantly higher probability of transitioning compared to PWOH during up to eight years of follow-up after the first visit with confirmed pre-DM. When waist-hip ratio was added into the multivariate model (Table 3 model B, Figure 1b) there was no longer a statistically significant association between HIV serostatus and the transition from pre-DM to DM (p=0.22).

An increased risk of transitioning from pre-DM to DM in PWH was associated with non-white race/ethnicity, more previous pre-DM to DM transitions, and higher BMI (all p≤0.05) (Table 3). However, a family history of DM in PWH was not significantly associated with an increased odds of transitioning from pre-DM to DM, while it was significant among PWOH (all p<0.01). A higher standardized waist-hip ratio was also significantly associated with an increased risk for transitioning among PWH, but not among PWOH (Table 3).

Among PWH, after adjustment for traditional risk factors, men with pre-DM were more likely to develop incident DM if they had lipoatrophy (p=0.02), a history of AIDS (p<0.01), or were using thymidine analogs (p<0.03; Table 3). After adding waist-hip ratio to the model, longer duration of known HIV infection became significantly associated with a reduced risk of transitioning from pre-DM to DM (p=0.03; Table 3).

Other transition models: DM to pre-DM and pre-DM to normal

HIV infection was significantly associated with 30% [95% CI: 0% to 50%] lower odds of transitioning from DM to pre-DM compared to PWOH (p=0.045). HIV infection was not

significantly associated with the probability of the transition from pre-DM to normal (aRR 0.9 [95% CI: 0.9, 1.0], p=0.08).

Discussion

This analysis of MACS data that spanned a median 12-year period is the largest study to date that has evaluated the risk of DM transition in pre-DM PWH and PWOH. We found that risk for incident DM was 40% higher among PWH than PWOH after adjustment for competing DM risk factors.

Pre-DM, including impaired fasting glucose (IFG), has been widely studied as a predictor for incident DM[6, 15–19], with ten year incidence ranging from 3 to 33% in European cohorts[15, 16, 19]. Other studies reported a higher proportion of incident DM – up to 72.7% in South America[17] – when impaired glucose tolerance (IGT) was added to IFG as a risk factor. In our study we found that 23% of pre-DM participants developed incident DM over a median of 12 years of follow-up using IFG alone. These rates are similar to other published data in Western countries that recognized pre-DM as a major risk factor for DM[6]. However, we were unable to identify persons with IGT (defined as a 2 hour glucose between 140 and 199 mg/dl after 75 g oral glucose load), as oral glucose tolerance tests have not been routinely performed in the MACS [20].

In the general population, incident DM has been associated with traditional risk factors such as ethnicity, family history of DM, gender, age, BMI, and waist circumference[21]. As expected, in our study, pre-DM participants were older with a higher average BMI and a greater likelihood of family history of DM, which is similar to people with DM from the general population[22–24]. For example, compared to people without a family history of DM, individuals who have a first degree relative with DM have a two to three times increased risk of developing DM[23, 25]. In our study, 67% of pre-DM PWOH who developed incident DM had a family history of DM, compared with a 51% prevalence of family history of DM among pre-DM PWOH who did not develop incident DM. Similarly, the prevalence of obesity – well-known as a risk factor for DM[24, 26] – was greater and the median BMI higher in pre-DM PWOH who developed incident DM than pre-DM PWOH who did not develop incident DM (median BMI 29.4 vs 26.5, respectively).

Among PWH with pre-DM, traditional risk factors were also associated with incident DM. However, compared to pre-DM PWOH, pre-DM PWH were younger, had a lower BMI, and were more likely to be non-white. Our results are in accordance with other published data showing that the prevalence of DM at an earlier age is likely to be higher in PWH[8, 27, 28], and is higher among African Americans in the general population[29]. In our study, history of AIDS was linked to incident DM in PWH after adjustment for traditional risk factors, which may reflect continued immune system dysregulation and inflammation, which are considered to be important drivers for comorbidities, including DM[10, 30]. We also found that longer use of NRTIs, especially stavudine, and lipoatrophy, were related to incident DM among PWH, highlighting the metabolic toxicity of these medications.

