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Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Integrase inhibitors Results from the EuroSIDA study.

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Objectives

Hypersensitivity reaction (HSR) and hepatotoxicity are rare but potentially serious side effects of antiretroviral use. We aimed to establish the incidence of discontinuation due to HSR and hepatotoxicity among dolutegravir (DTG), raltegravir (RAL) and elvitegravir (EVG) users.

Methods

HIV-positive people aged ≥16 years who started DTG, RAL or EVG between 16/1/2014–31/12/2015 were included and divided into four groups: DTG with or without abacavir (ABC) and EVG/RAL with or without ABC. The reasons for discontinuation for persons who discontinued any antiretroviral for any reason were independently reviewed. After review, the incidence of discontinuation due to HSR, hepatotoxicity and severe skin rash within each group was calculated.

Results

Baseline characteristics

- 1217 people started DTG, RAL or EVG during 700 PYFU, with a median follow-up of 0.5 (Interquartile range [IQR]: 0.3–0.8) years per person. **Table 1.**
- Of these, 657 started DTG (301 with ABC, 356 without) and 560 started RAL/EVG (79 with ABC, 481 without). **Table 1**.
- Those who started DTG, RAL or EVG were mainly male (75%), white (86%). Over half were aged over 50 years, half had a CD4 > 350 cells/mm^3 (50%) and 73% had a HIV-VL <400 copies/mL. **Table 1**.
- Less than 10% were cART naïve and 79% were integrase inhibitor naïve. **Table 1**.

Factors associated with starting DTG vs RAL/EVG

- Adjusted odds of DTG relative to RAL/EVG use was lower in people of non-white ethnicity, who contracted HIV through injecting drug use (IDU); and who were treatment naive. **Figure 1**.
- Lower adjusted odds of DTG use was observed in those from Argentina, Southern, East and East Central Europe. **Figure 1**.

Incidence of discontinuation.

- The rate of discontinuation for any reason in DTG treated patients was 15.0 (95%CI: 11.4,19.7)/100 PYFU and in the RAL/EVG treated group was 24.6 (95%CI: 19.9,30.3)/100 PYFU, P<0.01. **Figure 2**.
- After review, only two discontinuations were due to HSR (one each from DTG without ABC and RAL/EVG without ABC) **Figure 2**. Both HSR discontinuations were in treatment experienced patients, and one was integrase inhibitor experienced.
- There were no discontinuations due to hepatotoxicity or severe skin rash. **Figure 2**.

Conclusion

Early results indicate that the frequency of discontinuation due to HSR in users of integrase inhibitors is low and no discontinuations due to hepatotoxicity or severe skin rash were observed. The study will continue to monitor these events for another three years.

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Table 1. Characteristics at baseline[1]

	Total N (%)	DTG		RAL/EVG	
		ABC	No ABC	ABC	No ABC
Total	1,217 (100)	301 (100)	356 (100)	79 (100)	481 (100)
Age (years) > 50	620 (50.9)	143 (47.5)	213 (59.8)	38 (48.1)	226 (47.0)
Male gender	913 (75.0)	221 (73.4)	272 (76.4)	56 (70.9)	364 (75.7)
Non-white race[2]	177 (14.5)	41 (13.6)	48 (13.5)	8 (10.1)	80 (16.6)
HIV risk group: MSM	493 (40.5)	128 (42.5)	159 (44.7)	19 (24.1)	187 (38.9)
Prior AIDS	321 (26.4)	73 (24.3)	109 (30.6)	21 (26.6)	118 (24.5)
Prior non-AIDS[3]	187 (15.4)	45 (15.0)	68 (19.1)	13 (16.5)	61 (12.7)
Hepatitis C coinfected	447 (36.7)	89 (29.6)	113 (31.7)	41 (51.9)	204 (42.4)
Hepatitis B coinfected	52 (4.3)	15 (5.0)	14 (3.9)	1 (1.3)	22 (4.6)
HIV viral load < 400 copies/mL	884 (72.6)	241 (80.1)	267 (75.0)	57 (72.2)	319 (66.3)
CD4 ≥ 350 cells/mm^3	583 (47.9)	163 (54.2)	174 (48.9)	29 (36.7)	217 (45.1)
Treatment naïve	87 (7.1)	15 (5.0)	15 (4.2)	5 (6.3)	52 (10.8)
INSTI Naïve	962 (79.0)	249 (82.7)	229 (64.3)	73 (92.4)	411 (85.4)

