

RESEARCH ARTICLE

Diagnosis, risk factors and management of diabetes mellitus in HIV-infected persons in France: A real-life setting study

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Abstract

Background

Diabetes mellitus (DM) is a major and increasing public health problem that may be underdiagnosed and undertreated among persons living with HIV (PLWH).

Objective

To describe the diagnosis, treatment and follow-up of DM among PLWH.

Methods

This study was performed inside a monocentric cohort of 1494 PLWH. DM was defined as having a FG \geq 126 mg/dL twice or a HbA1c \geq 6.5%, or a history of diabetes, or receiving anti-diabetic treatment. The first visit mentioning a diagnosis of DM was considered as the baseline visit. Chi-Square or Fisher exact test were used to examine the association between categorical variables and DM, Wilcoxon or Student t-test were used for continuous variables.

Results

156 PLWH with DM were included. Compared to non-diabetic participants, they were more likely to be native of Sub Saharan Africa (31.6% vs. 22.4%, $p = 0.027$) and older (54.6 vs. 49.9 years, $p < 0.001$), to have a higher BMI (> 25 for 46.1% vs. 35.3%, $p = 0.020$) and a poorer control of HIV (HIV RNA < 50 copies/mL: 80.1% vs. 89.5%, $p < 0.001$). The diagnosis of DM was missed in 37.8% of PLWH, and 47.2% of PLWH treated for DM did not reach a HbA1c $< 7\%$. PLWH with DM were more frequently on antihypertensive and/or lipid-lowering

medications: 94.2% had a LDL-cholesterol <70 mg/dL and 60.9% had a blood pressure <140/90 mmHg.

Conclusion

In a setting of HIV-control, HIV care providers should focus on metabolic issues. The management of DM and associated risk factors is mandatory to prevent cardiovascular disease in PLWH.

Introduction

Diabetes mellitus (DM) is a major public health problem with a worldwide prevalence of 8.5% according to WHO's (World Health Organization) last report that is expected to increase in the next decades [1]. In 2015, more than 5% of the French population was on glucose-lowering treatment and 25% of persons with diabetes were untreated or ignored their status [2]. People living with HIV (PLWH) are highly impacted by DM, with an estimated prevalence up to 15% [3] and an incidence of 10/1000 person-years, which contributes to an increased risk of cardiovascular diseases [4–6].

Given the improved effectiveness of antiretroviral therapies (ARTs) resulting in a drastic drop in HIV-related conditions, a higher life expectancy but also a longer ART exposure, management of DM is crucial to improve quality of life and avoid complications in PLWH. A previous study has shown that DM is four-fold more common in ART-treated PLWH than HIV-negative persons [7]. Similar to the general population, DM in PLWH has been associated with age, gender, body mass index (BMI), waist circumference, metabolic syndrome, family history of DM, ethnicity as well as dyslipidemia and high blood pressure [3,6,8]. However, specific HIV-related risk factors may contribute to the increased prevalence of DM in PLWH, including cumulative ART exposure [9], use of 'metabolically unfriendly' antiretroviral drugs such as first-generation protease inhibitors and nucleoside analogues [10–12], lipodystrophy, as well as prolonged HIV exposure duration, low CD4 nadir [7] and persistent inflammation [3,6,8].

International guidelines for DM management in PLWH are similar to those in the general population. However, the response to glucose-lowering therapies may be poorer in PLWH as compared to the general population [13–15].

The purpose of our study was to identify, in a 'real life' setting, the risk factors, circumstances of diagnosis and management of DM in a cohort of PLWH routinely monitored in an academic hospital in Paris, in an attempt to improve the routine management of diabetes in this population.

Materials and methods

Study population, inclusion criteria and laboratory analyses

This study was conducted inside the prospective OVIHD cohort [16] (Observatoire VIH de l'Hôtel-Dieu), a single center cohort of 1494 PLWH enrolled since February 11th, 2010 at the Hôtel-Dieu University Hospital, APHP, Paris, France. The aim of the OVIHD study is to evaluate the efficacy and safety of combined ART and the occurrence of comorbidities. Participants attend annual visits that include physical examination, longitudinal data regarding all medications received (including antidiabetic and antiretroviral therapies) and blood collection

for routine laboratory testing (immunovirological profile, viral hepatitis B and C coinfection status, fasting glucose, HbA1c, fasting lipids and kidney function) and storage. All HIV-infected participants were included if they were adults (age > 18 years old) and gave informed written consent for the use of their socio-demographic, clinical and standard-of-care biological data as well as one of their blood samples to be frozen and stored for further analysis to be used. All data were collected in a centralized database (using NADIS[®] as computerized medical record) [17]. The OVHID study protocol was approved by the Ethics Committee « Ile de France II » (N° ID RCB: 2010-A00417-32) and by the French general data protection regulation (CNIL). Approval was obtained from our institutional review board and the study was conducted according to the Declaration of Helsinki.

We studied HIV-infected participants, enrolled from February 11th 2010 to December 31st 2018, with a diagnosis of DM, according to the American Diabetes Association (ADA) criteria [18] (defined as having a 8-hour fasting glucose (FG) \geq 126 mg/dL twice or a HbA1c \geq 6.5%), or currently being on antidiabetic medication or having a personal history of DM as recorded in the OVIHD NADIS[®] database. Patients diagnosed with type 1 DM or transient DM were excluded from our analysis. The first visit mentioning a diagnosis of DM was considered as the baseline visit. If DM was diagnosed prior to the inclusion in OVIHD, we used the date of February 11th 2010 as the baseline visit.

