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Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir.

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Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir.

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We have read with interest the Concise Communication of de Boer et al. [1] on the intolerance of dolutegravir (DGV)-containing combined antiretroviral therapy (cART) regimens in real life clinical practice. After a median follow-up time of 225 days, the Authors observed a relatively high rate of early discontinuation of DGV (15.3%), mainly due to intolerability (76/85). DGV was stopped more likely (adjusted rate ratio 1.92, 95% confidence interval (CI) 1.09-3.38) if the cART regimen included abacavir (ABC). These results are surprisingly different from those found in randomized controlled trials [2-4], where the frequency of adverse events that caused discontinuation of DGV at week 48 was remarkably lower.

In the frame of SCOLTA (Surveillance Cohort Long-term Toxicity Antiretrovirals/antivirals) Project, an online reporting system for adverse reactions to antiretroviral drugs, designed by the CISAI (Italian Coordination for the Study of Allergy and HIV Infection) group, we started collecting information on patients taking their first DGV-containing regimen since July 2014. Patients undergo their follow up at 6-month intervals and adverse events (AE) are notified when they are clinically observed. Complete data collection and follow-up procedures for the cohorts are described elsewhere [5].

Four hundred and thirty-seven patients were enrolled in the study: 295 had at least one follow-up visit (median observation time 258 days, interquartile range, IQR, 180-396) and were included in the analysis. Follow-up time was defined from the day of DGV initiation until the day of discontinuation or the day of last follow-up visit. In our sample, median age was 48 years (IQR 42-53), females were 25.1%, 46.1% were in CDC stage A and 25.4% were HCV-coinfected. Fifty-four subjects (18.3%) were treatment naïve.

In our observational cohort, 32 subjects (10.8%) withdrew their DGV-containing regimen (Table 1). Sixteen patients (5.4% of subjects, 50% of those who stopped their treatment) interrupted DGV because of an adverse event (AE). The AE list included one hypersensitivity reaction in a subject on ABC/lamivudine (3TC)/DGV, two cases of muscle-skeletal pain and two of abdominal pain, renal

impairment in three patients, vomiting (1) and diarrhea (1), one liver enzymes increase, two skin rash, one ischemic ictus and two central nervous system (CNS) symptoms (one somnolence, one headache). Median time to interruption due to an AE was 180 days (IQR 106-353).

As far as their drug backbone, the majority of patients who withdrew DGV for an AE were on ABC/3TC (9), or on tenofovir/emtricitabine containing regimens (4); one was taking darunavir/ritonavir, one maraviroc+3TC and one rilpivirine. We did not observe any association between interruption (overall and due to AEs) and backbone therapy: 11 (10.5%) interruptions occurred (nine due to EA, 8.6%) out of 105 ABC-containing regimens. The corresponding figures for TDF/FTC were 12/100 (12.0%) and 4/100 (4.0%).

Grade 3-4 AEs not leading to interruption were recorded in eight patients: in two cases (hypophosphatemia and creatinephosphokinase increase) they were possibly related to DGV, associated to TDF/FTC.

Hazard ratios (HR) were calculated and logistic regression was used to adjust simultaneously for the potentially confounding effects of selected variables, according to the Cox model.

At univariate analysis, older age and being naïve at study entry were associated to interruption for any reason. Patients in CDC stage B and C were increasingly more likely interrupting DGV, but we did not find any significant association. Age and naïve status, simultaneously included in the equation, remained statistically significant: HR of interruption for increasing age was 1.04 (by 1 year, 95% CI 1.01-1.08, p=0.017) and 3.05 for naïve patients as compared to experienced (95% CI 1.39-6.70, p=0.005), respectively. When we considered the cART duration, attributing 0 to naïve patients and using them as the reference category, the risk of interruption decreased for each quartile. This finding emerged with an irregular trend, thus not supporting the conclusion that a longer cART is protective against interrupting treatment independently of age.

The same analysis was performed with interruption for AEs as the outcome (other interruptions were censored at the time of discontinuation). In this model, age at study entry was the only determinant of interruption (HR 1.06, 95% CI 1.00-1.11, p=0.037). As regards the drug backbone, no regimen was significantly associated with interruptions, although a trend toward protection was suggested for tenofovir/emtricitabine (HR 0.76, 95% CI 0.31-1.85) and no effect for ABC (HR=1.00, 95% CI 0.47-2.17).

In conclusion, DGV was well tolerated in our cohort, as confirmed by the low rate of both total DGV-based regimen discontinuations (10.8%) and interruptions related to AEs (5.4%). Furthermore, CNS events were infrequent in our study but a longer follow-up is warranted to better evaluate this kind of side effects.

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Table 1. Demographic and clinical baseline characteristics of 295 patients enrolled in the dolutegravir cohort.

	Naive (n=54, 18.3%)	**Experienced (n=241, 82.7%)**
Age (years, median, IQR)	42 (31-49)	49 (44-54)
Female (n,%)	12 (22.2)	62 (25.7)
HIV transmission category (n,%)		
IVDU	3 (5.6)	61 (25.3)
Sexual	41 (75.9)	139 (57.7)
Other or unknown	10 (18.5)	41 (17.0)
CDC stage (n,%)		
A	31 (57.4)	105 (43.6)
B	12 (22.2)	61 (25.3)
C	11 (20.4)	75 (31.1)
CD4 count (cells/μL) (n,%)		
<200	19 (35.2)	53 (22.0)
200-499	16 (29.6)	80 (33.2)
≥ 500	19 (35.2)	108 (44.8)
Undetectable HIV VL at study entry (n,%)	0	178 (73.9)
HCV positive(n,%)	1 (1.9)	74 (30.7)
Previous antiretroviral therapy (years, median, IQR)	0	11.9 (5.4-17.7)
Concomitant treatment (n,%)		
ABC/3TC	12 (22.2)	93 (35.6)
TDF/FTC	42 (77.8)	58 (24.1)
Other	0	90 (37.3)
Observation period (days, median, IQR)	184 (144-257)	291 (186-404)

Discontinuation (n,%)	9 (16.7)	23 (9.5)
Death	1	2
Virological failure	0	4
Adverse events	3	13
Simplification	4	1
Lost to follow-up	0	2
Other	1	1

IQR= interquartile range; IVDU= intravenous drug use; VL= viral load; HCV=hepatitis C virus; ABC=abacavir; 3TC=lamivudine; TDF=tenofovir; FTC=emtricitabine