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Clinical experience with the integrase inhibitors Dolutegravir and Elvitegravir in HIV-infected patients: efficacy, safety and tolerance

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Abstract

Two integrase inhibitors (INSTIs), dolutegravir (DTG) and elvitegravir/cobicistat (EVG/COBI), have joined recently the pharmacotherapy arsenal against HIV. This study evaluated the efficacy and tolerability of these INSTIs in the last two years. A retrospective observational study in patients who started DTG or EVG/COBI from January 2015 to January 2017 at a reference hospital in north-western Spain was done. Epidemiological, clinical and immunovirological data were recorded. A statistical analysis was performed with SPSS software. A total of 542 DTG (n = 275)- or EVG/COBI (n = 267)-based therapies were initiated during the study period. Overall, more than 90% of naïve and pre-treated patients had virological suppression in both groups after 48 weeks of initiation of treatment per-protocol snapshot analysis. During follow-up, 10.2% of patients were treated with DTG and 4.5% of those treated with EVG discontinued due to adverse events (AE). In the case of DTG mainly related to neuropsychiatric disturbances (70.4%) and for EVG/COBI with gastrointestinal discomfort (50%). Female sex [HR 2.255 (95%CI 1.121–4.535), $p = 0.023$] and DTG treatment [HR 2.453 (95%CI 1.221–4.931), $p = 0.012$] were associated with AE discontinuations. Specifically for neuropsychiatric events, DTG treatment [HR 5.906 (95%CI 1.954–17.846), $p = 0.002$] and receiving abacavir/lamivudine/DTG [HR 4.380 (95%CI 1.348–14.233), $p = 0.014$] were identified as predictive risk factors for treatment discontinuations in two different multivariate analyses. A high percentage of AE discontinuations not previously described in clinical trials has been observed, especially with DTG. Female gender and DTG treatment were identified as risk factors for AE discontinuation. DTG-based therapies, especially in combination with abacavir/lamivudine, were associated with an increased risk of treatment discontinuation due to neuropsychiatric AE.

The great advances in antiretroviral therapy (ART) have dramatically changed the prognosis of HIV infection with significant decrease in morbidities and mortalities related to AIDS. Nowadays, national and international HIV guidelines recommend treating all HIV-infected patients regardless of their immunological status [1-3]. Antiretroviral regimen for initial ART generally consists of two nucleoside reverse-transcriptase inhibitors (NRTIs) in combination with a third drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI).

Based on the high efficacy and safety profile demonstrated in clinical trials, INSTIs (raltegravir, elvitegravir and dolutegravir) are positioned as preferred options [1-3]. They inhibit the catalytic activity of the HIV integrase and prevent the insertion of the HIV genome into the host cell genome, avoiding HIV replication. Elvitegravir (EVG) and dolutegravir (DTG) have been licensed the latest being available in fixed-dose combinations with a NRTI backbone in one tablet given once daily.

EVG is currently available in two fixed-dose coformulated pills in combination with the pharmacokinetic enhancer cobicistat (COBI). The first licensed was coformulated with tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) and the latest with FTC in combination with the new tenofovir alafenamide fumarate (TAF), a targeted tenofovir pro-drug with a 90% reduction in plasma tenofovir concentrations that significantly improves renal and bone safety compared with TDF.

DTG, a second-generation integrase inhibitor, has a high genetic barrier for the development of resistance mutations, with no need for pharmacological enhancement, in combination with either TDF/FTC or abacavir/lamivudine (ABC/3TC) (the last, coformulated in one pill with DTG).

As we encountered many patients who stopped DTG and EVG/COBI because of adverse events (AE), we analysed the experience with these INSTIs in our whole patient population. Therefore, this study evaluates the real-life effectiveness and safety of DTG and EVG/COBI among a large cohort of naïve and treatment-experienced patients.

