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The Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Individuals Receiving Integrase Strand Transfer Inhibitors: Results from the EuroSIDA Study

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BACKGROUND

Hypersensitivity reaction (HSR) and hepatotoxicity are rare but potentially serious side effects of antiretroviral use. This post-authorisation safety study aimed to establish the incidence of discontinuations due to HSR, hepatotoxicity or severe skin rash among users of dolutegravir (DTG) compared to raltegravir (RAL) or elvitegravir (EVG) in a real-world setting.

METHODS

HIV-positive individuals in EuroSIDA aged ≥18 years who started a combination antiretroviral therapy (cART) regimen containing DTG, RAL or EVG between 16/01/2014 and 23/01/2019 were analysed in four groups: DTG ± abacavir (ABC) and RAL or EVG ± ABC. All discontinuations were reviewed, and any suspected HSR, hepatotoxicity or severe skin rash events were adjudicated by an independent event review committee. The incidence of discontinuations within each group was calculated.

RESULTS

- In total, 4366 individuals started at least one cART regimen including DTG, RAL or EVG with or without ABC (**Table 1**).
- Individuals started altogether 5116 integrase strand transfer inhibitor (INSTI)-containing cART regimens, contributing 9180 person-years of follow-up (PYFU), with median follow-up 1.6 (interquartile range, IQR 0.7-2.8) years per treatment episode. Of the treatment episodes, 3074 (60.1%) were with DTG and 2042 (39.9%) were with RAL or EVG.
- There were 649 discontinuations in 5649 PYFU of DTG-containing regimens and 612 in 3531 PYFU of RAL- or EVG-containing regimens. The discontinuation rate for any reason for DTG was 115 (95% CI 106-124)/1000 PYFU and for RAL or EVG was 173 (CI 160-188)/1000 PYFU).
- After independent review, there were five HSR discontinuations, two for DTG (discontinuation rate 0.35, 95% CI 0.04-1.28/1000 PYFU), and three for RAL or EVG (0.85, CI 0.18-2.48/1000 PYFU). There was one hepatotoxicity discontinuation on DTG with ABC (0.18, CI 0.00-0.99/1000 PYFU), and no severe skin rash discontinuation (**Table 2 and Figure 1**).
- Among those who discontinued, the most common reasons for discontinuing an INSTI-containing regimen were toxicity and physician's decision (**Figure 2**).
- After adjustment, the rate of discontinuation of RAL- or EVG-containing regimens was >50% higher than for DTG regimens (aIRR 1.56, 95% CI 1.38-1.77, p <0.0001). Apart from toxicity, the rate of discontinuations for all reported reasons was significantly higher among those on RAL or EVG (**Figure 3**).

DISCUSSION AND CONCLUSIONS

- During this five-year post-authorisation study in a real-world observational cohort, individuals contributed >9,000 PYFU on INSTI-containing cART regimens
- Around 25% of INSTI regimens were discontinued, with discontinuation rates significantly higher among those on RAL- or EVG-containing regimens compared to DTG.
- In this real-world setting, discontinuations due to HSR or hepatotoxicity in INSTI users were very rare.
- After independent review, there were five HSR and one hepatotoxicity events, equivalent to one severe adverse event in approximately 1,500 person-years of INSTI use; the low number of severe events precluded detailed analyses.
- As this is an observational study, treatment decisions are made by the treating physician and confounding by indication cannot be excluded.

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Table 1. Characteristics of INSTI users at baseline*

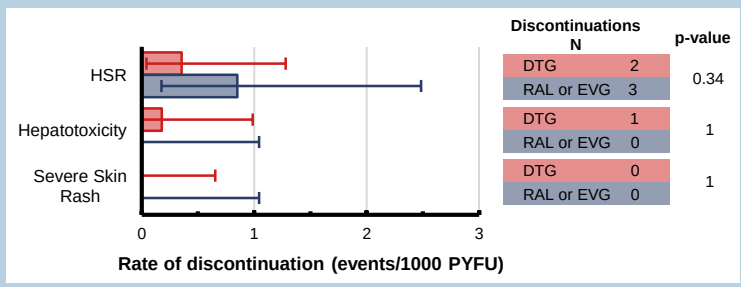
Number of individuals	Total N (%) 4366	DTG With ABC 1545	DTG No ABC 1166	RAL or EVG With ABC 239	RAL or EVG No ABC 1416
Age ≥50 years	2369 (54.3)	861 (55.7)	683 (58.6)	104 (43.5)	721 (50.9)
Sex male	3215 (73.6)	1123 (72.7)	875 (75.0)	160 (66.9)	1057 (74.6)
Ethnic group white	3587 (82.2)	1285 (83.2)	947 (81.2)	211 (88.3)	1144 (80.8)
HIV exposure group MSM	1640 (37.6)	611 (39.5)	456 (39.1)	49 (20.5)	524 (37.0)
HIV viral load <400 cp/ml	3248 (74.4)	1208 (78.2)	890 (76.3)	158 (66.1)	992 (70.1)
CD4 count ≥350 cells/µl	2500 (57.3)	928 (60.1)	613 (52.6)	137 (57.3)	822 (58.1)
ARV treatment-naïve	166 (3.8)	57 (3.7)	21 (1.8)	12 (5.0)	76 (5.4)
INSTI-naïve	3587 (82.2)	1331 (86.1)	830 (71.2)	226 (94.6)	1200 (84.7)