In adjusted models, PWH had a 40% greater risk of transitioning from pre-DM to DM compared to PWOH, but after additional adjustment for waist-hip ratio, the magnitude of the effect diminished and statistical significance was no longer present. This suggests that the difference by HIV serostatus in the transition from pre-DM to DM may be related to regional body composition. In the general population, fat distribution is an important determinant of the risk of insulin resistance and DM, and may be explained by genetic and environmental factors[31, 32]. Among PWH, ART-associated lipoatrophy or lipohypertrophy are recognized as DM risk factors[33, 34]. Our findings suggest that waist-hip ratio is a potential mediator in the pathway between HIV infection and incident DM among pre-DM men and should be explored in future studies.

Our results also demonstrated that while non-white race/ethnicity was significantly associated with increased odds of transition from pre-DM to DM in univariate models, after controlling for the effects of HIV and HCV serostatus, BMI, and family history of DM, the effect of race/ethnicity was no longer significant. This is an important finding, as it suggests that it is not race/ethnicity that is specifically associated with DM risk among pre-DM men in our cohort, but rather downstream factors that differ by race/ethnicity – potentially stemming from structural inequalities – that are associated with an elevated DM risk.

Current guidelines emphasize a patient-centered approach in the management of people with DM[6]. Based on the results of the Diabetes Prevention Program, metformin use should be considered to prevent DM in persons with pre-DM who are <60 years old, have a BMI >35 kg/m^2, or have a history of gestational diabetes. It is unclear whether HIV serostatus should also be considered a risk factor which may prompt the use of metformin among persons with pre-DM. Given the increased odds of DM transition among pre-DM PWH compared to pre-DM PWOH, it would be prudent to monitor pre-DM PWH closely to avoid the development of DM, and institute lifestyle modifications, including diet and physical activity changes, to prevent DM conversion[26, 35]. Even modest weight loss can have an impact on long term glycemic control[36, 37]. Finally, ART medications that are associated with weight gain, including integrase inhibitors and tenofovir alafenamide[38, 39], should be used carefully in PWH with pre-DM. Future studies should examine treatment strategies to avoid or switch from these medications to evaluate effects on glucose metabolism in persons with pre-DM.

Our study has several limitations. First, we did not perform oral glucose tolerance tests so we were unable to examine conversion of IGT to DM. This may have underestimated the pre-DM population. We were unable to examine the role of genetics, physical activity, or diet on DM development, but these are important factors to examine in future studies.

As previously mentioned, HCV status after the latest HCV RNA and/or antibody measure was assumed to be constant. Some of the men in our study who had a positive HCV status held constant initiated direct acting antivirals (DAA) while under follow-up. However, we did not have updated HCV RNA or antibody measures for these men following their DAA initiation, so could not assess the presence of a sustained virologic response. Since HCV is associated with abnormalities in glucose metabolism, it could be hypothesized that HCV

cure may decrease the risk of transition to DM in those with pre-DM. However, when we attempted to examine the impact of time before and after DAA initiation on the transition from pre-DM to DM for men with HCV infection, we found no transitions from pre-DM to DM in these individuals and were unable to address this important question. Finally, our study included only men and whether findings can be extrapolated to women is unknown.