Materials and Methods

This is an observational study in adult HIV-1-infected patients who started ART with DTG or EVG/COBI from 1 January 2015 to 31 January 2017 at a reference hospital in north-western Spain. Only those patients who had signed the informed consent and with at least one follow-up visit were included. Those patients participating in clinical trials were excluded of the study. Epidemiological, clinical, immunovirological data and information regarding ART were retrospectively recorded. A per-protocol snapshot analysis (HIV-1 RNA < 50 copies/mL at Week 48) for assessment of the efficacy was done (we excluded patients without viral load assessments in the week 48 analysis window for reasons other than discontinuation because of poor efficacy). The time of follow-up was defined since the day of DTG or EVG/COBI initiation until the day of discontinuation or the last visit to the pharmacy.

A statistical analysis was performed with SPSS v.19. software. Group differences were compared using the Pearson chi-square or Fisher's exact test and Student's *t*-test or the Mann–Whitney *U*-test, respectively, for categorical and continuous variables. Repeated measurements were compared using paired Student's *t*-test or Wilcoxon signed-rank test. The incidence rate and 95% confidence interval [IR (95% CI)] of discontinuations due to AE were estimated as the ratio of the number of discontinuations by 100 patients/year of follow-up. We estimated time to treatment discontinuation of DTG and EVG/COBI for AE by Kaplan–Meier method. Univariate analyses were performed with all the covariates. Multivariate Cox regression analysis, among the statistically significant univariate covariates plus those clinically relevant, was performed to identify risk factors for discontinuation because of AE. *p*-Values of 0.05 or less were considered statistically significant.

Results

Baseline characteristics of the study population

A total of 542 DTG- or EVG/COBI-based therapies were initiated within the observation period: 275 patients started DTG and 267 EVG/COBI. The combination ABC/3TC/DTG in a single pill was chosen for 195 patients, TDF/FTC/EVG/COBI for 151 patients, TAF/FTC/EVG/COBI for 116 patients and DTG combined with other antiretrovirals (i.e. NRTIs and NNRTIs) for 80 patients.

The majority of patients were Caucasian (90.0%) and men (77.1%) with a median age of 46.4 years (range 21–83), and pre-treated (83.2%). Subjects treated with DTG were significantly older, more frequently co-infected with HCV, in late-stage disease of HIV (C stage of CDC classification) and with higher viral load compared to EVG/COBI group. Epidemiological, clinical, immunological and other baseline characteristics of each group are depicted in table 1. The median time of follow-up was 287.5 ± 186.3 days. The reasons for switching ART were simplification (45.3%), to avoid intolerance or AE (39.2%), drug–drug interactions (9.2%) and detectable viral load (6.3%). In most patients, the previous NRTIs were TDF/FTC (73.7%), with a PI/r (31.7%), NNRTI (29.5%) or an INSTI (26.5%).

Table 1. Baseline characteristics of the study population

Variables	DTG (n = 275)	EVG/COBI (n = 267)	*p*-Value
Demographic–epidemiological			
Male (%)	73.1	79.8	$p = 0.067$
Age (years ± S.D.)	48.5 ± 10.5	44.7 ± 9.6	$p < 0.001$
Routes of HIV transmission			
MSM (%)	25.1	37.8	
Heterosexual (%)	28.7	30.7	
IDU (%)	40.7	27.7	
Vertical (%)	1.8	1.5	
Unknown (%)	3.6	2.2	
Race			
Caucasian (%)	92.0	88.4	
Latin (%)	6.5	9.4	$p = 0.366$
Black (%)	1.5	2.2	
Co-infections			
Anti-HCV positive (%)	42.9	26.6	$p < 0.001$
HBsAg positive (%)	2.9	3.7	$p = 0.587$
CDC stage			
A (%)	59.3	74.9	
B (%)	7.3	3.7	$p < 0.001$
C (%)	33.5	21.3	
HIV status in Naïve (%)	12.7	24.0	$p < 0.001$
Mean CD4 (cells/μL ± S.D.)	346.7 ± 311.5	440.4 ± 342.7	$p = 0.182$
Mean RNA-HIV (log copies/mL ± S.D.)	5.3 ± 0.8	4.7 ± 0.8	$p < 0.001$
HIV status in pre-treatment patients			
Mean CD4 (cells/μL ± S.D.)	587.3 ± 348.1	634.4 ± 304.9	$p = 0.113$
RNA-HIV basal (%VL<50 copies/ml)	80.2	86.5	$p = 0.064$
Reasons for switching in pre-treatment patients			
Simplification	45.8	48.8	
AE and intolerance	27.5	45.8	$p < 0.001$
Drug–drug interactions	17.5	1.5	
Detectable VL	9.2	3.9	