Laboratory analyses were performed using standard procedures. Plasma FG levels were measured after at least 8-hour fasting. HbA1c was measured by immunoassay (Cobas, Roche Diagnostics) centralized at the biology laboratory of the Cochin-Hôtel-Dieu hospital, Paris.

Cardio-metabolic risk factors

DM properly controlled was defined as a HbA1c below 7% at 6 months after DM treatment initiation [18,19]. Patients were defined as having hypertension if receiving antihypertensive treatment, as reported in the NADIS[®] database or with a confirmed blood pressure \geq 140/90 mmHg at a subsequent visit. Controlled hypertension was defined a blood pressure \leq 140/90 mmHg [20,21].

Hypercholesterolemia was defined as being on a lipid-lowering medication as collected in the NADIS database or having low-density lipoprotein cholesterol (LDL-c) > 0.7 g/L. This threshold was chosen since this target was required for most patients with DM at the time of the study.

BMI (weight in kilograms divided by the square of height in meters) was used to define: normal weight (BMI \leq 25), overweight (BMI between 25 and 30) and obesity (BMI > 30).

Cardiovascular history was recorded as a risk factor in case of personal history of stroke or heart attack.

Renal dysfunction was defined as an estimated glomerular function rate (eGFR) \leq 60 ml/min using the MDRD equation.

Smoking was considered as a risk factor if patients were current smokers or if they had stopped within the past 3 years.

Statistical analysis

All statistical analyses were done using RStudio software version 3.5.1 (www.r-project.org). Continuous variables were summarized as the median and interquartile range (IQR), and categorical variables as the frequency and percentage. The Chi-Square test or Fisher exact test was used to determine if there is a significant relationship between categorical variables and the group of patients, and either a Student t-test or a Wilcoxon test to compare the level of

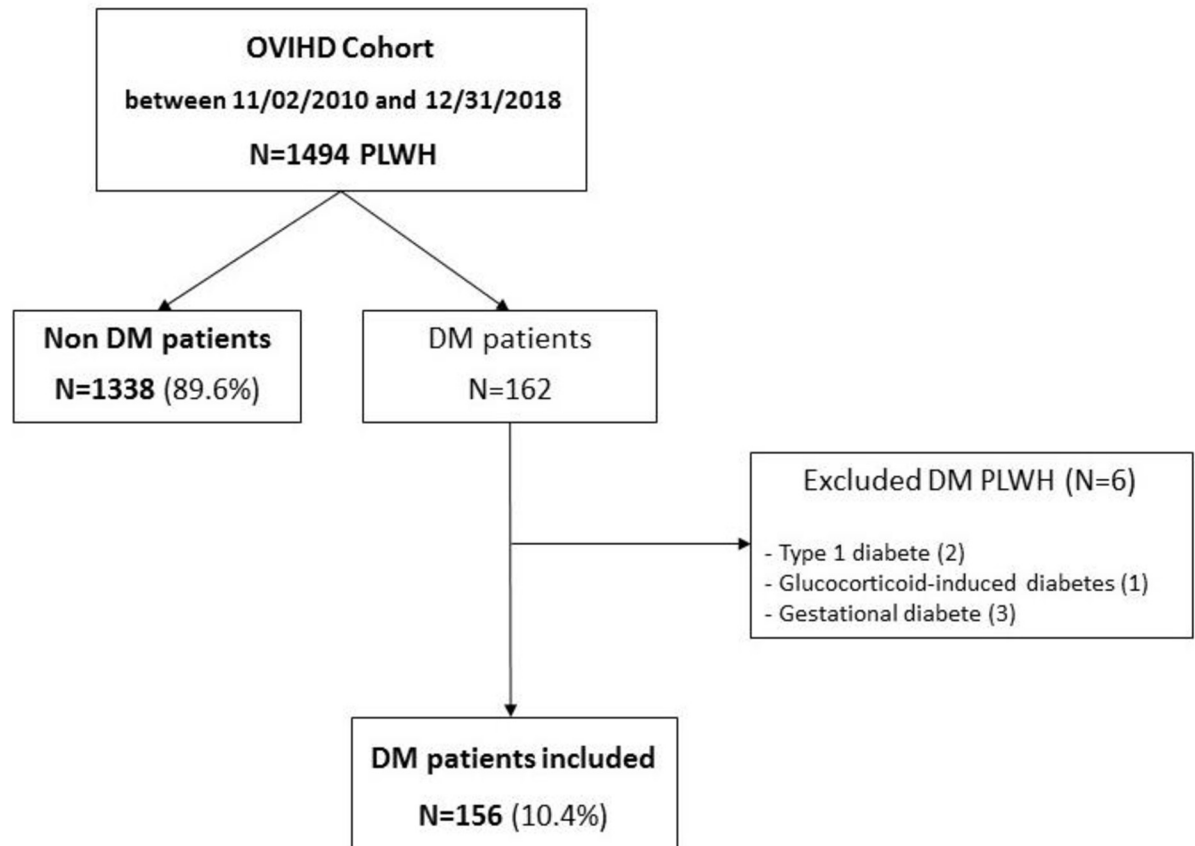


Fig 1. Flow chart of the study population. OVIHD: Observatoire VIH de l'Hôtel-Dieu; PLWH: People living with HIV; DM: Diabetes mellitus.

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continuous variables between the two groups of patients. Statistical tests were two-tailed and *p* values less than 0.05 were considered to denote statistical significance.

Results

Between February 11th 2010 and 31st December 2018, a total of 1494 PLWH were included in the OVIHD cohort. They were mostly men ($n = 1137$, 76.1%), Caucasians ($n = 953$, 63.8%), with a median age of 50.4 [IQR: 44.9–56.3], a normal BMI for 63.6% of them ($n = 947$) and a median follow up of 4.6 years [IQR: 2.3–6.6]. At baseline, 98.4% of the population was on ARTs.