*Baseline was the earliest of date of initiation of an INSTI after 16 Jan 2014.
MSM – men who have sex with men

Table 2. Discontinuations of INSTI regimens

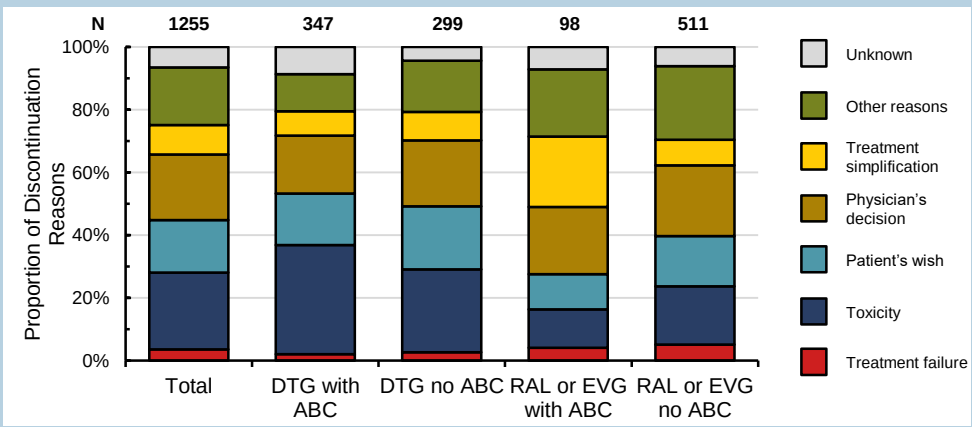
	Total N (%)	DTG With ABC	DTG No ABC	RAL or EVG With ABC	RAL or EVG No ABC
Number of INSTI episodes	5116	1738	1336	286	1756
Person-years of follow-up	9180	3204	2445	493	3038
Episodes discontinued (% of episodes)	1261 (24.6)	349 (20.1)	300 (22.5)	98 (34.3)	514 (29.3)
Validated HSR	5 (0.4)	1 (0.3)	1 (0.3)	0 (0.0)	3 (0.6)
Validated Hepatotoxicity	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Severe Skin Rash (not HSR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Figure 1. Discontinuation rates for serious adverse events



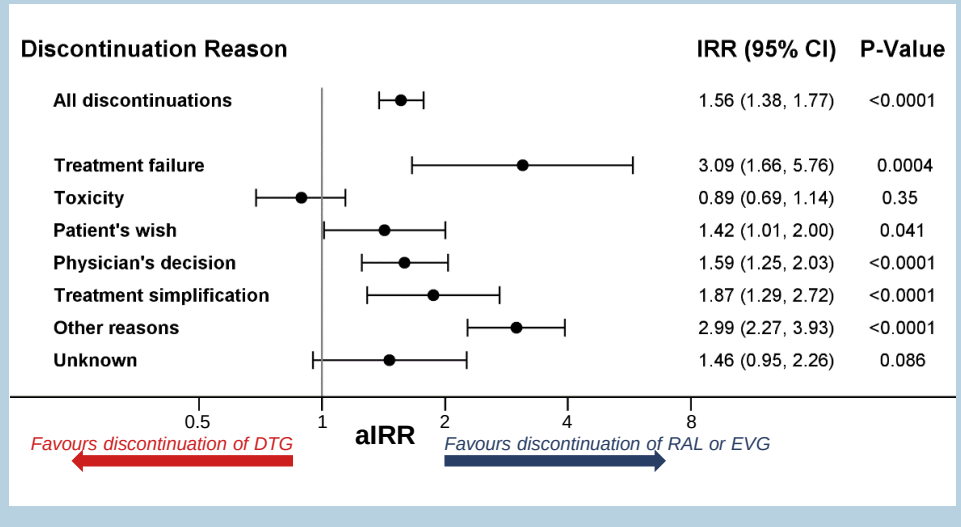
Bars show 95% confidence intervals. p-values are for the discontinuation incidence rate ratios.

Figure 2. Discontinuation reasons by treatment group



'Other reasons' includes concern for comorbidities, dyslipidaemia, abnormal fat redistribution, allergic reactions (not HSR), pregnancy-related and other treatment changes. The number of discontinuations for each treatment group is shown above the bars

Figure 3. Adjusted discontinuation incidence rate ratios (IRRs) comparing discontinuations of RAL- or EVG-containing regimens with DTG discontinuations (reference)



Multivariable Poisson regression models were adjusted for participant's characteristics at baseline (sex, ethnicity, risk group, region, ART naïve or INSTI naïve, prior use of PIs, NNRTIs or DTG, EVG or RAL, the total number of ARVs previously exposed to, and time since first ARV use) or time-updated variables (age, BMI, smoking status, AIDS or non-AIDS clinical conditions, diabetes, hypertension, anaemia, HCV and HBV infection, as well as current and peak viral load, current and nadir CD4 counts, eGFR, ALT and AST levels and the proportion of follow-up time with low CD4 counts or high viral load). Confounding and effect-modifying factors that were significant in univariate analyses (p<0.1) were included in multivariate models; excluded variables were added in turn to determine if their inclusion improved the fit of the model (Note: Due to low numbers of events, the aIRR for treatment failure was only adjusted for sex, CD4 cell counts at baseline and ARV treatment naïve).

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