MSM, men who have sex with men; IDU, intravenous drug use; CDC, Centers for Disease Control; VL, viral load; AE, adverse event

Efficacy

Among pre-treated patients, 80.2% of patients who started DTG and 86.5% of patients who started EVG/COBI had HIV-RNA < 50 copies/mL at baseline. In both treatment groups, the proportion of patients with virological suppression (<50 copies/mL) increased from baseline to week 48 in 125 from 135 (92.6%) of patients who started DTG and in 71 from 74 (95.9%) of patients receiving EVG/COBI; $p = 0.3893$.

Within naïve patients, at 48 weeks, 20 from 22 patients (90.9%) in the DTG group and 10 from 11 (90.9%) in the EVG/COBI group achieved HIV-RNA < 50 copies/mL ($p = 0.999$).

Safety and tolerability

During follow-up, the global incidence of discontinuations was 8.5%, and 6.6% were due to side effects [IR 8.4 per 100 patients/year (6.2–10.6)]. The neuropsychiatric disorders were the main AE of discontinuation [59%, IR 4.9 by 100 patients/year (3.2–6.7)]. Overall, 11.6% patients discontinued DTG and 7.1% EVG/COBI during the study period ($p = 0.070$). In the case of DTG, 87.5% [i.e. 10.2% of overall patients treated with DTG and IR 13.9 per 100 patients/year (9.2–20.2)] were due to AE: 70.4% related to neuropsychiatric disturbances [IR 9.8 per 100 patients/year (5.9–15.3)], 22.2% gastrointestinal discomfort [IR 3.1 per 100 patients/year (1.1–6.7)], 3.7% alterations of renal function [IR 0.5 per 100 patients/year (0.0–2.9)] and 3.7% haematology toxicity [IR 0.5 per 100 patients/year (0.0–2.9)]. Most patients reported more than one neuropsychiatric toxicity including abnormal dreams, insomnia, headache, dizziness, nervousness, irascibility, anxiety, depressive symptoms and suicidal ideation.

Among the remaining patients who discontinued DTG, 9.4% were deaths (n = 3, not related with DTG) and 3.1% due to virological failure.

In the case of EVG/COBI, 63.1% [i.e. 4.5% of overall patients treated with EVG/COBI and IR 4.4 per 100 patients/year (2.3–7.8)] treatment discontinuations were due to AE: 50% gastrointestinal discomfort [IR 2.2 per 100 patients/year (0.8–4.8)], 33.3% related to neuropsychiatric disorders [IR 1.5 per 100 patients/year (0.4–3.8)] or 16.7% alterations of renal function [IR 0.7 per 100 patients/year (0.1–2.7)]. The rest of discontinuations in EVG/COBI were 21.1% by pharmacological interactions and 15.8% due to virological failure. Statistically significant differences have been found between the percentage of patients who discontinue DTG and EVG/COBI due to adverse events [10.2% *versus* 4.5%, respectively, $p = 0.015$; HR 2.747 (95%CI 1.382–5.461), $p = 0.004$] and neuropsychiatric AEs (6.9% *versus* 1.5%, $p = 0.001$). In most cases, all reported side effects disappeared quickly once these drugs were stopped. The time between the start of DTG and EVG/COBI and its suspension by AEs was 175.7 ± 137.3 and 83.6 ± 68.5 days, respectively ($p = 0.030$) (fig. 1).