162 out of 1494 participants were diagnosed with DM. Six patients were excluded from our analysis (two patients with type 1 DM, and four patients with transient DM due to corticosteroid treatment or gestational diabetes). A total of 156 DM patients (10.4% of the entire OVIHD cohort) and 1338 non DM patients (89.6%) were included in our analysis (Fig 1). The median duration of follow up was 5.6 years [IQR: 3.1–7.5] for participants with DM and 4.5 years [IQR: 2.3–6.5] for participants without DM ($p < 0.001$). The median duration of ART exposure was similar in the two groups.

Characteristics of PLWH at baseline (Table 1)

Similarly to the non DM participants from the OVIHD cohort, DM participants were mostly male (75%). Patients from the DM group were more likely to be native of Sub-Saharan Africa

Table 1. Characteristics of the study population at baseline.

		OVIHD Cohort N = 1494 patients		P value
		DM group	Non DM group	
		N = 156 (10.4%)	N = 1338 (89.6%)	
Gender (male)		117 (75.0)	1020 (76.3) ^a	0.771
Age (Years)	Median (IQR)	54.6 (48.9 - 62.1)	49.9 (44.6–55.8)	<0.001
Region of birth	Europe	86 (55.5) ^b	867 (65.5) ^c	0.027
	Sub Saharan Africa	49 (31.6)	297 (22.4)	
	others	20 (12.9)	160 (12.1)	
BMI (kg/m ²)	normal ≤ 25	84 (53.9)	863 (64.7) ^d	0.020
	overweight >25–30	54 (34.6)	333 (25.0)	
	obesity >30	18 (11.5)	137 (10.3)	
HIV transmission group	heterosexual	74 (47.4)	461 (34.5)	0.009
	MSM	48 (30.8)	603 (45)	
	IDU	12 (7.7)	85 (6.3)	
	Others	16 (10.3)	133 (9.9)	
	Unknown	6 (3.8)	56 (4.2)	
Duration of HIV infection (known)	Median (IQR)	15.2 (9.2 - 22.7)	15.4 (8.6 - 21.9)	0.879
Year of HIV infection	≤1995	72 (46.2)	521 (38.9)	0.188
	1996–2005	52 (33.3)	480 (35.9)	
	≥2006	32 (20.5)	337 (25.2)	
Hepatitis co-infections	hepatitis B	13(8.3)	107 (8.0)	0.876
	hepatitis C	18(11.5)	189 (14.1)	0.446
CDC stage C		36 (23.1)	289 (21.6)	0.748
CD4 cell count nadir (cells/mm ³)	<200	79 (50.6)	583(43.6)	0.110
Current CD4 cell count (cells/mm ³)	Median (IQR)	595 (414–851)	590 (423–793)	0.830
	≥500	97 (62.2)	873 (65.2)	0.502
Current viral load (copies/mL)	<50	125 (80.1)	1199 (89.5)	<0.001
	≥50 : Median (IQR)	256 (90–14955)	434 (100 - 13558)	
Patients on ART		149 (95.5)	1321 (98.7)	
Duration of ART exposure	Median (IQR)	12.7 (7.3–17.2)	11.7 (5.8 - 17.0)	0.420

Data are presented as count (proportion on initial sample size) and median (interquartile range).

^{a-d}: Values of first and third quartiles; BMI: body mass index, IDU: injecting drug use. MSM: Men who have sex with men; ART: antiretroviral therapy^a with 3 transexual people; ^{b-d}:number of missing values; ^b: 1, ^c: 14, ^d: 5.

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as compared with patients from the non DM group (31.6% and 22.4%, respectively, $p = 0.027$) and significantly older (median age of 54.6 [IQR: 48.9–62.1] versus 49.9 [IQR: 44.6–55.8], respectively, $p < 0.001$). As expected, DM participants were more frequently overweight or obese (BMI > 25: 46.1% and 35.3%, in the DM and non DM group, respectively, $p = 0.020$). By crossing data on BMI and region of birth, we found that among patients from Sub-Saharan Africa (23.2% [n = 346] of the OVIHD population), 62.9% (n = 217) were overweight or obese. The route of HIV transmission was different between DM and non DM with 47.4% of heterosexuals in the DM group and 45% of men who have sex with men (MSM) in the non DM group ($p = 0.009$).

We found a poorer control of HIV infection in the DM group compared to the non-DM group (HIV < 50 copies/ml in 80.1% and 89.5% of participants, respectively, $p < 0.001$). No differences were found between DM and non DM participants in terms of cumulative years of

