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Incident diabetes in course of antiretroviral therapy

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Abstract

Objective: Recent reports of excessive weight gain in people living with HIV (PWH) have raised increasing concerns on the possible increase of diabetes mellitus (DM) risk in course of integrase inhibitor (INSTIs) treatment. In this study, we aimed at describing DM incidence in course of antiretroviral therapy (ART) and identifying the factors associated with new DM onset.

Design: Observational prospective SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) cohort.

Methods: All people enrolled in SCOLTA between January 2003 and November 2021 were included. Multivariable Cox regression yielded adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for incident DM.

Results: 4,366 PWH were included, 72.6% male, with mean age 45.6 years, and median CD4 460 (IQR 256-710) cells/mm^{3}cells/mm^3. During the follow up, 120 incident cases of DM occurred (1.26 cases/100 person year-follow up, 95% CI 1.05-1.50).

Baseline weight, but not the amount of weight gain, resulted significantly correlated to diabetes incidence (aHR by 1 Kg 1.03; 95%CI 1.01-1.04), as well as older age (aHR 1.03 by 1 year; 95%CI 1.01-1.06), being ART-experienced with detectable HIV RNA at study entry (aHR 2.27, 95%CI 1.48-3.49), having untreated high blood pressure (aHR 2.90; 95%CI 1.30-6.45) and baseline blood glucose >100 mg/dL (aHR 5.47; 95%CI 3.82-7.85). Neither the INSTI class nor individual antiretrovirals were associated with an increased risk of DM.

Conclusions: baseline weight, but not weight gain or the ART class, was associated with incident DM in this observational cohort.

Keywords: diabetes; insulin resistance; integrase inhibitors, protease inhibitors, weight gain, obesity, metabolic health.

Introduction

Recent reports of excessive weight gain in course of integrase inhibitors (INSTIs) antiretroviral therapy (ART) have raised concerns on the possible increase of diabetes mellitus (DM) risk [1–4].

In fact, while weight gain in HIV has not to date been correlated with adverse outcomes in terms of overall survival or cardiovascular risk [4–7], people with HIV (PWH) who gain weight are indeed at increased risk of developing diabetes [4,5,7]. The question then arose whether drugs that are associated with greater weight gain, such as INSTIs, might also be associated with an increased risk of diabetes. On the other hand, INSTIs have a neutral profile on plasma lipids [8,9] and for this reasons are often chosen as treatment in PWH with dyslipidemia or who are considered at high pre-treatment risk of developing DM or metabolic syndrome [9,10], making comparisons between INSTI- and non-INSTI-treated PHW often unbalanced in observational studies, due to a selection bias of PHW in INSTI cohorts. Regarding the specific evaluation of insulin resistance (IR) during INSTIs, the studies have not reached an agreement to date, as a neutral [11,12] or improving [13,14] effect has been reported compared to other antiretrovirals in some studies, but even a worse effect has emerged in others [15]. Also, studies directly focused on incident cases of diabetes on ART showed conflicting results, with some large observational studies founding a neutral effect of exposure to INSTIs [16–18], or rather a role of protease inhibitor (PI) class [16,19–22], while in a recent study, performed on US health insurance data, an association between INSTIs and DM incidence was actually found [23]. In the present study, we aimed at describing DM incidence in course of different ART regimens in a large multicenter prospective cohort and identifying the factors associated with new DM onset.

Methods

We analyzed data from SCOLTA (Surveillance Cohort Long-Term Toxicity Antiretrovirals) prospective database. The SCOLTA project is a multicenter observational study that involves 25 Italian Infectious Disease Centers. It started in 2002 and follows prospectively PWH who start a treatment with new antiretroviral drugs, to identify toxicities in a real-life setting [24]. Both ART naïve- and experienced-patients can be included in SCOLTA, if they are >18 years and start a newly marketed antiretroviral drug. They remain in observation until treatment discontinuation or cohort closing. Complete data collection and follow-up procedures have been previously described [25–27].

