Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice

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Objective: Dolutegravir (DGV) is one of the preferred antiretroviral agents in first-line combination antiretroviral therapy (cART). Though considered to be a well tolerated drug, we aimed to determine the actual rate, timing and detailed motivation of stopping DGV in a real-life clinical setting.

Design: A cohort study including all patients who started DGV in two HIV treatment centers in The Netherlands.

Methods: All cART-naïve and cART-experienced patients who had started DGV were identified from the institutional HIV databases. Clinical data, including motivation and timing of discontinuation of DGV, were extracted from the patient files. Factors that potentially influenced discontinuation of DGV were compared between patients who stopped or continued DGV by multivariate and Kaplan–Meier analyses.

Results: In total, 556 patients were included, of whom 102 (18.4%) were cART-naïve at initiation of DGV. Median follow-up time was 225 days. Overall, in 85 patients (15.3%), DGV was stopped. In 76 patients (13.7%), this was due to intolerability. Insomnia and sleep disturbance (5.6%), gastrointestinal complaints (4.3%) and neuropsychiatric symptoms such as anxiety, psychosis and depression (4.3%) were the predominant reasons for switching DGV. In regimens that included abacavir, DGV was switched more frequently (adjusted relative risk 1.92, 95% confidence interval 1.09–3.38, \(P\) log-rank 0.01). No virologic failures were observed.

Conclusion: A relatively high rate of preliminary discontinuation of DGV due to intolerability was detected in our patient population. In particular, DGV was stopped more frequently if the regimen included abacavir. Multiple factors may explain these unexpected postmarketing observations, which warrant further investigation.

Keywords: dolutegravir, integrase inhibitor, side effects, toxicity
Introduction and study objective

At present, integrase inhibitors are considered first-choice drugs as one of the components of combination antiretroviral therapy (cART) [1]. Dolutegravir (DGV) is available in a combination tablet with abacavir and lamivudine (Triumeq; ViiV Healthcare UK Ltd, Brentford, UK) and as a 50-mg single drug tablet (Tivicay; ViiV Healthcare UK Ltd), registered for treatment of both experienced and cART-naive patients. Because of its reported favorable efficacy and safety profile, DGV rapidly gained increasing popularity among medical teams providing care for individuals living with HIV. DGV has a limited risk of interaction with concomitant medication and, in several randomized controlled trials, the frequency of reported severe side effects that caused discontinuation of DGV at week 48 was reported to be low, that is not exceeding 2–3% [2–4]. Because we observed an unexpectedly high rate of patients who stopped DGV and switched to a different cART regimen, we conducted a study investigating the frequency, timing and detailed motivation of stopping DGV-containing cART in two hospitals in The Netherlands.

Methods

In the Leiden University Medical Center (LUMC) and the OLVG Medical Center (OLVG), Amsterdam, The Netherlands, all cART-naive and cART-experienced individuals who were prescribed DGV between August 2014 and March 2016 were identified from the institutional HIV databases. These contain a complete list of all HIV+ patients in care for any period of time. Data about patient characteristics, previous cART, time of initiation and stopping DGV, and motivation for not continuing DGV were obtained from the electronic patient files. Follow-up time was defined as the day of initiation of DGV-containing cART until either the day of discontinuation of DGV, the end of the study period or the day a patient was last spoken with if lost to follow-up. In both centers, standard follow-up after start or switch of cART consisted of outpatient visits at 4, 12, 24 and 48 weeks, but patient-tailored deviations from this schedule and telephone consultations in between visit dates were regular practice. Treatment monitoring is usually intensified in case of suspicion of a relevant side effect of cART. Reported drug-related side effects were categorized as shown in Table 1. Variables with potential influence on continuation or discontinuation of DGV were compared between patients who stopped and continued DGV. Pearson’s chi-square test, Student’s t-test or the Mann–Whitney U-test were performed for univariate analyses of bivariate and continuous data, respectively. Kaplan–Meier analyses and multivariate logistic regression analyses were performed to adjust for follow-up time and confounding variables. In addition, a subanalysis was performed with the endpoint of discontinuing DGV because of neuropsychiatric symptoms only. Consequently, in these survival analyses, patients who stopped DGV for other reasons were censored at the time point of discontinuation.