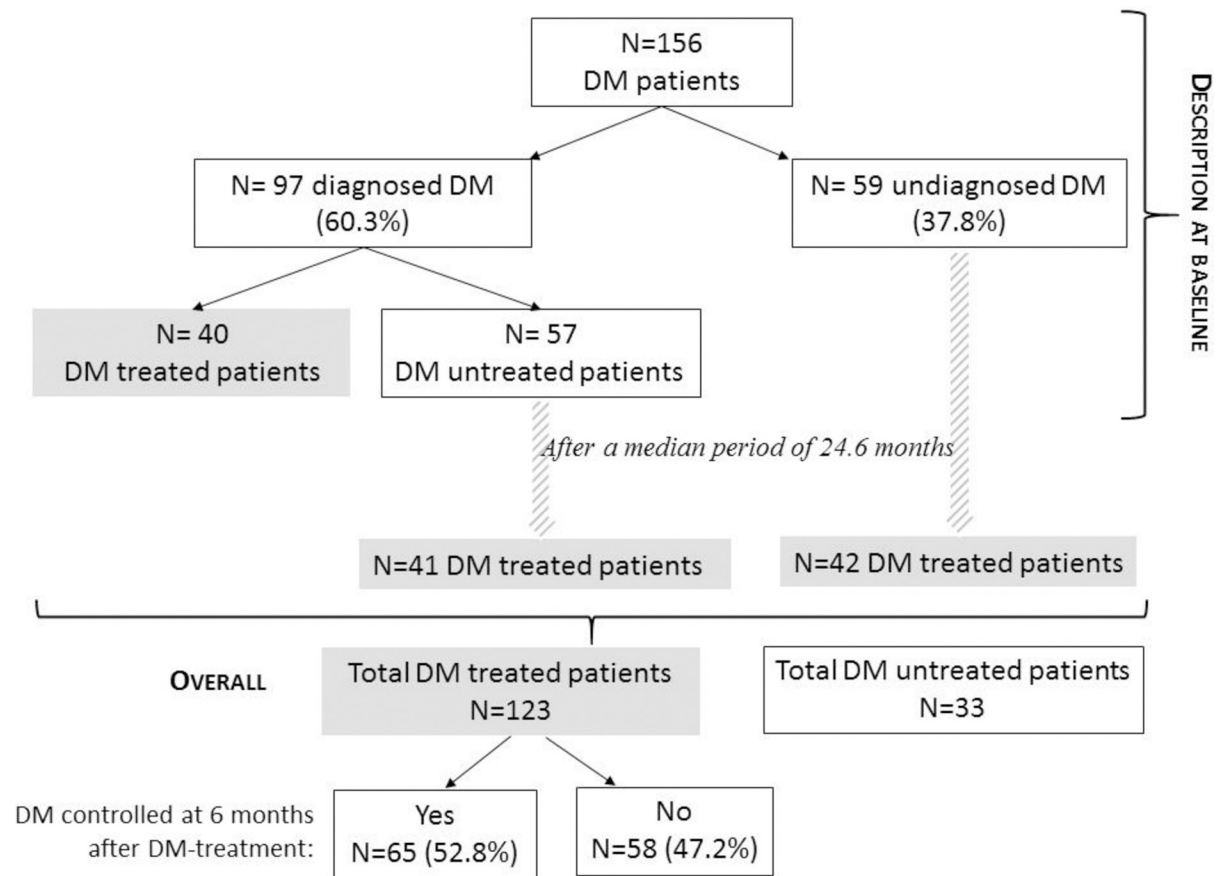


Fig 2. The cascade from diagnosis to DM control. DM treated: Treated by hypoglycemic agents; DM untreated: Without pharmaceutical hypoglycemic treatment.

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known HIV exposure, duration of ART exposure, viral hepatitis co-infections, CDC C-stage or nadir and current CD4 T cell counts.

The cascade from DM diagnosis to DM control

Among the DM group, 60.3% of patients ($n = 97/156$) were already diagnosed with DM at baseline: 25.6% of them ($n = 40/156$) were on glucose-lowering treatment. A HbA1c level below 7% was obtained in 60.9% (25/40) of patients treated with oral antidiabetics (Fig 2).

Among patients treated for DM at baseline ($n = 40$), 65% of participants ($n = 26/40$) received a monotherapy, mostly metformin, and 22.5% of them ($n = 9/40$) received sulfonylureas. Few patients received other antidiabetics and/or combined hypoglycemic therapies (1 with metformin and DDP4 inhibitor, 2 with alpha glucosidase inhibitor and 2 with gliptines).

Diabetes was undiagnosed in 59 participants out of 156 (37.8%) at baseline. The DM diagnosis was missed for 29 participants (18.6%) who previously had twice 8-hour FG ≥ 126 mg/dL (≥ 7 mmol/l) and 30 participants (19.2%) who previously had a HbA1c level greater than 6.5%.

Overall, 116 participants were or should have been diagnosed with DM at baseline but remained untreated (57 already diagnosed and 59 participants who should have been diagnosed). From them, within a median of 24.6 months [IQR: 8.7–46.4], 83 participants started a hypoglycemic treatment, mainly based on metformin monotherapy ($n = 74$, 89.2%). A HbA1c

level of less than 7% was reached at 6 months by 52.8% (n = 65/123) of DM participants on hypoglycemic therapy.

Cardiovascular risk factors and comorbidities at baseline (Table 2)

As expected, DM participants had more cardiovascular risk factors compared to non-DM participants. Although they were less frequently current smokers (21.7% vs. 36.9%, $p = 0.001$). PLWH with diabetes were more frequently treated with anti-hypertensive (22.4% vs. 14.3%, $p = 0.010$) and/or lipid-lowering medications (37.8% vs. 24.9%, $p < 0.001$) and they had more frequently reported personal history of cardiovascular events (5.1% vs. 1.9%, $p = 0.017$). In addition, PLWH with DM presented more frequently renal dysfunction (12.4% and 7.1%, respectively $p = 0.030$).

Choosing a blood pressure target below 140/90 mmHg to define hypertension control, 60.9% of the DM patients were controlled vs. 88% in the non-DM group ($p < 0.001$). Setting the target below 130/80 mmHg, hypertension control rates falls to of 32.1% in the DM group (n = 50) and 64.6% (n = 865) in the non-DM group ($p < 0.001$).

Regarding dyslipidemia, 94.2% of DM participants (n = 147/156) had a LDL-c below 70 mg/dl. Setting the target below 55 mg/dl, only 87.2% (n = 136/156) of the DM participants were controlled. However, diabetics had a better control of dyslipidemia than non DM patients, either with a LDL-c target at 55 mg/dl or at 70 mg/dl ($p = 0.001$).