Conclusion

Among men with pre-DM, HIV infection was associated with a greater risk of incident DM, which was related to regional fat distribution. In addition to controlling for classic risk factors associated with DM, such as diet or physical inactivity, additional strategies to prevent DM among PWH with pre-DM should be investigated, including ART strategies that minimize weight gain and use of metformin or other medications that have been shown to prevent DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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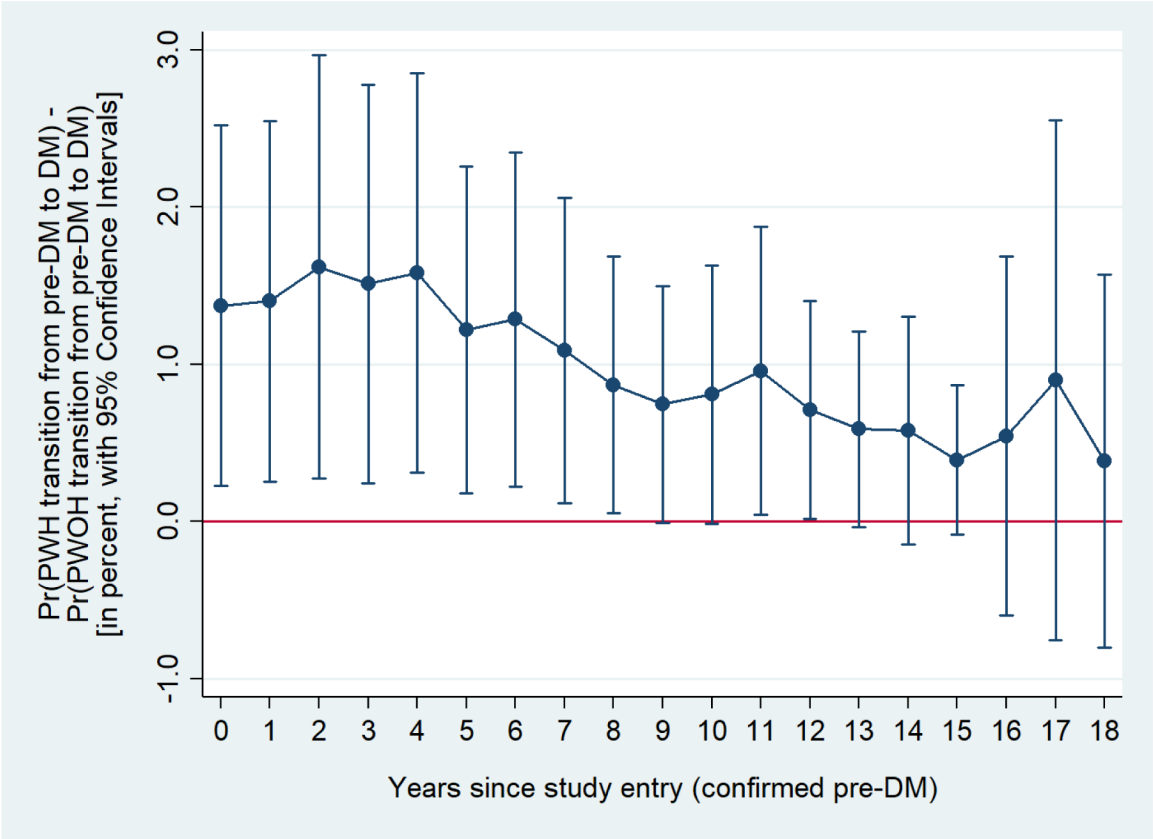

Figure 1a.

Difference in the probability of transitioning from pre-DM to DM between PWH and PWOH at each year in time since the first visit with confirmed pre-DM.

Estimates adjusted for age, number of previous transitions from pre-DM to DM, race/ethnicity, HCV infection as per last measurement, BMI, and family history of DM.

BMI = body mass index; DM = diabetes mellitus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Pre-DM = pre-diabetes mellitus; PWH = persons with HIV; PWOH = persons without HIV.