For the present study, DM was defined by confirmed fasting glucose ≥126 mg/dl or single value ≥200 mg/dl at any time or new starting of an antidiabetic drug, in people not previously diagnosed with DM. Since routine evaluation of fasting glucose was introduced in SCOLTA in 2003, all people enrolled between January 2003 and November 2021 were included. PWH were enrolled and followed-up in different calendar periods according to the cohort: 2003-2008 for atazanavir/ritonavir (ATV/r) [28]; 2006-2008 for darunavir/ritonavir (DRV/r) [29]; 2016-2018 for darunavir/cobicistat (DRV/c) [30]; 2013-2017 for rilpivirine (RPV) [31]; 2007-2014 for raltegravir (RAL) [32]; 2014-2017 for elvitegravir (EVG) [33]; 2014-ongoing for DTG [2,26]; and 2019-ongoing for bictegravir (BIC).

The original study protocol was approved on 18 September 2002, and a new protocol amendment was approved on 13 June 2013 by the coordinating center at Hospital "L. Sacco"-University of Milan, (Italy) and thereafter by all participating centers. Written consent for study participation was obtained from all participants, and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and by Italian national laws.

The primary study objective was to evaluate the incidence of DM during ART treatment with newly approved drugs and identify associated factors. Secondary objective was to examine the impact of different ART regimens on incident DM.

We performed the analyses on two datasets, the first to perform an analysis by anchor drugs (analysis by cohort) and the second to perform an analysis by ART regimen (analysis by drug class: INSTI, PI, NNRTI, PI+NNRTI, PI+INSTI, INSTI+NNRTI, or PI+INSTI+NNRTI).
To test baseline differences among study cohorts, we used the chi-square test, analysis of variance, and Kruskal-Wallis test, as appropriate. Baseline weight was imputed, when missing, as the mean weight calculated by sex and CDC stage, corrected for age and height, if the latter variable was available.

Multivariable Cox regression yielded crude and adjusted hazard ratios (HRs) and 95%CI for incident DM. All variables that retained a p value in the age- and sex-adjusted model <0.05 were included in the multivariate model. All p-levels were two-sided, at the significance level <0.05. All statistical analyses were performed using SAS for Windows 9.4 (SAS Institute, Cary, NC).

Results

Among 4,597 PWH enrolled in SCOLTA during the study period, 231 (5.0%) were excluded because of preexisting DM diagnosis (Supplementary Table 1, http://links.lww.com/QAD/C836).

Among the 4,366 study participants, 3,170 (72.7%) were male, mean age was 45.6 ± 10.7 years, and median CD4+T count was 460 (IQR 256-710) cells/mm^3. At baseline, 356 (8.2%) were on statin treatment, and mean weight was 70.5 ± 13.3 Kg. 1,288 PWH were on PI (582 ATV and 706 DRV), 451 on NNRTI (451 RPV), 2,627 on INSTIs (495 RAL, 325 EVG, 1269 DTG, 538 BIC). Characteristics of the study participants are shown in Table 1 and Supplementary Table 2, http://links.lww.com/QAD/C836. The mean weight increase in the study population was 0.7 Kg (95%CI 0.5-0.8) and 1.3 Kg (95%CI 1.1-1.5) at 1- and 2-year follow-up. Weight trends in different study cohorts are shown in Supplementary Table 3, http://links.lww.com/QAD/C836. During the follow up, 120 incident cases of DM occurred, with an estimated incidence of 1.26 cases/100 PYFU (95% CI 1.05-1.50). Time to DM onset in each study cohort is shown in Supplementary Figure 1, http://links.lww.com/QAD/C836. At multivariable analysis, baseline weight (aHR 1.03 for each additional kg, 95%CI 1.01-1.04), but not the amount of weight gain, resulted significantly correlated to diabetes incidence, as well as older age (aHR by one year 1.03, 95%CI 1.01-1.06), having untreated hypertension (aHR 2.90, 95%CI 1.30-6.45) and having a higher baseline fasting glucose (aHR for fasting glucose >100mg/dL 5.47, 95%CI 3.82-7.85). ART-experienced PWH with detectable HIV RNA at study entry resulted more at risk of incident diabetes as compared to PWH with HIV RNA < 50 copies/mL (aHR 2.27, 95%CI 1.48-3.49). Among cohorts of antiretrovirals, none showed a significant association with the risk of DM. In a second model considering the drug classes included in the ART regimen instead of the single anchor agents, no ART class resulted associated to the risk of incident diabetes. The full analysis is shown in Table 2 and Supplementary Table 4, http://links.lww.com/QAD/C836.