Discussion

Few studies provide a description of diabetes care among PLWH. We show that DM is underdiagnosed and undertreated by hypoglycemic agents in almost 20% in this population, based on the observation of routine care practices, in France. Indeed, in our study, the diagnosis of DM was missed in 37.8% of PLWH, and 47.2% of PLWH treated for DM did not reach the HbA1c goal (< 7%) considered as the optimum objective in most patients.

Prevalence and risk factors for DM

In developed countries DM prevalence has increased in aging people, including PLWH. Nevertheless, geographical disparities have been well documented [22]. For example, the estimated

Table 2. Cardiometabolic comorbidities in the OVIHD cohort.

	DM patients	Non DM patients	P value
	N = 156	N = 1338	
Personal history of Cardio vascular event, n (%)	8 (5.1)	25 (1.9)	0.017
Current smokers, n (%)	33 (21.7) ^a	477 (36.9) ^b	<0.001
Renal dysfunction, n (%)	19 (12.4) ^c	95 (7.1) ^d	0.030
Anti-hypertensive treatment, n (%)	35 (22.4)	191 (14.3)	0.010
Blood pressure \leq 140/90 mmHg	95 (60.9)	1178 (88.0)	<0.001
Dyslipidemia treatment, n (%)	59 (37.8)	333 (24.9)	<0.001
LDL-cholesterol < 0.7 g/L	147 (94.2)	1124 (84.3) ^e	<0.001
LDL-cholesterol < 0.55 g/L	136 (87.2)	739 (55.4) ^e	<0.001

Data are presented as count (proportion on initial sample size); ^{a-c}: number of missing values

^a: 4

^b: 48

^c: 3

^d: 4

^e: 6.

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DM prevalence in the general population reaches 9.4% in the United States vs. 5% in France [18,22,23]. Similarly, DM prevalence in PLWH has been reported to vary from 3 to 9.7% in European cohorts [24–26] whereas other studies reported higher prevalences up to 15% in the United Kingdom, Northern America and Australia [3,5,27,28]. In our study, we found a DM prevalence at 9% (when defined as FG > 126 mg/dL, twice) or 10.4% (when defined as FG > 126 mg/dL twice or HbA1c > 6.5%). These rates are higher than those reported in the Data Collection on Adverse Events of Anti-HIV Drug (D:A:D) study (3%) [29] and the EuroSIDA study (6.3%) [30] but similar to other published data from HIV cohorts in Western Europe [24,25,31].

Age is a well-known risk factor for DM [32]. However, the prevalence of DM at a younger age is likely to be higher in PLWH than in the general population in most countries including France [20]. This is true even when the prevalence of DM in the general population in France includes persons with untreated and/or undiagnosed DM [2,33]. The higher DM prevalence in PLWH may be explained by an over-representation of risk factors such as older age, male gender, higher BMI or minority ethnicity [1,2,32,34,35]. However, in our study, PLWH with DM were older than their non DM counterparts (54.6 vs. 49.9 years old, respectively) but younger than people with DM in the French general population [2,36]. The OVID cohort is mainly composed of men (76.1%). However, in our study, the proportion of men is not significantly different between DM and non-DM PLWH.

In our study, participants with DM had more frequently a BMI above 25 than non DM participants. However, obese persons were underrepresented in our study (21.8%) compared to the French DM population, in whom the prevalence of obesity is around 41% [33]. In a meta-analysis of 44 studies, Nansseu [6] reported a higher burden of DM among patients treated for HIV with an incidence rate of 13.7 per 1,000 person years of follow up. Similar to our findings, aging and overweight were reported as major risk factors for DM [2]. However, we did not find any differences in terms of cumulative years of known HIV exposure or duration of cART exposure previously reported as major contributor to hyperglycemia [7], except for stavudine (47.7% and 36.4% ever exposed to d4T, in the DM group and non DM group respectively, $p < 0.01$), between DM and non DM PLWH. Indeed, the first generation of antiretroviral drugs have been shown to favor metabolic dysfunction [37], including insulin resistance syndromes, dyslipidemia, lipodystrophy and DM [10]. Considering the multiple confounding factors associated to combined regimen and the length of patient follow-up, these factors were difficult to identify more specifically.

In addition to traditional risk factors, HIV-specific risk factors may contribute to the high prevalence of DM in our cohort of PLWH. We did not find a lower CD4 cell count nadir in the DM group even if it was previously reported as a risk for decreased insulin sensitivity and/or developing DM in PLWH [7,10,38]. However, our study suggests that uncontrolled plasma viral load could contribute to the risk of DM.

The route of HIV transmission seems associated with DM in our study. However, this association could be a result of confusion factors such as BMI. In fact, heterosexuals with DM had a higher BMI (63.9% with BMI > 25) than MSMs with DM (19.4%), $p < 0.001$.

Finally, it has been recognized that the rate of several non AIDS complications including DM could be different among ethnic groups [39]. In our study, patients with DM were less frequently native of Europe than patients without DM. However we did not study the role of socioeconomic biases that could contribute to these differences.

DM diagnoses tools in HIV-infected patients

French guidelines define DM according to WHO criteria, i.e. having a 8 hours FG level above 126 mg/dl (7 mmol/l) twice, or a plasma FG above 200 mg/dl (>11.1 mmol/l) at 2-hours of an

oral glucose tolerance test (OGTT) or during a random analysis, with evocative clinical signs (polyuria, polydipsia, loss of weight) [19,34].

In the French general population, it has been recognized that around 20% of persons aged 18 to 74 with FG levels meeting the criteria for DM ignore their DM status. However, the proportion of underdiagnosed DM decreases with age (30% between 30 and 54 and 13% between 55 and 74). In our study, 18.6% of DM PLWH with a median age of 54.6 ignored their DM status, similarly to the general population in France [2].