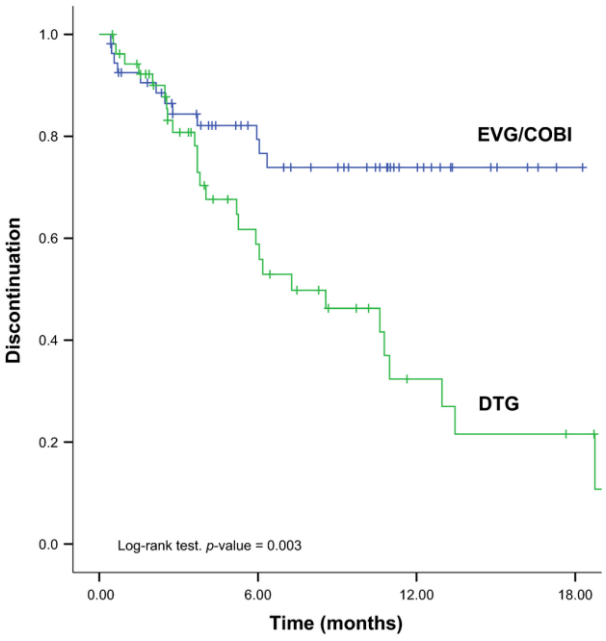

Figure 1. Relationship between discontinuations due to adverse events after EVG/COBI*versus*DTG initiation. Kaplan–Meier curves for EVG/COBI and DTG exposure and discontinuations because of adverse events. DTG, dolutegravir; EVG/COBI, elvitegravir/cobicistat.

A univariate analysis of risk factors for discontinuations due to AE was performed considering age, gender, race, routes of HIV transmission, CDC stage, HBV and HCV co-infection, treatment experience (naive *versus* pre-treated), ART (DTG *versus* EVG/COBI) and the NRTI combination. Age [HR 1.033 for every one year (95%CI 1.002–1.065), $p = 0.035$] was associated with a higher risk of interruptions for AE in patients treated with both EVG/COBI and DTG. Females were at higher risk of discontinuations than men [HR 2.389 (95%CI 1.196–4.772), $p = 0.014$] in patients treated with both EVG/COBI and DTG. Among those treated with DTG, patients receiving ABC/3TC/DTG were more likely to interrupt treatment due to side effects compared with those on DTG associated with other antiretrovirals [HR 5.183 (95%CI 1.960–13.701), $p = 0.001$].

In the multivariate Cox regression model, female gender [HR 2.255 (95%CI 1.121–4.535), $p = 0.023$] and treatment with DTG [HR 2.453 (95%CI 1.221–4.931) $p = 0.012$] were significantly associated with discontinuations due to AE.

Neither age nor the female gender was associated with an increased risk of discontinuations due to neuropsychiatric adverse events in the multivariate analyses. However, in a multivariate analysis comparing DTG- *versus* EVG/COBI-based therapies, without considering the concomitant antiretrovirals used, the use of DTG was identified as a predictor factor for having higher risk of discontinuation due to neuropsychiatric adverse events [HR 5.906 (95%CI 1.954–17.846), $p = 0.002$]. More specifically, in the multivariate analysis including the specific ART combination DTG/abacavir/lamivudine, EVG/COBI/FTC/TDF, EVG/COBI/FTC/TAF, or DTG combined with other NRTI or NNRTI, the use of DTG/abacavir/lamivudine was associated with higher rates of discontinuations because of neuropsychiatric adverse events [HR 4.380 (95%CI 1.348–14.233), $p = 0.014$]. There were no significant associations between any of the study variables and an increased risk of gastrointestinal and renal function disturbances.

Discussion

In this cohort of 542 HIV-infected patients who initiated DTG- or EVG/COBI-based therapies, the high efficacy of these INSTIs both for naïve and for treatment-experienced patients has been confirmed, as already demonstrated by clinical trials [4-13]. More than 90% of patients achieved or maintained virological suppression within the 48 weeks after DTG or EVG/COBI initiation among treatment-experienced patients, and about 91% of naïve patients achieved virological suppression through the first 48 weeks, as obtained by per-protocol analysis.