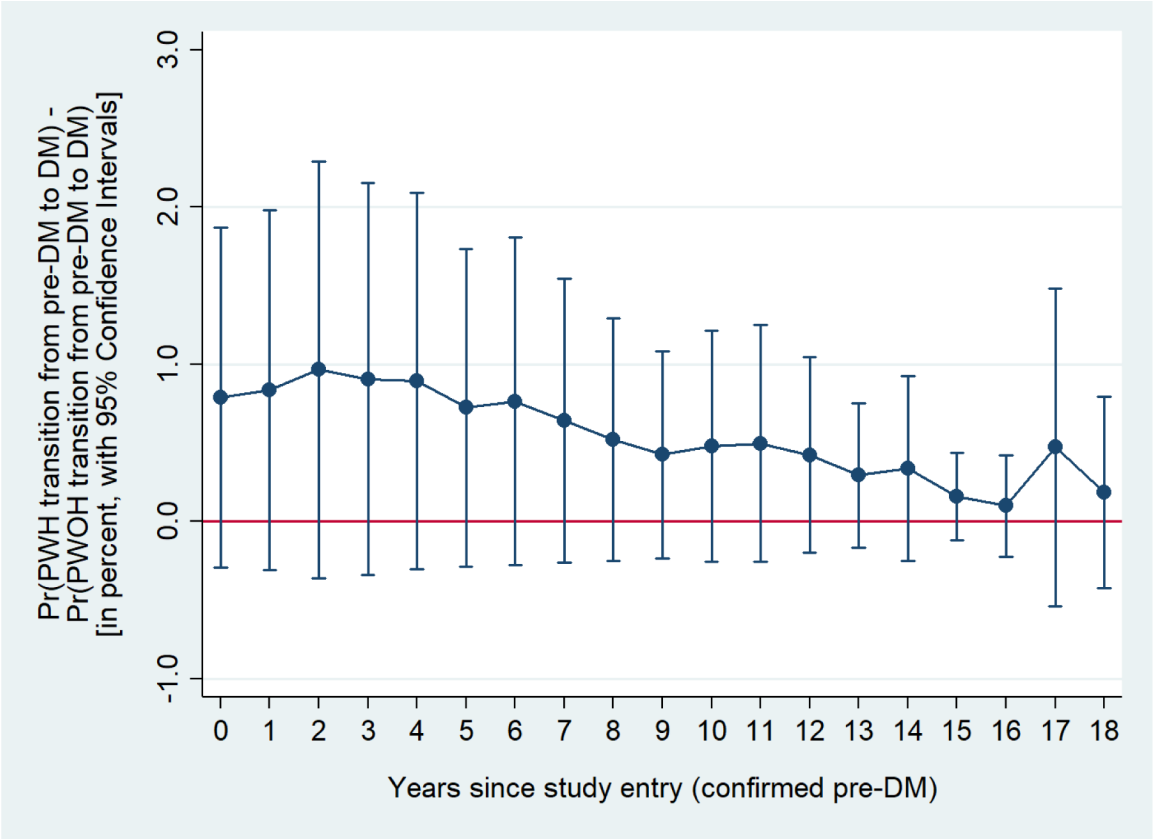

Figure 1b.

Difference in the probability of transitioning from pre-DM to DM between PWH and PWOH at each year in time since the first visit with confirmed pre-DM.

Estimates adjusted for age, number of previous transitions from pre-DM to DM, race/ethnicity, HCV infection as per last measurement, BMI, family history of DM, and waist-hip ratio.

BMI = body mass index; DM = diabetes mellitus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Pre-DM = pre-diabetes mellitus; PWH = persons with HIV; PWOH = persons without HIV

Table 1.

Baseline participant characteristics.

Characteristic	A Pre-DM PWOH N = 791	B Pre-DM PWH N = 793	C MACS[a] PWOH N = 1718	D MACS[a] PWH N = 1854	*P* A vs. B	*P* A+B vs. C+D
Age (years), median (IQR)	51.3 (45.1–57.9)	47.7 (41.5–53.6)	45.1 (37.9–52.4)	41.7 (35.7–47.5)	<0.01	<0.01
Calendar year, median (IQR)	2005 (2004–2008)	2006 (2004–2009)	2002 (2000–2003)	2002 (2000–2003)	<0.01	<0.01
Non-white race/ethnicity, n (%)	236 (30)	372 (47)	616 (36)	885 (48)	<0.01	0.02
Smoking status, n (%)					0.048	<0.01
Never smoked	236 (30)	221 (29)	545 (33)	544 (30)		
Former smoker	330 (42)	298 (39)	547 (33)	543 (30)		
Current smoker	213 (27)	256 (33)	582 (35)	719 (40)		
HCV co-infection per last measure, n (%)	35 (4)	66 (8)	91 (5)	162 (9)	<0.01	0.31
BMI (kg/m^2), median (IQR)	27.0 (24.4–30.3)	25.5 (23.1–28.3)	25.7 (23.2–28.7)	24.8 (22.7–27.5)	<0.01	<0.01
Waist-hip ratio, median (IQR)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.9 (0.9–1.0)	0.09	<0.01
Weight change since last visit (kg), median (IQR)	0.7 (−0.8–2.4)	0.3 (−1.2–2.2)	0.9 (−1.74–3.6)	0.0 (−1.8–1.8)	0.01	0.22
Moderate/severe lipoatrophy, n (%)	14 (2)	44 (6)	44 (3)	259 (14)	<0.01	<0.01
Family history of diabetes, n (%)	431 (55)	458 (59)	851 (51)	985 (55)	0.14	0.02
Duration of HIV infection (years), median (IQR)	-	18 (14.1–21.9)	-	12.7 (12.2–18.0)	-	<0.01[b]
History of AIDS, n (%)	-	74 (9)	-	196 (11)	-	0.36[b]
HIV viral load < 50copies/mL, n (%)[c]	-	488 (62)	-	691 (41)	-	<0.01[b]
Cumulative years of NRTI use, median (IQR)	-	5.5 (2.0–9.5)	-	2.2 (0.1–4.9)	-	<0.01[b]
Current thymidine analog use, n (%)	-	252 (32)	-	823 (46)	-	<0.01[b]
Cumulative years of stavudine use, median (IQR)	-	0.0 (0.0–2.9)	-	0.0 (0.0–1.5)	-	<0.01[b]
Cumulative years of PI use, median (IQR)	-	2.0 (0.0–5.1)	-	0.3 (0.0–2.5)	-	<0.01[b]