In the last decade, the American Diabetes Association (ADA) introduced the threshold of 6.5% of HbA1c as an additional screening test for the diagnosis of DM [18]. In our study, almost 20% of PLWH with a missed diagnosis of diabetes ($n = 30$) could have been diagnosed on the basis of their HbA1c greater than 6.5%. Despite the fact that HbA1c may underestimate FG in PLWH [40–42], our results, supported by other studies [43,44], suggest that HbA1c, in addition to FG or a 2-hour OGTT could be useful for the diagnosis of DM in PLWH. Further studies are needed to determine whether a cutoff below 6.5% should be considered in that setting.

French and international guidelines define DM control as reaching a HbA1c value below 7% for most patients. In France, between 2001 and 2007, in the general population of patients treated with antidiabetic drugs ($n = 9781$), 41% did not reach this goal [33]. Our findings are consistent with these data since in 55 patients out of 123 under antidiabetic drugs (44.7%) did not reach the 7% goal of HbA1c. These figures are higher than those from a previous study conducted by Satlin et al. among 142 PLWH from New York in which 33% of patients on hypoglycemic therapy (IC_{95%} 25%–42%) had a HbA1c > 7.5% [15]. Similarly to our findings, it has been recognized that a significant rate of DM people in France should have a reconsideration of their DM treatment combination therapy to reach the HbA1c goal below 7% [33,45].

Focusing on DM drugs use in our study, it appeared that the treatment regimens were different to those observed in the French general population: 88.6% vs. 43% of patients with DM were on a monotherapy (mostly metformin) in the OVIHD and in the general population, respectively, and only 11.4% of our PLWH with DM were on a combined oral therapy or more recent drugs [33,46]. In a study performed by Han et al. in American veterans, 50% of participants received metformin [14]. Also, some patients were probably controlled on diet alone but we were unable to collect this data.

Prevalence and management of cardio-metabolic comorbidities among PLWH with DM

DM represents one of the multiple cardiovascular risk factors leading PLWH to have a higher rate of cardiovascular diseases, occurring at an earlier age, than the general population [4,47]. In our study, we found a lower rate of current smokers in DM (21.7%) compared to non DM (36.9%) participants ($p < 0.001$), similar to the general population (smokers are 18% among French patients with DM [45] and 36.4% in the general population [48]). This probably reflects the awareness about the risks of tobacco smoking among diabetics.

As expected, a higher proportion of PLWH with DM were treated by anti-hypertensive drugs and statins as compared to non DM participants. Antihypertensive drugs were used in 29.4% of the DM patients from the present study, which is higher compared to 14% reported in the DAD study [29] but similar to what was found in EuroSIDA [30]. However it is lower than the prevalence of 75% in the ENTRED study [45], representative of patients with DM in France. Almost 61% of our participants were controlled for their hypertension (blood pressure < 140/90 mmHg), while among patients with anti-hypertensive treatment, in the French general population, only 55% have a controlled arterial pressure below 140 mmHg

[49]. In our study, 37.8% of PLWH with DM were treated by statins compared to 42% in the DAD study [29] and 45% in the EuroSIDA study [30], 94.2% of DM participants reached a LDL-c level below 70 mg/dl and. Recently, Clement et al showed in a cohort of HIV/HCV co-infected patients that only 22.7% out of 50.7% of patients who required statins reached the LDL-c target value [50].

We found that the prevalence of renal dysfunction was higher in DM participants than non DM participants (12.4% vs. 7.1%, $p = 0.030$), but lower compared to the general population (19%) [45]. Obviously, the impact of uncontrolled comorbidities has several long term consequences including renal impairment.

Our study has several limitations. Clinical and biological data were already collected in our database as well as DM medication, with a retrospective analysis. Moreover, we were unable to provide the duration of DM. However by analyzing the routine management of cardio-metabolic risk factors in an urban academic HIV clinic, our study points to factors that could rapidly improve the patient care in a real-life setting.

Conclusion

Despite excellent HIV control, it is necessary to increase awareness of HIV care providers on metabolic issues. In particular, despite a regular monitoring of glucose levels, the diagnosis of DM is missed in almost 20% of patients. We may also consider HbA1c as a tool for DM diagnosis. Management of DM associated risk factors is also mandatory to avoid cardiovascular diseases in PLWH. Furthermore, our data suggest that screening for DM should be carried out at a substantially earlier age for PLWH compared with HIV uninfected patients, possibly a decade in advance and that the therapeutic management of diabetes should be strengthened.

Supporting information

S1 Data.

(7Z)