However, an unexpected high rate of discontinuations due to adverse events, previously not described in clinical trials, was recognized. The overall rates were 10.2% and 4.5% for patients under DTG and EVG/COBI, respectively. The discontinuations due to neuropsychiatric AEs were significantly higher among patients receiving DTG compared with those on EVG/COBI (6.9% *versus* 1.5%). Thus, a patient under a DTG-based regimen had 5.9 times more risk of discontinuation due to a neuropsychiatric disorder than a patient receiving EVG/COBI, especially if DTG was administered in combination with ABC/3TC. The most frequent patterns of neuropsychiatric AE were abnormal dreams, mood changes, sleep disturbances, anxiety, depression and suicidal ideation. All of them quickly disappeared after discontinuation of DTG.

Similarly, the occurrence of unexpected discontinuations due to side effects of DTG was reported in three recent observational real-life studies [14-16]. In one of them, the commonest reason leading to DTG discontinuation was neuropsychiatric adverse events (5.6%), particularly among women and older patients. In the other, the rates of discontinuations due to neuropsychiatric events were 9.9%, and in this case, DTG was stopped more frequently if the regimen included the NRTI abacavir.

All these figures are unexpectedly higher than those previously reported in DTG clinical trials related to neuropsychiatric disorders leading to discontinuations that remained below 1% [8-13]. Similarly, in EVG/COBI register studies, the rate of discontinuations due to gastrointestinal or neuropsychiatric disorders was also below 1.1% [4-7].

Herein, age and female gender were associated with a higher risk of treatment interruption for any adverse event in patients treated with both EVG/COBI and DTG. Moreover, patients under DTG treatment and specially those receiving ABC/3TC/DTG were at higher risk of discontinuations due to adverse events. However, only female gender and the use of DTG were finally identified as independent risk factors for treatment discontinuation due to any adverse event. Therefore, women on treatment with EVG/COBI were at higher risk of discontinuations due to adverse events. This is a new finding for EVG/COBI not previously described in real-life studies.

The median time to interruption treatment due to an adverse event was significantly different between DTG and EVG (about 6 *versus* 3 months, respectively). These times are in accordance with times reported in other real-life studies [14, 17] for DTG and clinical trials for EVG [7].

Regarding discontinuations due to neuropsychiatric adverse events, we did not find any association with older age or female gender in the multivariate analysis, conversely to what has recently been published in an observational study [14]. Similar to our results, the ARIA study – which evaluated the efficacy of ABC/3TC/DTG compared to TDF/FTC in combination with atazanavir/r only in women – did not observe higher rates of discontinuations due to neuropsychiatric events related to DTG in women [18]. In our cohort, only the use of DTG, especially in combination with ABC/3TC, was identified as an independent risk factor for discontinuations due to neuropsychiatric events. These findings are in agreement with the results reported by Boer *et al*., who found that DTG was switched more frequently in those regimens that include abacavir [15]. However, these findings have not been confirmed in a recent study presented by Llibre *et al*. [19]. Conversely, we did not find significant associations between any of the study variables and an increased risk of discontinuations due to gastrointestinal and renal function disturbances, more frequently observed in patients receiving EVG/COBI compared with DTG. These observations might be explained in part by the concomitant use of cobicistat and TDF in patients receiving EVG/COBI-based therapies.

The reasons for the conflicting results observed between trials and some cohorts such as our data remain unclear and probably several factors including the heterogeneity of the studies populations, time of follow-up and the observational research design might partially explain these findings. For the present study, the main limitations were small sample size, single-centre study and the retrospective observational design that might have introduced uncontrolled bias.

In conclusion, DTG and EVG/COBI demonstrated high efficacy in both treatment-naïve and pre-treated patients. However, an unexpectedly higher rate of discontinuation due to adverse events than that described in clinical trials, especially by neuropsychiatric AEs, was observed. Particularly, DTG especially in concomitant use with abacavir is identified as a predictor for discontinuations due to neuropsychiatric adverse events. The reason underlying the potential interaction between abacavir and dolutegravir in real clinical practice deserves further research, as several real-life studies have concluded an increased risk of neuropsychiatric adverse events that lead to treatment withdrawal. Differences between patients treated with DTG and EVG/COBI should be cautiously interpreted, as this is an observational retrospective study, and therefore, both populations were not comparable. These findings should be considered in the real-life setting when using EVG/COBI and DTG.

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