[1] Baseline was the earliest of date of initiation of first integrase inhibitor after Jan 2014 or first visit.
[2] Includes other and unknown ethnicity
[3] Pancreatitis, grade 3 or 4 hepatic encephalopathy or liver-related death, myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, carotid endarterectomy, and end-stage renal disease [90]

Figure 1. Adjusted odds ratios of starting DTG compared to RAL/EVG

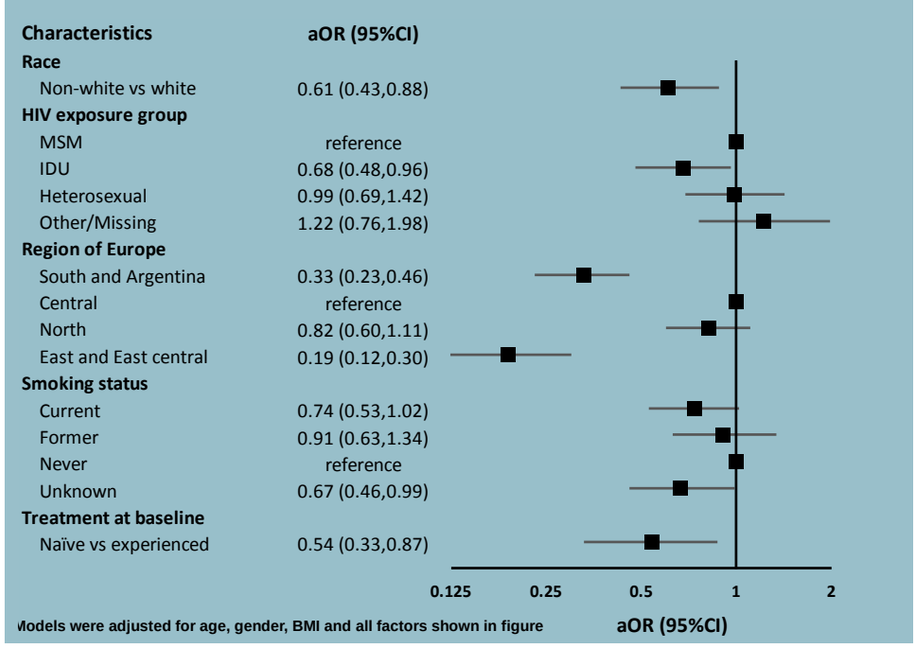
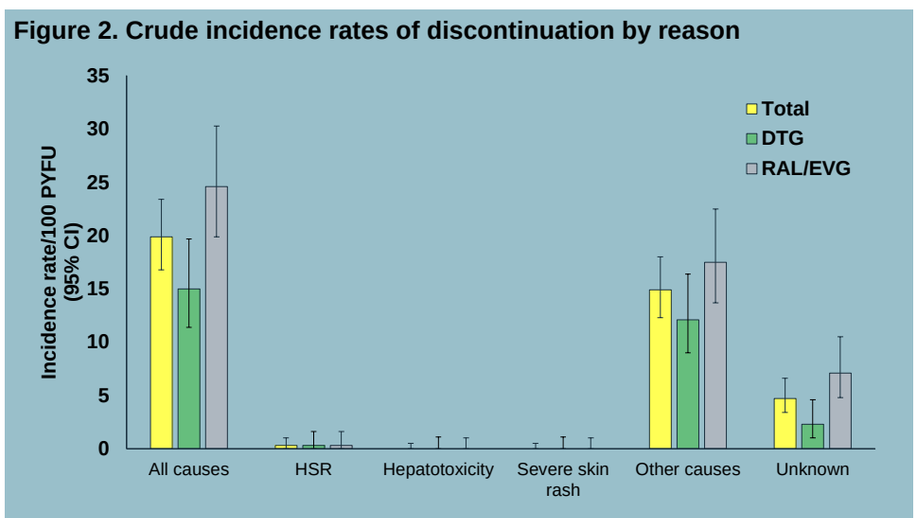


Figure 2. Crude incidence rates of discontinuation by reason



Number of events						
Total	**139**	**2**	**0**	**0**	**104**	**33**
DTG	51	1	0	0	42	8
RAL/EVG	88	1	0	0	62	25

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