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References

1. WHO. Diabetes. <http://www.who.int/fr/news-room/fact-sheets/detail/diabetes>. 2017.

2. France SP. Prévalence et incidence du diabète. Données épidémiologiques. <http://invssantepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Diabete/Donnees-epidemiologiques/Prevalence-et-incidence-du-diabete>. 2019.
3. Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. *PLoS One*. 2018; 13(3):e0194199. <https://doi.org/10.1371/journal.pone.0194199> PMID: 29529066
4. Boccara F. Cardiovascular health in an aging HIV population. *AIDS*. 2017; 31 Suppl 2:S157–S63.
5. McMahon CN, Petoumenos K, Hesse K, Carr A, Cooper DA, Samaras K. High rates of incident diabetes and prediabetes are evident in men with treated HIV followed for 11 years. *AIDS*. 2018; 32(4):451–9. <https://doi.org/10.1097/QAD.0000000000001709> PMID: 29381559
6. Nansseu JR, Bigna JJ, Kaze AD, Noubiap JJ. Incidence and Risk Factors for Prediabetes and Diabetes Mellitus Among HIV-infected Adults on Antiretroviral Therapy: A Systematic Review and Meta-analysis. *Epidemiology*. 2018; 29(3):431–41. <https://doi.org/10.1097/EDE.0000000000000815> PMID: 29394189
7. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005; 165(10):1179–84. <https://doi.org/10.1001/archinte.165.10.1179> PMID: 15911733
8. Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am*. 2014; 43(3):685–96. <https://doi.org/10.1016/j.ecl.2014.05.003> PMID: 25169561
9. Obel N, Thomsen HF, Kronborg G, Larsen CS, Hildebrandt PR, Sorensen HT, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis*. 2007; 44(12):1625–31. <https://doi.org/10.1086/518285> PMID: 17516408
10. Capeau J, Bouteloup V, Katlama C, Bastard JP, Guiyedi V, Salmon-Ceron D, et al. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS*. 2012; 26(3):303–14. <https://doi.org/10.1097/QAD.0b013e32834e8776> PMID: 22089377
11. Group DADS, Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007; 356(17):1723–35. <https://doi.org/10.1056/NEJMoa062744> PMID: 17460226
12. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, Clinical Epidemiology Group from the French Hospital D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003; 17(17):2479–86. <https://doi.org/10.1097/00002030-200311210-00010> PMID: 14600519
13. Han JH, Crane HM, Bellamy SL, Frank I, Cardillo S, Bisson GP, et al. HIV infection and glycemic response to newly initiated diabetic medical therapy. *AIDS*. 2012; 26(16):2087–95. <https://doi.org/10.1097/QAD.0b013e328359a8e5> PMID: 22951636
14. Han JH, Gordon K, Womack JA, Gibert CL, Leaf DA, Rimland D, et al. Comparative Effectiveness of Diabetic Oral Medications Among HIV-Infected and HIV-Uninfected Veterans. *Diabetes Care*. 2017; 40(2):218–25. <https://doi.org/10.2337/dc16-0718> PMID: 27634393
15. Satlin MJ, Hoover DR, Glesby MJ. Glycemic control in HIV-infected patients with diabetes mellitus and rates of meeting American Diabetes Association management guidelines. *AIDS Patient Care STDS*. 2011; 25(1):5–12. <https://doi.org/10.1089/apc.2010.0237> PMID: 21214374
16. Ghosn JAH, Fellahi S, Merlet A, Salmon D, Morini JP, Deleuze J, Blacher J, Capeau J, Bastard JP, VIARD JPPrevalence of silent atherosclerosis and other comorbidities in an outpatient cohort of adults living with HIV: associations with HIV parameters and biomarkers. *AIDS Res Hum Retroviruses* (in press).
17. Pugliese P, Cuzin L, Enel P, Agher R, Alfandari S, Billaud E, et al. [NADIS 2000, development of an electronic medical record for patients infected by HIV, HBV and HCV]. *Presse Med*. 2003; 32(7):299–303. PMID: 12610445
18. Association AD. Diagnosis and Classification of Diabetes Mellitus Diabetes care. 2020; 43(Supplement 1).
19. santé HAd. Diabète de type 2. https://www.has-santefr/portail/jcms/c_1359382/en/diabete-de-type-2-strategie-medicamenteuse-du-controle-glycémique 2017.
20. d'experts Rdg. Prise en charge médicale des personnes vivant avec le VIH. 2019:14–5.
21. Santé HAd. Prise en charge de l'hypertension artérielle de l'adulte. 2016.
22. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol*. 2014; 2(1):56–64. [https://doi.org/10.1016/S2213-8587\(13\)70112-8](https://doi.org/10.1016/S2213-8587(13)70112-8) PMID: 24622669
23. Mandereau Bruneau LDP, Fagot-Campagna A., Fosse-Edorh S. Prevalence of people pharmacologically treated for diabetes and territorial variations in France in 2012. Institut National de Veille Sanitaire