Discussion

In this study, in a large cohort of PWH with a DM incidence of 1.26 cases/100 PYFU), we found that INSTI treatment was not associated with the risk of developing diabetes and that baseline weight, and not weight gain, was the main anthropometric factor associated with DM. The incidence we found is in agreement with the estimate of a large meta-analysis reporting data on PWH [34], however, the incidence of DM is heterogeneous in the literature, [4,7,16–22,35–40], with notable differences likely due to the different characteristics of the participants in terms of sex, age, weight, HIV duration, and diabetes ascertainment methodology. Of note, in our study, the mean weight gain was moderate, 0.7 and 1.3 Kg at 1- and 2-years, probably explaining why weight gain did not associate with increased risk of DM, contrary to expectations [4,7,35,41]. On the other hand, this feature may be important in assessing the impact of ART but also of other factors and comorbidities, in a context of moderate weight gain, far from that described in some large non-European studies, whose results are not always exportable to other cultural and social contexts [16,42]. In this cohort, the traditional risk

factors for DM were confirmed, including older age [18–21,36,37,39,40,43], higher baseline BMI [18–20,36,39,43] and increased baseline fasting glucose [21,34,37]. Moreover, untreated hypertension was associated with DM occurrence, as also observed in the general population, where the impact of IR in the nitric-oxide pathway, the stimulatory effect of hyperinsulinaemia on sympathetic drive, smooth muscle growth, and sodium-fluid retention, and the excitatory effect of hyperglycemia on the renin-angiotensin-aldosterone system seem to be plausible mechanisms underlying this association [44,45]. In addition, we analyzed the relationship among DM, HIV control, and ART exposure. We found that ART-experienced participants with detectable HIV RNA had a risk of more than two times higher than those having HIV RNA<50 copies/mL. This observation could be probably explained because uncontrolled infection may influence the inflammatory pathway, which in turn can be associated with the risk of DM [46–52], as also suggested by the higher incidence of DM described in PWH with higher levels of IL-6 and hsCRP [43], lower CD4 count or nadir [21,22] and Centers for Disease Control and Prevention stage C [20,37]. It is also possible that an apparent effect of uncontrolled viremia on incident DM could be actually mediated by unmeasured behavioral factors, associated with both poor ART adherence and weight increase.

Finally, we explored possible associations between DM, ART classes and individual anchor drugs. We found no associations with any of the antiretroviral classes and drugs studied, including those used in people who had greater weight gain. Only RAL exposure appeared to increase the risk of DM by about 70% compared with DTG, with borderline significance. Some previous studies have also shown an increased risk of DM in course of RAL [16], a greater increase in waist circumference compared to PIs [53], and thus a possible increase in visceral fat accompanied by insulin resistance [12], and an increased fibrosis in adipose tissue and reduced insulin sensitivity in adipocytes [54]. These observations could support the plausibility of the association, which, however, has not been confirmed in other studies [13,17] and should be interpreted with caution. Indeed, RAL was the first INSTI available in clinical practice, to which most PWH with metabolic issues, deemed to be at high cardiovascular risk and often with history of multiple failures to other antiretrovirals were channeled first. Also in our study, most PWH on RAL had a high baseline triglyceride/HDL ratio, suggesting an increased insulin resistance even before starting the drug [55] and were more frequently co-infected with HCV, another factor that has been associated with DM risk [56,57].

The study has several limitations. Since this was an observational design, treatment allocation was not randomized, and residual confounders related to the reasons why physicians prescribed a particular antiretroviral may persist even after statistical adjustment. In addition, the study variables did not include insulin levels, anthropometric measures of visceral adipose tissue accumulation or information on the dietary habits and physical activity of the study participants. Moreover, the modest weight increase observed, and the study population composed mostly by male Caucasians, do not allow to generalize the study results to other populations and cultural contexts.