[a]: Baseline characteristics for all men measured at the earliest visit after April 1, 1999 (when fasting glucose began to be collected).

[b]: PWH only.

[c]: Excluding the three MACS men with an HIV viral load measured at the lower limit of detection of 400 copies/mL, via the Roche 2nd generation assay.

AIDS = acquired immunodeficiency syndrome; BMI = body mass index; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Pre-DM = pre-diabetes mellitus; PWH = persons with HIV; PWOH = persons without HIV.

Table 2.

Baseline characteristics of pre-DM PWOH and PWH who did and did not develop incident DM.

Characteristic	A PWOH No Incident DM N=611	B PWOH Incident DM N=180	C PWH No Incident DM N=613	D PWH Incident DM N=180	A vs B *P*	C vs D *P*
Age (years), median (IQR)	51.5 (45.2–58.1)	50.3 (45.1–57.1)	47.7 (41.2–53.7)	48.0 (42.5–53.0)	0.5	0.68
Calendar year, median (IQR)	2006 (2004–2008)	2004 (2003–2006)	2006 (2004–2010)	2004 (2002–2007)	<0.01	<0.01
Non-white race/ethnicity, n (%)	175 (29)	61 (34)	287 (47)	85 (47)	0.19	0.93
Smoking status, n (%)					0.02	0.85
Never smoked	188 (31)	48 (27)	170 (28)	51 (29)		
Former smoker	264 (44)	66 (37)	228 (38)	70 (40)		
Current smoker	149(25)	64 (36)	201 (34)	55 (31)		
HCV co-infection per last measure, n (%)	23 (4)	12 (7)	48 (8)	18 (10)	0.10	0.36
BMI (kg/m^2), median (IQR)	26.5 (23.9–29.5)	29.4 (26.1–33.8.0)	25.2 (23.0–28.0)	26.2 (23.8–29.3)	<0.01	<0.01
Waist-hip ratio, median (IQR)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	<0.01	<0.01
Weight change since last visit (kg), median (IQR)	0.6 (−0.9–2.2)	0.9 (−0.7–3.4)	0.3 (−1.2–2.1)	0.5 (−1.2–2.3)	0.051	0.40
Moderate/severe lipoatrophy, n (%)	8 (1)	6 (3)	30 (5)	14 (8)	0.10	0.14
Family history of diabetes, n (%)	310 (51)	121 (67)	338 (56)	120 (68)	<0.01	<0.01
Duration of HIV infection (years), median (IQR)	-	-	18.0 (14.2–22.4)	16.8 (13.5–20.1)	-	0.01
History of AIDS, n (%)	-	-	50 (8)	24 (13)	-	0.04
HIV viral load < 50 copies/mL, n (%)	-	-	386 (64)	102 (57)	-	0.12
Cumulative years of NRTI use, median (IQR)	-	-	5.3 (1.8–9.4)	6.2 (3.5–9.9)	-	0.02
Current thymidine analog use, n (%)	-	-	163 (27)	89 (51)	-	<0.01
Cumulative years of stavudine use, median (IQR)	-	-	0.0 (0.0–2.8)	0.6 (0.0–3.2)	-	0.03
Cumulative years of PI use, median (IQR)	-	-	1.8 (0.0–5.2)	2.9 (0.0–4.8)	-	0.12

AIDS = acquired immunodeficiency syndrome; BMI = body mass index; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IQR = interquartile range; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Pre-DM = pre-diabetes mellitus; PWH = persons with HIV; PWOH = persons without HIV.

Table 3.