- (INVS). 2014; Bulletin Epidémiologique hebdomadaire (BEH): 30–31. <https://doi.org/10.1152/ajplegacy.1975.229.3.570> PMID: 2014
24. Dufouil C, Richert L, Thiebaut R, Bruyand M, Amieva H, Dauchy FA, et al. Diabetes and cognitive decline in a French cohort of patients infected with HIV-1. *Neurology*. 2015; 85(12):1065–73. <https://doi.org/10.1212/WNL.0000000000001815> PMID: 26156515
 25. Gunter J, Callens S, De Wit S, Goffard JC, Moutschen M, Darcis G, et al. Prevalence of non-infectious comorbidities in the HIV-positive population in Belgium: a multicenter, retrospective study. *Acta Clin Belg*. 2018; 73(1):50–3. <https://doi.org/10.1080/17843286.2017.1339965> PMID: 28622754
 26. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010. *Ann Intern Med*. 2014; 160(8):517–25. <https://doi.org/10.7326/M13-2411> PMID: 24733192
 27. Levy ME, Greenberg AE, Hart R, Powers Happ L, Hadigan C, Castel A, et al. High burden of metabolic comorbidities in a citywide cohort of HIV outpatients: evolving health care needs of people aging with HIV in Washington, DC. *HIV Med*. 2017; 18(10):724–35. <https://doi.org/10.1111/hiv.12516> PMID: 28503912
 28. Monroe AK, Fu W, Zikusoka MN, Jacobson LP, Witt MD, Palella FJ, et al. Low-Density Lipoprotein Cholesterol Levels and Statin Treatment by HIV Status Among Multicenter AIDS Cohort Study Men. *AIDS Res Hum Retroviruses*. 2015; 31(6):593–602. <https://doi.org/10.1089/AID.2014.0126> PMID: 25664922
 29. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care*. 2008; 31(6):1224–9. <https://doi.org/10.2337/dc07-2013> PMID: 18268071
 30. Pelchen-Matthews A, Ryom L, Borges AH, Edwards S, Duvivier C, Stephan C, et al. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. *AIDS*. 2018; 32(16):2405–16. <https://doi.org/10.1097/QAD.0000000000001967> PMID: 30134296
 31. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis*. 2011; 53(11):1130–9. <https://doi.org/10.1093/cid/cir626> PMID: 21998280
 32. Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. *JAMA*. 2014; 312(12):1218–26. <https://doi.org/10.1001/jama.2014.11494> PMID: 25247518
 33. Robert J. RC, Poutignar N., Fagot-Campagna A., Weill A., Rudnichi A., Thammavong N., Fontbonne A., Detournay. Prise en charge des personnes diabétiques de type 2 en France en 2007 et tendances par rapport à 2001. *Bulletin Epidémiologique Hebdomadaire (BEH)*. 2009; 42–43:455–6.
 34. WHO. Global report on diabetes. <https://www.who.int/publications-detail-redirect/global-report-on-diabetes> 2016.
 35. Bays HE, Chapman RH, Grandy S, Grp SI. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. *International Journal of Clinical Practice*. 2007; 61(5):737–47. <https://doi.org/10.1111/j.1742-1241.2007.01336.x> PMID: 17493087
 36. Sabin CA, Reiss P. Epidemiology of ageing with HIV: what can we learn from cohorts? *Aids*. 2017; 31:S121–S8. <https://doi.org/10.1097/QAD.0000000000001374> PMID: 28471942
 37. Noubissi EC, Katte JC, Sobngwi E. Diabetes and HIV. *Curr Diab Rep*. 2018; 18(11):125. <https://doi.org/10.1007/s11892-018-1076-3> PMID: 30294763
 38. Boufassa F, Goujard C, Viard JP, Carlier R, Lefebvre B, Yeni P, et al. Immune deficiency could be an early risk factor for altered insulin sensitivity in antiretroviral-naive HIV-1-infected patients: the ANRS COPANA cohort. *Antivir Ther*. 2012; 17(1):91–100. <https://doi.org/10.3851/IMP1916> PMID: 22267473
 39. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. *Diabetes Res Clin Pract*. 2010; 87(3):415–21. <https://doi.org/10.1016/j.diabres.2009.12.013> PMID: 20061043
 40. Diop ME, Bastard JP, Meunier N, Thevenet S, Maachi M, Capeau J, et al. Inappropriately low glycosylated hemoglobin values and hemolysis in HIV-infected patients. *AIDS Res Hum Retroviruses*. 2006; 22(12):1242–7. <https://doi.org/10.1089/aid.2006.22.1242> PMID: 17209766
 41. Slama L, Palella FJ Jr, Abraham AG, Li X, Vigouroux C, Pialoux G, et al. Inaccuracy of haemoglobin A1c among HIV-infected men: effects of CD4 cell count, antiretroviral therapies and haematological parameters. *J Antimicrob Chemother*. 2014; 69(12):3360–7. <https://doi.org/10.1093/jac/dku295> PMID: 25096078

42. Eckhardt BJ, Holzman RS, Kwan CK, Baghdadi J, Aberg JA. Glycated Hemoglobin A(1c) as screening for diabetes mellitus in HIV-infected individuals. *AIDS Patient Care STDS*. 2012; 26(4):197–201. <https://doi.org/10.1089/apc.2011.0379> PMID: 22324292
43. Droumaguet C, Balkau B, Simon D, Caces E, Tichet J, Charles MA, et al. Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). *Diabetes Care*. 2006; 29(7):1619–25. <https://doi.org/10.2337/dc05-2525> PMID: 16801588
44. Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, et al. A1C level and future risk of diabetes: a systematic review. *Diabetes Care*. 2010; 33(7):1665–73. <https://doi.org/10.2337/dc09-1939> PMID: 20587727
45. (INVS) INdVS. ENTRED 2007–2010. Échantillon national témoin représentatif des personnes diabétiques, Entred 2007–2010 Caractéristiques, état de santé, prise en charge et poids économique des personnes diabétiques. http://opacinvssantefr/doc_numphp?explnum_id=9074. 2018.
46. Bregigeon-Ronot S, Cheret A, Cabie A, Prazuck T, Volny-Anne A, Ali S, et al. Evaluating patient preference and satisfaction for human immunodeficiency virus therapy in France. *Patient Prefer Adherence*. 2017; 11:1159–69. <https://doi.org/10.2147/PPA.S130276> PMID: 28744106
47. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011; 53(11):1120–6. <https://doi.org/10.1093/cid/cir627> PMID: 21998278
48. (INVS) INdVS. L'état de santé de la population en France <http://invssantepubliquefrancefr/Publications-et-outils/Rapports-et-syntheses/Populations-et-sante/L-etat-de-sante-de-la-population-en-France>. 2018.
49. Perrine A-L, LC, Blacher J., Olié V. Hypertension in France: Prevalence, treatment and management in 2015 and temporal trends since 2006. *Bulletin Épidémiologique Hebdomadaire (BEH)*. 2018.
50. Clement ME, Park LP, Navar AM, Okeke NL, Pencina MJ, Douglas PS, et al. Statin Utilization and Recommendations Among HIV- and HCV-infected Veterans: A Cohort Study. *Clin Infect Dis*. 2016; 63(3):407–13. <https://doi.org/10.1093/cid/ciw289> PMID: 27143663