Despite these limitations, this study allowed to evaluate multiple clinical and therapeutic factors and their impact on the risk of incident DM in a large prospective cohort of PWH, and

confirmed a lack of significant association between DM and INSTI use [16–18,58]. In this cohort characterized by a moderate weight gain during follow up, baseline weight and not weight gain was associated with the risk of DM.

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Table 1: Baseline characteristic of the study population by cohort, according to the type of anchor drug used in course of ART.

	Total N=4366	ATV N=582	DRV* N=706	RPV N=451	RAL* N=495	EVG N=325	DTG N=1269	BIC N=538	p
Age (years), mean ± SD	45.6 ± 10.7	42.3 ± 7.7	45.6 ± 9.4	43.4 ± 10.4	45.5 ± 9.0	43.3 ± 10.7	47.7 ± 12.0	47.6 ± 12.0	<.0001
Male sex, n (%)	3170 (72.6)	392 (67.4)	515 (72.9)	327 (72.5)	326 (65.9)	250 (76.9)	957 (75.4)	403 (74.9)	<.0001
Ethnicity (Caucasian), n (%)	3989 (91.4)	543 (93.3)	662 (93.8)	413 (91.6)	461 (93.1)	292 (89.8)	1144 (90.1)	474 (88.1)	0.002
Weight (kg), mean ± SD	70.5 ± 13.3	67.5 ± 11.7	69.7 ± 13.2	71.0 ± 13.3	68.7 ± 13.5	70.7 ± 11.7	71.1 ± 13.4	74.5 ± 14.2	<.0001
BMI (kg/m^2), mean ± SD	24.1 ± 4.0	n.a.	23.7 ± 4.2	24.0 ± 3.6	23.6 ± 4.0	23.8 ± 3.2	24.1 ± 4.1	25.2 ± 4.4	<.0001
Risk factor for HIV acquisition IVDU, n (%) Unprotected sex, n (%) Other, n (%)	1067 (24.4) 2816 (64.5) 483 (11.1)	249 (42.8) 292 (50.2) 41 (7.0)	249 (35.5) 363 (51.1) 94 (13.4)	70 (15.5) 353 (78.3) 28 (6.2)	176 (35.6) 274 (55.4) 45 (9.1)	50 (15.3) 244 (75.2) 31 (9.5)	200 (15.8) 930 (73.3) 139 (11.0)	73 (13.6) 360 (66.9) 105 (19.5)	<.0001
Naïve, n (%)	733 (16.8)	20 (3.4)	56 (7.9)	133 (29.5)	28 (5.7)	101 (31.0)	311 (24.5)	84 (15.6)	<.0001
ART duration (years), median (IQR)	9.7 (4.3-14.8)	7.7 (4.1-10.5)	11.6 (6.5-16.1)	6.4 (3.0-12.7)	11.8 (7.4-14.0)	7.9 (2.8-16.3)	10.3 (4.9-18.0)	7.5 (3.2-15.3)	<.0001
CDC stage C, n (%)	1160 (26.6)	199 (34.2)	260 (36.8)	66 (14.6)	186 (37.6)	74 (22.8)	268 (21.1)	107 (19.9)	<.0001
Current CD4+ (cells/mm^3), median (IQR)	460 (256-710)	338 (211-494)	340 (165-586)	537 (370-760)	336 (190-524)	468 (264-720)	583 (350-825)	574 (354-802)	<.0001
Detectable HIVRNA (copies/mm^3), n (%) (exp. N=3633)	1321 (36.4)	368 (65.5)	354 (54.5)	45 (14.2)	269 (57.6)	61 (27.2)	146 (15.2)	78 (17.2)	<.0001
HCV-Ab +, n (%)	1173 (26.9)	250 (43.0)	258 (36.5)	85 (18.8)	183 (37.0)	63 (19.4)	247 (19.5)	87 (16.2)	<.0001
Fasting glucose (mg/dL), mean ± SD	89.3 ± 13.8	89.6 ± 13.7	87.7 ± 13.9	88.3 ± 11.8	88.6 ± 15.0	89.2 ± 13.4	89.6 ± 13.7	91.9 ± 14.3	<.0001
TGL/HDL, median (IQR)	2.9 (1.8-4.9)	3.7 (2.3-7.2)	3.5 (2.2-6.1)	2.5 (1.7-4.1)	3.6 (2.2-6.3)	2.7 (1.8-4.6)	2.7 (1.7-4.5)	2.3 (1.5-3.6)	<.0001
TGL/HDL>2.0, n (%)	2707 (62.0)	290 (49.8)	492(69.7)	276 (61.2)	370 (74.7)	205 (63.1)	775 (61.1)	299 (55.6)	<.0001
Statin use, n (%)	356 (8.2)	22 (3.8)	47 (6.7)	28 (6.2)	35 (7.1)	21 (6.5)	143 (11.3)	60 (11.2)	<.0001

