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Incidence of diabetes in HIV-infected patients treated with first-line integrase strand transfer inhibitors: a French multicentre retrospective study

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Background: Integrase strand transfer inhibitors (INSTIs) are increasingly used in patients living with HIV due to their safety, effectiveness and high genetic barrier. However, an association with weight gain has recently been suggested and several cases of diabetes mellitus have been reported with raltegravir and dolutegravir. The long-time metabolic impact of these recent molecules remains unclear.

Objectives: To assess if an INSTI as a third agent is statistically associated with new-onset diabetes mellitus compared with an NNRTI or a PI.

Patients and methods: Patients undergoing first-line combined ART (cART) without diabetes at baseline were retrospectively included from the Dat'AIDS French cohort study (ClinicalTrials.gov NCT02898987). Incident diabetes mellitus was defined as a notification of new diabetes in the medical history, a glycated haemoglobin (HbA1c) level superior to 7.5% or the start of a diabetes therapy following the initiation of ART.

Results: From 2009 to 2017, 19 462 patients were included, among which 265 cases of diabetes mellitus occurred. Multivariate and survival analyses did not highlight an increase in new-onset diabetes in patients undergoing cART with an INSTI as a third agent compared with an NNRTI or a PI. BMI >30 kg/m^2, age >37 years old (in survival analysis), black race or Hispanic ethnicity, arterial hypertension and AIDS were associated with a higher proportion of incident diabetes.

Conclusions: INSTIs were not statistically associated with new-onset diabetes. However, clinicians should remain aware of this possible metabolic comorbidity, particularly in patients with a high BMI and older patients.

Introduction

Nowadays, in resource-rich countries, the improvement in management of patients living with HIV has completely changed the prognosis of this illness. The proportion of deaths due to opportunistic infections and AIDS-defining cancers has dramatically decreased over time, improving life expectancy and transforming HIV infection into a chronic disease. The ageing population is now exposed to cardiovascular diseases, non-AIDS defining cancers and other comorbidities.[1] The aim of care is to limit the long-term toxicity of combined ART (cART).

Diabetes mellitus is a major cardiovascular risk factor.[2] Its incidence is higher among patients living with HIV receiving cART;[3] it peaked in 1999–2000 and decreased markedly thereafter.[4] In addition to the traditional risk factors, such as older age, greater BMI (particularly with a high waist circumference), family history of diabetes, dyslipidaemia, black race or Hispanic ethnicity and

cirrhosis,[5] numerous studies have assessed the relationship between diabetes and cumulative exposure to ART.[6] PIs, especially indinavir, as well as early NRTIs, such as stavudine, didanosine and zidovudine, have been associated with new-onset diabetes.[4,6]

Integrase strand transfer inhibitors (INSTIs) are the most recently developed antiretrovirals and have become, in association with NRTIs, one of the recommended first-line treatments for newly diagnosed patients.[7] They are well tolerated, rapidly effective and the newest molecules, including dolutegravir and bictegravir, possess a high genetic barrier.[8] However, their long-term toxicity is unknown. Several studies have reported a metabolic impact consisting of a higher weight gain compared with NNRTI- or PI-based combinations.[9] Case reports of hyperglycaemia following treatment with dolutegravir,[10]new-onset diabetes after the use of raltegravir[11] and diabetic ketoacidosis after the use of raltegravir[12] have been published.

The main objective of this study was to assess the incidence of new-onset diabetes mellitus in newly diagnosed HIV-infected patients treated with an INSTI as the third agent compared with an NNRTI or a PI.

Patients and methods

Medical records were collected from the Dat'AIDS cohort study, which is a collaboration of 23 HIV treatment centres in France and overseas (ClinicalTrials.gov NCT02898987). These centres maintain prospective cohorts of HIV-1-infected individuals who provide written informed consent via a common electronic medical record. Anonymized data for clinical events, laboratory test results and therapeutic history collected by the networking organization have been submitted to the French National Commission on Informatics and Rights (CNIL Registration number: 2001/762876/nadiscnil.doc).

Patients included were adults living with HIV-1, initiating a first-line cART from 2009 to 2017, consisting of two NRTIs and a third agent, which could be an INSTI, an NNRTI or a boosted PI. Patients with a diagnosis of diabetes mellitus at baseline were excluded. Patient data were censored when changing cART.

Data collected from Nadis® software consisted of demographic characteristics (age and sex), medical centre location (east, north, west, south and south-east of France, Paris and overseas) and geographical origin (Africa, South America, France and other/unknown). We also investigated classical risk factors of diabetes and cardiovascular diseases, such as BMI at baseline, dyslipidaemia, smoking, arterial hypertension and alcohol consumption. Finally, HIV-related factors were examined, consisting of type of cART (INSTI, NNRTI or PI as the third agent), year of treatment initiation divided into three groups (cART initiation in 2009–11, 2012–14 or 2015–17), CDC 1993 classification, HIV risk group, drug abuse and HBV/HCV coinfection. All variables were collected at cART initiation.

Incident diabetes mellitus was defined as a notification of new diabetes in the medical history, a glycated haemoglobin (HbA1c) level superior to 7.5% or the start of a diabetes therapy following the initiation of ART. Blood glucose results were not used, as it was unknown whether patients were fasting or not.