Multivariate odds of transition from pre-DM to DM among the 1584 pre-DM men

	MODEL A			MODEL B		
Variable	**PWOH+PWH OR (95% CI), *P***	**PWOH OR (95% CI), *P***	**PWH OR (95% CI), *P***	**PWOH+PWH OR (95% CI), *P***	**PWOH OR (95% CI), *P***	**PWH OR (95% CI), *P***
Seropositive for HIV [ref = Seronegative]	1.4 (1.0, 1.8), 0.04	-	-	1.2 (0.9, 1.6), 0.22	-	-
Age, per 10 years	1.1 (0.9, 1.3), 0.38	1.0 (0.8, 1.2), 0.73	1.3 (1.0, 1.7), 0.051	1.0 (0.8, 1.2), 0.87	0.9 (0.7, 1.1), 0.47	1.2 (0.9, 1.5), 0.22
Number of previous pre-DM to DM transitions	3.9 (2.9, 5.1), <0.01	3.4 (2.6, 4.5), <0.01	7.0 (3.4, 14.2), <0.01	3.8 (2.8, 5.1), <0.01	3.4 (2.6, 4.4), <0.01	7.5 (3.3, 17.2), <0.01
Non-white [ref = Non-Latino white]	1.2 (0.9, 1.6), 0.29	1.3 (0.8, 2.1), 0.27	1.5 (1.0, 2.3), 0.048	1.2 (0.9, 1.7), 0.18	1.4 (0.8, 2.2), 0.19	1.6 (1.1, 2.5), 0.03
Last measure seropositive for HCV [ref = Last measure seronegative]	1.3 (0.8, 2.1), 0.36	1.4 (0.8, 2.8), 0.27	1.0 (0.4, 2.3), 0.98	1.2 (0.7, 2.0), 0.45	1.3 (0.7, 2.7), 0.43	0.9 (0.4, 2.0), 0.83
BMI, per five kg/m^2	1.5 (1.3, 1.7), <0.01	1.5 (1.3, 1.7), <0.01	1.6 (1.4, 2.0), <0.01	1.3 (1.2, 1.5), <0.01	1.4 (1.2, 1.7), <0.01	1.4 (1.1, 1.8), <0.01
Family history of diabetes [ref = No family history]	1.7 (1.3, 2.3), <0.01	2.0 (1.3, 2.9), <0.01	1.3 (0.9, 1.9), 0.20	1.7 (1.3, 2.3), <0.01	2.0 (1.3, 3.0), <0.01	1.3 (0.9, 2.0), 0.18
Waist-hip ratio, standardized	-	-	-	1.3 (1.1, 1.5), <0.01	1.2 (0.9, 1.4), 0.19	1.4 (1.1, 1.6), <0.01
Examiner-assessed lipoatrophy [ref = No lipoatrophy]	-	-	2.2 (1.1, 4.4), 0.02	-	-	2.3 (1.2, 4.5), 0.02
Duration of HIV infection, per five years	-	-	0.8 (0.7, 1.0), 0.07	-	-	0.8 (0.7, 1.0), 0.03
History of AIDS [ref = No history]	-	-	2.9 (1.7, 5.0), <0.01	-	-	2.8 (1.6, 4.8), <0.01
Cumulative HIV viral copy-years after baseline, per 1,000,000 copy-years	-	-	0.2 (0.0, 1.5), 0.10	-	-	0.2 (0.0, 1.7), 0.13
Cumulative years of stavudine use, per five years	-	-	1.3 (1.0, 1.7), 0.09	-	-	1.3 (1.0, 1.7), 0.10
Cumulative years of NRTI use, per five years	-	-	1.2 (0.9, 1.5), 0.17	-	-	1.2 (0.9, 1.5), 0.26
Cumulative years of PI use, per five years	-	-	1.1 (0.9, 1.3), 0.34	-	-	1.1 (0.9, 1.4), 0.16
Thymidine analog use [ref = No thymidine analog use]	-	-	1.6 (1.0, 2.5), 0.03	-	-	1.7 (1.1, 2.6), 0.02

Model A: multivariate transition model with odds of transition from pre-DM to DM among pre-DM PWOH and PWH adjusted for traditional risk factors. Model B: multivariate transition model with odds of transition from pre-DM to DM among pre-DM PWOH and PWH adjusted for traditional risk factors plus waist-hip ratio.