Hypertension, n (%) Untreated Treated	587 (13.4) 75 (1.7) 512 (11.7)	22 (3.8) 1 (0.2) 21 (3.6)	100 (14.2) 16 (2.3) 84 (11.9)	50 (11.1) 5 (1.1) 45 (10.0)	74 (14.9) 8 (1.6) 66 (13.3)	33 (10.2) 2 (0.6) 31 (9.5)	207 (16.3) 28 (2.2) 179 (14.1)	101 (18.8) 15 (2.8) 86 (16.0)	<.0001 <.0001
Time on study (months), median (IQR)	23 (12-39)	24 (11-36)	23 (13-44)	17 (10-24)	32 (16-49)	30 (17-39)	31 (14-58)	16 (8-21)	<.0001

ART: antiretroviral therapy; ATV: atazanavir; BIC: bictegravir; BMI: body mass index; DRV: darunavir; DTG: dolutegravir; EVG: elvitegravir; HCV-Ab: Hepatits C Virus Antibodies; HDL: high density lipoprotein cholesterol; IDU: intravenous drug use; n.a.: not available; PWH: people living with HIV; RAL: raltegravir; RPV: rilpivirine; TGL: triglycerides.

*180 people started DRV and RAL at the same date and were enrolled in both cohorts.

Table 2. Factors associated with incident diabetes in SCOLTA, by cohort (N= 4,366), and by antiretroviral therapy (ART) class (N=4,192).

	Age- and sex-adjusted analysis			**Multivariable analysis by cohort**			**Multivariable analysis by ART class**		
Variable	**Age- and sex-adjusted HR***	**95% CI**	**P value**	**Adjusted hazard ratio§**	**95% CI**	**P value**	**Adjusted hazard ratio§**	**95% CI**	**P value**
Age (by 1 year)	1.04	1.03-1.06	<.0001	1.03	1.01-1.06	0.001	1.03	1.01-1.05	0.009
Sex (ref. M)	0.65	0.42-1.01	0.055	0.96	0.59-1.56	0.87	1.07	0.66-1.75	0.88
Ethnicity (ref. Caucasian)	1.44	0.73-2.88	0.30						
Weight (by 1 Kg)	1.03	1.02-1.05	<.0001	1.03	1.01-1.04	<.0001	1.03	1.01-1.04	0.0003
BMI (by 1) (n=3215)	1.13	1.09-1.18	<.0001	1.11	1.06-1.16	<.0001	1.10	1.05-1.15	<.0001
Weight gain** (by 1 Kg)	0.98	0.95-1.01	0.17						

Rik factor for HIV acquisition (ref. sexual)	1.90	1.30-2.77	0.0009	1.46	0.85-2.51	0.17	1.67	0.96-2.90	0.07
IDU	1.40	0.84-2.45	0.18	1.34	0.77-2.33	0.30	1.26	0.72-2.22	0.42
Other/unknown									
ART duration (by 1 year), experienced pts (n=3749)	1.02	0.99-1.05	0.18						
CD4 (ref. <250 cells/mm^3)									
250-500	0.94	0.61-1.46	0.78						
>500-750	0.66	0.38-1.09	0.10						
>750	0.62	0.36-1.06	0.08						
missing	1.59	0.49-5.20	0.44						
CDC stage (ref. A)									
B	1.35	0.89-2.03	0.16						
C	1.25	0.81-1.92	0.31						
Naïve status (ref. Exp. With undetectable HIVRNA)									
Naïve	0.71	0.35-1.45	0.35	0.90	0.43-1.88	0.78	0.94	0.45-1.97	0.87
Experienced with detectable HIVRNA	2.07	1.43-3.00	<.0001	2.27	1.48-3.49	0.0002	2.53	1.62-3.96	<.0001
HCV coinfection (ref. N)	1.59	1.11-2.29	0.01	1.05	0.63-1.76	0.84	0.95	0.56-1.61	0.85
TGL/HDL (ref.≤2.0)									
>2.0	1.80	1.12-2.90	0.02	1.24	0.76-2.02	0.40	1.22	0.75-2.01	0.42
missing	1.52		0.25	1.20		0.64	1.42		0.37