The sample characteristics are described by frequencies and compared by χ^2 tests according to first-line cART (third agent). Because the precise date of diabetes onset was not always known for those developing diabetes, a logistic regression model was first used. We then ran a survival model by excluding those for whom the date of diabetes onset was unknown.

All the variables statistically associated with incident diabetes mellitus in bivariate analyses with a P value threshold of 0.10 or less were included in the multivariate models. All these analyses were run using R software (R.app GUI 1.70, S. Urbanek & H.-J. Bibiko, R Foundation for Statistical Computing, 2016).

Results

Among 19 462 patients initiating cART between 2009 and 2017, new-onset diabetes mellitus occurred in 265 cases. Population characteristics regarding the third antiretroviral agent are described in Table 1. Among 3403 patients treated with an INSTI, 35% received elvitegravir, 30% received raltegravir, 35% received dolutegravir and <1% received bictegravir. The median follow-up time was 572 days.

Pairwise analysis showed that the incidence of diabetes mellitus was different, increasing with age ($P<0.001$), BMI ($P<0.001$), arterial hypertension ($P<0.001$), AIDS status ($P=0.001$), former year of treatment initiation ($P<0.001$), female sex ($P=0.018$), coinfection with HBV and/or HCV ($P=0.090$), overseas medical centre ($P<0.001$), African or South American place of birth ($P<0.001$) and heterosexual contamination ($P<0.001$). The incidence of diabetes mellitus was less frequent in the case of active smoking ($P=0.001$), alcohol consumption ($P=0.002$) and drug abuse ($P<0.001$). There was no difference concerning dyslipidaemia ($P=0.770$).

New-onset diabetes mellitus occurred in 0.91% (31/3403) of patients treated with an INSTI, 1.37% (77/5601) of patients treated with an NNRTI and 1.50% (157/10 458) of patients treated with a PI.

The logistic regression model did not show any difference between the third agents in terms of diabetes occurrence (Table 2). cART initiation in the 2012–14 (OR = 0.48, 95% CI = 0.33–0.69, $P<0.001$) and 2015–17 (OR = 0.33, 95% CI = 0.19–0.58, $P<0.001$) periods was a protective factor. Geographical origin different from Africa, South America or France was also a protective factor (OR = 0.52, 95% CI = 0.29–0.96, $P=0.036$). Classical risk factors for diabetes mellitus, such as BMI >30 kg/m^2 (OR = 3.54, 95% CI = 2.00–6.27, $P<0.001$) and age >46 years old (OR = 4.56, 95% CI = 2.61–7.98, $P<0.001$), were associated with increased incidence of diabetes mellitus.

Among 19 300 participants for whom a follow-up time was available, a date of diabetes mellitus onset was clearly established for 197 patients. Survival analysis of these patients found an incidence of 4.2/1000 person-years follow-up (PYFU). There was no significant difference in new-onset diabetes mellitus based on the third agent used in cART either. Compared with an INSTI, an NNRTI had an HR of 0.90 (95% CI = 0.53–1.52, $P=0.686$) and a PI had an HR of 1.18 (95% CI = 0.73–1.90, $P=0.513$). This analysis confirmed BMI >30 kg/m^2 (HR = 2.83, 95% CI = 1.67–4.77, $P<0.001$), age >46 years old (HR = 3.44, 95% CI = 2.07–5.71, $P<0.001$) and age >37 to 46 years old (HR = 1.73, 95% CI = 1.01–2.93, $P=0.044$) as risk factors for diabetes mellitus. Patients native from elsewhere than Africa and South America (HR = 0.56, 95% CI = 0.37–0.83, $P=0.004$ for France and HR = 0.42, 95% CI = 0.25–0.72, $P=0.001$ for others) were less likely to develop diabetes. On the other hand, arterial hypertension (HR = 2.04, 95% CI = 1.35–3.09, $P=0.001$) and AIDS (HR = 1.66, 95% CI = 1.16–2.39, $P=0.006$) were significantly associated with incident diabetes mellitus. The year of cART initiation was not associated with new-onset diabetes mellitus in this analysis, with an HR of 1.00, 0.90 (95% CI = 0.53–1.52) and 1.18 (95% CI = 0.73–1.90) for

