Dettaglio abstract

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Title: Treatment with integrase inhibitors among antiretroviral naïve patients is not associated with increased risk of diabetes mellitus

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Diabetes, cardiovascular diseases and STis. A wide range of comorbidities

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Abstract
Background: Integrase-strand inhibitors (INSTI) are components of the majority of antiretroviral (ARV) regimens currently recommended for treatment naïve patients. However, some INSTI have been associated with unintended weight gain. While the underlying mechanisms of this side effect is yet to be determined, it has been suggested that it may lead to an increased risk of metabolic complications, such as diabetes mellitus (DM).
Methods: All ARV-naïve patients enrolled in the ICONA cohort initiating first line ARV after Jan 1st 2009 were included, provided that baseline and ≥1 follow-up fasting glucose and weight were available. Patients were classified according to their initial ARV regimen into 3 groups (INSTI-, protease inhibitor (PI)- or non-nucleoside reverse transcriptase (NNRTI)-based treatment). Weight change after 18 months (time-window: 7-24 months) of ARV was compared between them using a linear regression model. Hazards of DM, defined as two consecutive fasting glucose >126 mg/dl, were compared, using uni- and multivariable Cox regression analyses. The following possible confounders measured at baseline were considered: age, ethnicity, baseline body mass index (BMI), presence of dyslipidemia, calendar year and use of TAF.
Results: Among the 4,808 patients included, 1,331 had initiated a regimen based on INSTI, 1,866 on PI and 1591 on NNRTI. Table 1 represents the characteristics of the enrolled patients. Those on INSTI were slightly older, less likely to have dyslipidemia and more likely to receive TAF and to initiate ARV more recently than the others. After ARV initiation, mean weight gains of 3.6 (SD 7.1), 3 (SD 7.2) and 1.4 (SD 6.1) Kg were observed INSTI, PI or NNRTI groups, respectively. Use of INSTI and PI were associated with a significantly higher additional weight gain than NNRTI (weight gain difference, INSTI vs NNRTI +2.1 [95%CI 1.4-2.8]; PI vs NNRTI +1.5 [95%CI 0.91-2.17]). No statistically significant difference was found comparing those who received INSTI vs. PI (INSTI vs PI, +0.6 [95%CI -0.1-1.23]). Over a median follow-up of 62 (IQR: 35-90) months, 110 new diagnoses of DM were observed, 20 (1.5%) among INSTI recipients, 54 (2.9%) and 36 (2.3%) among those treated with PI and NNRTI. From fitting a univariable Cox regression model there was no evidence for an association between the class of the anchor dug of first line regimen and risk of DM (INSTI vs. PI HR 1.07; 95%CI 0.63-1.82; P=0.796 vs. NNRTI HR 0.83; 95%CI 0.47-1.45; P=0.504). Lack of a statistically significant association between anchor drug class and risk of DM was confirmed after adjustment for possible confounders (Table 2).
Conclusions: Although patients initiating ARV using INSTI experienced, on average, higher weight gain compared to those treated with other drug classes, this difference appears of little clinical importance. In addition, no evidence of increased risk of DM was found among INSTI recipients, regardless of weight gain and other possible risk factors.

Table 1 Patients' characteristics by antiretroviral treatment (ART) group

	Anchor drug in first ART			
Characteristics at ART initiation	**INSTI**	**PI**	**NNRTI**	**p-value***
	N= 1351	N= 1866	N= 1591	
Gender, n(%)				<.001
Female	252 (18.7%)	446 (23.9%)	262 (16.5%)	
Age, years				<.001
Median (IQR)	40 (32, 49)	39 (32, 47)	38 (31, 46)	
Mode of HIV Transmission, n(%)				<.001
PWID	76 (5.6%)	162 (8.7%)	114 (7.2%)	
MSM	713 (52.8%)	787 (42.2%)	801 (50.3%)	
Heterosexual contacts	506 (37.5%)	834 (44.7%)	591 (37.1%)	
Other/Unknown	56 (4.1%)	83 (4.4%)	85 (5.3%)	
Nationality, n(%)				<.001
Not Italian	643 (47.6%)	490 (26.3%)	342 (21.5%)	
Calendar year of starting ART				<.001
Median (IQR)	2016 (2015, 2018)	2012 (2011, 2014)	2013 (2011, 2014)	
CD4 count, cells/mmc				<.001
Median (IQR)	346 (169, 529)	280 (127, 414)	390 (296, 504)	
Blood glucose, mg/dL				0.007
Median (IQR)	86 (79, 94)	85 (79, 93)	87 (81, 94)	
BMI, cm/Kg2				
Median (IQR)	23.0 (21.1, 25.1)	22.9 (20.9, 25.1)	23.2 (21.5, 25.5)	
Weight, Kg				
Median (IQR)	70 (62, 78)	69 (60, 76)	70 (64, 79)	
TAF in backbone, n(%)				<.001
Yes	416 (30.8%)	96 (5.1%)	2 (0.1%)	
Dyslipidemia, n(%)				<.001
Yes	907 (67.1%)	1337 (71.7%)	1178 (74.0%)	

*Chi-square or Kruskal-Wallis test as appropriate

Table 2 Relative hazards of developing new-onset diabetes mellitus from fitting Cox regression models

	Unadjusted and adjusted relative hazards		
	INSTI	**PI**	**NNRTI**
Models			
Unadjusted	1.00	1.07 (0.63, 1.82) 0.796	0.83 (0.47, 1.45) 0.504
Adjusted[1]	1.00	1.72 (0.92, 3.22) 0.087	1.29 (0.68, 2.45) 0.429
Adjusted[2]	1.00	1.61 (0.88, 2.94) 0.122	1.24 (0.67, 2.29) 0.497
Adjusted[3]	1.00	1.55 (0.85, 2.83) 0.157	1.22 (0.64, 2.31) 0.545
Adjusted[4]	1.00	1.41 (0.80, 2.48) 0.238	1.12 (0.61, 2.05) 0.708

[1]age, ethnicity, baseline BMI, dyslipidemia and year of starting ART
[2]age, ethnicity, baseline weight, dyslipidemia and year of starting ART
[3]TAF in NRTI baseline backbone, age, baseline BMI, dyslipidemia and ethnicity
[4]TAF in NRTI baseline backbone, age, baseline weight, dyslipidemia and ethnicity