		0.75-3.11			0.55-2.62			0.66-3.06	
Fasting glucose (by 1 mg/dL)	1.05	1.04-1.06	<.0001	1.04	1.04-1.05	<.0001	1.04	1.04-1.05	<.0001
Fasting glucose >100 mg/dL (ref. ≤100)	6.10	4.27-8.71	<.0001	5.47	3.82-7.85	<.0001	5.72	3.93-8.32	<.0001
Statin use (ref. no)	1.78	1.11-2.86	0.02	1.46	0.88-2.64	0.14	1.44	0.86-2.41	0.17
Hypertension (ref. no)									
Yes, untreated	3.14	1.43-6.90	0.004	2.90	1.30-6.45	0.009	2.54	1.07-6.04	0.04
Yes, treated	1.68	1.07-2.65	0.02	1.41	0.88-2.25	0.15	1.56	0.97-2.52	0.07
Cohort (ref. DTG)									
ATV	1.22	0.63-2.36	0.56	0.97	0.46-2.07	0.94	-	-	-
DRV§	1.31	0.77-2.21	0.32	1.02	0.57-1.82	0.95	-	-	-
RPV	0.88	0.34-2.25	0.68	1.10	0.42-2.86	0.84	-	-	-
RAL§	2.14	1.33-3.46	0.002	1.71	0.99-2.94	0.052	-	-	-
EVG	1.37	0.68-2.76	0.38	1.54	0.76-3.16	0.23	-	-	-
BIC	1.31	0.64-2.66	0.45	1.10	0.53-2.26	0.80	-	-	-
Anchor drug class (ref. INSTI alone)									
PI alone	0.86	0.51-1.46	0.59	-	-	-	0.62	0.33-1.15	0.13
NNRTI alone	0.76	0.30-1.91	0.56	-	-	-	0.96	0.38-2.43	0.93
PI+NNRTI	1.01	0.25-4.15	0.99	-	-	-	0.74	0.17-3.13	0.68
PI+INSTI	1.58		0.052	-	-	-	1.15		0.59
INSTI+NNRTI	1.07		0.89	-	-	-	1.13		0.79

PI+INSTI+NNRTI	2.99	0.99-2.52 0.43-2.67 1.22-7.68	0.02	-	-	-	1.85	0.69-1.94 0.45-2.86 0.69-4.96	0.22

95%CI: 95% Confidence Interval; ART: antiretroviral therapy; ATV: atazanavir; BIC: bictegravir; BMI: body mass index; DRV: darunavir; DTG: dolutegravir; EVG: elvitegravir; HCV-Ab: Hepatits C Virus Antibodies; HDL: high density lipoprotein cholesterol; HR: Hazard Ratio; IDU: intravenous drug use; INSTI: integrase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; PWH: people living with HIV; RAL: raltegravir; RPV: rilpivirine; TGL: triglycerides.

* Age and sex are mutually adjusted.

** at last visit before diabetes diagnosis or at last visit

§PWH who started DRV and RAL at the same time were included in both cohorts (n=180).

Variables were included in the multivariate model if their p value in the age- and sex-adjusted model was <0.05. Sex remained in the multivariable model even if its age-adjusted p was >0.05. aHRs for all variables but BMI derived from the model including weight in Kg and blood glucose > 100 mg/dL. Blood glucose >100 mg/dL and blood glucose as a continuous variable were not included in the model at the same time.