Table 1. Characteristics of participants according to the third agent prescribed

	Total	Third agent (%)			Pearson χ^2
		INSTI	NNRTI	PI	
Age (years)					
≤30	4960	17	29	54	$P<0.001$
>30 to ≤37	4531	16	31	53	
>37 to ≤46	4930	16	29	55	
>46	5041	20	26	54	
Sex					
female	5606	14	26	60	$P<0.001$
male	13 654	19	30	51	
transgender	202	15	45	40	
Medical centre					
overseas	1547	16	20	64	$P<0.001$
east of France	1990	14	25	61	
north of France	1327	16	30	54	
west of France	2245	20	27	53	
Paris	5547	18	32	50	
south of France	4689	19	31	50	
south-east of France	2117	17	24	59	
Geographical origin					
Africa	5629	14	29	57	$P<0.001$
South America	1258	14	34	52	
France	9281	19	28	53	
other/unknown	3294	19	29	52	
BMI (kg/m^2)					
≤25	6176	22	25	53	$P<0.001$
>25 to ≤30	1811	22	26	52	
>30	725	19	29	52	
NA	10 750	14	31	54	
Dyslipidaemia					
yes	98	12	35	53	$P=0.253$
no	19 364	17	29	54	
Smoking					
yes	5693	18	28	54	$P<0.001$
no	6450	15	29	56	
past smoker	1269	19	27	54	
NA	6050	19	30	51	
Arterial hypertension					
yes	733	20	27	53	$P=0.105$
no	18 729	17	29	54	
Alcohol consumption					
yes	7727	18	28	54	$P<0.001$
no	3827	15	27	58	
NA	7908	18	30	52	
Year of cART initiation					
2009–11	7434	6	32	62	$P<0.001$
2012–14	6912	11	34	55	
2015–17	5116	43	18	39	
AIDS					
yes	2361	19	16	65	$P<0.001$
no	17 101	17	31	52	
HIV risk group					
MSM	8447	20	31	49	$P<0.001$
heterosexual	8641	14	27	59	
IVDU	591	19	26	55	
others	1783	18	30	52	
Drug abuse					
yes	1704	23	27	50	$P<0.001$
no	8326	16	29	55	
detoxed	1266	17	23	60	
NA	4748	30	52	18	
Coinfection					
HBV	834	15	28	57	$P=0.126$
HCV	1346	19	29	52	
HBV and HCV	109	15	25	60	
no	17 173	17	29	54	

NA, not available.

Table 2. Multivariate analysis of factors associated with new-onset diabetes

	Incident diabetes		
	OR	95% CI	*P*
Third agent			
INSTI	1	NA	NA
NNRTI	1.39	0.72–2.66	0.325
PI	1.46	0.79–2.68	0.225
Year of cART initiation			
2009–11	1	NA	NA
2012–14	**0.48**	**0.33–0.69**	**<0.001**
2015–17	**0.33**	**0.19–0.58**	**<0.001**
Geographical origin			
Africa	1	NA	NA
South America	0.94	0.48–1.86	0.861
France	0.71	0.46–1.10	0.126
other/unknown	**0.52**	**0.29–0.96**	**0.036**
BMI (kg/m^2)			
≤25	1	NA	NA
>25 to ≤30	1.38	0.78–2.44	0.267
>30	**3.54**	**2.00–6.27**	**<0.001**
NA	1.45	0.97–2.17	0.071
Age (years)			
≤30	1	NA	NA
>30 to ≤37	1.67	0.90–3.12	0.104
>37 to ≤46	1.81	0.99–3.33	0.054
>46	**4.56**	**2.61–7.98**	**<0.001**

NA, not applicable.
Statistically significant comparisons are shown in bold.

periods 2009–11, 2012–14 and 2015–17, respectively, suggesting a role of exposure time rather than older molecules in the logistic regression model.

Discussion

The rate of incident diabetes mellitus in patients living with HIV on cART was lower in our cohort (4.2/1000 PYFU) than previously described[4,6,13–15] and similar to the studies of Ledergerber *et al.*[16] and Riyaten *et al.*[17] who found an incidence of 4.4/1000 PYFU and 5/1000 PYFU, respectively. This emphasizes the reduced side effects of cART over time and the greater viral suppression. However, this result could also be due to the low number of new-onset diabetes included in the survival analysis.

In our study, INSTI-based regimens were not significantly associated with incident diabetes compared with regimens containing an NNRTI or a PI. However, several studies described an association between an INSTI and weight gain[9] and as a consequence a potential increased risk of diabetes.[18] A possible physiopathology has previously been outlined, involving magnesium chelation and a decrease in insulin sensitivity.[11] Each patient was treated with only one therapeutic regimen and old toxic drugs were rare (considering NRTIs, 81.3% of patients were treated with emtricitabine/tenofovir disoproxil fumarate; data not shown), making the results suitable to current practice.

Others risk factors of diabetes highlighted in this study, such as age >37 years old, BMI >30 kg/m^2, arterial hypertension, African or South American place of birth and AIDS, are in accordance with current knowledge.[5,16,19]

Limitations of this study include its retrospective design. Other known risk factors for diabetes, such as a family history of diabetes mellitus or gestational diabetes, could not be investigated and may introduce a bias in the analysis. We were not able to evaluate BMI variation and its relationship with an INSTI. Some diagnoses of diabetes mellitus might not have been notified in the medical electronic record, resulting in underestimation of its incidence. NRTI backbones potentially responsible for mitochondrial toxicity were not controlled; nevertheless, there should not be more diabetes mellitus with one or another association.[20] Only two of our patients were treated with bictegravir and none with cabotegravir, the newest INSTI, and we should stay aware of eventual side effects of these molecules.

In conclusion, we didn't observe an increased risk of new-onset diabetes mellitus with INSTI-based regimens compared with regimens with other third agents. These results must be confirmed for a longer follow-up.

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Transparency declarations

None to declare.

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