Results

A total of 556 patients (LUMC, n = 169; OLVG, n = 387) taking DGV were included during the period of study. The median age was 48 years (range 19–85 years), and the male-to-female ratio was 7.18. The majority (66.3%) of the cohort consisted of men who have sex with men, whereas only a minority were known (ex)intravenous drug users (2.2%). At initiation of DGV, 102 (18.4%) patients were cART-naive. Triumeq was used by 319 (57.4%), DGV in any combination with abacavir by 356 (64.0%), DGV in combination with tenofovir by 165 (29.7%) and DGV in combination with a boosted protease inhibitor (atazanavir or darunavir) by 59 (10.6%) patients. Prior to the use of abacavir, all patients were checked for the absence of an HLA-B57 haplotype. Non-nucleoside reverse transcriptase inhibitor combinations with DGV were rare [n = 7 (1.3%)]. Overall, in 85 (15.3%) patients, the DGV regimen was stopped. This was reported to be due to adverse drug reactions in 76 (13.7%) patients. Median follow-up time was 225 days (interquartile range 133–296 days). If DGV was stopped, this occurred after a median use of 73 days, range 5–327 days. Within 48 weeks after initiation, 81 out of 85 patients (95%) had stopped taking DGV.

The frequencies of reported adverse reactions are listed in Table 1. Practically all reported side effects subsided, once DGV was stopped.

| Table 1. Reported adverse reactions leading to discontinuation of dolutegravir* |
|---------------------------------------------|-----------------|
| Adverse drug reaction                      | n (%)           |
| Sleep disturbance, insomnia               | 31 (5.6)        |
| Gastrointestinal complaints               | 21 (3.8)        |
| Joint, tendon and/or muscle pain          | 11 (2.0)        |
| Psychological/psychiatric symptomsb       | 14 (2.5)        |
| Neurologic symptoms                       | 10 (1.8)        |
| General malaise (headache and severe fatigue) | 24 (4.3)        |
| Respiratory tract complaints              | 5 (0.9)         |
| Other                                       | 9 (1.6)         |

*Numbers and percentages do not add up to total because multiple negative side effects were diagnosed or reported in 31 (39%) patients who stopped dolutegravir for this/these reason(s); in 11 (14%) patients more than two negative side effects were reported.

bIncluding depression, anxiety, agitation, emotional instability and one case of psychosis.
415 men (15%) \( (P=0.56) \). Of cART-naïve patients, 19 (18.6%) stopped DGV compared with 66 (14.5%) of cART-experienced patients \( (P=0.30) \). Abacavir-containing regimens were used by 356 (64%) patients and were stopped in 58 cases (16.3%) due to adverse drug reactions \( [\text{adjusted relative risk (RR)} 1.92, 95\% \text{ confidence interval (95\% CI)} 1.09–3.38, \ P=0.02] \). The proportion of patients on DGV cART with and without abacavir over time is depicted in Fig. 1. Combinations that contained both DGV and a protease inhibitor were associated with a lower incidence of discontinuation due to adverse drug reactions \( [\text{adjusted RR} 0.20, 95\% \text{ CI} 0.05–0.86, \ P=0.03] \).

In the subanalysis for DGV discontinuation due to neuropsychiatric side effects (including insomnia, psychological/psychiatric symptoms and other neuropsychological side effects), the adjusted RR for discontinuation of DGV associated with use of abacavir was 2.34 \( (95\% \text{ CI} 1.10–5.00) \).

All reported RRs above are adjusted for age, sex and cART-naïve (yes or no). No virologic failures were observed.

**Discussion**

In this multicenter, postmarketing observational study, in a ‘real life’ clinical setting of DGV use in cART, we found that, in general, DGV was tolerated very well by most patients, but it was stopped at a much higher rate than reported in randomized controlled trials [5]. In nearly 90% of situations, the reason for interruption of DGV was drug intolerability. The most frequently reported events were neuropsychological or psychiatric (sleeping disturbances, insomnia, mood alterations, anxiety and psychosis) and gastrointestinal in nature. Both types of side effects have been reported in the registrational studies as well, though at a much lower frequency. Because especially the neuropsychological events have not been reported in studies with raltegravir, it seems unlikely to consider these events as class effects of integrase strand transfer inhibitor (INSTI). Thus far, the occurrence of unexpected neuropsychiatric side effects of DGV was only reported in a small case series [6]. Gastrointestinal events were described in patients on

![](Figure1.png)
elvitegravir, but always in combination with a booster (either ritonavir or cobicistat) [7].

The constitution of the cART regimen significantly influenced the risk of switching to a non-DGV-containing cART. Although DGV was interrupted also without abacavir, the risk for discontinuation of DGV was significantly higher when abacavir was included in the combination. Because the type of adverse events was distributed similarly between abacavir users compared with nonabacavir users, and most of these effects have not been reported for abacavir alone, we considered that there might be an interaction between the drugs, leading to more treatment interruption. Interestingly, both drugs are metabolized via hepatic glucuronidation by UDP-glucuronosyltransferase [8,9]. To our knowledge, the potential interaction between DGV and abacavir mediated by this common degradation pathway has not been studied.

The study is, in part, limited by its observational design due to the risk of introduction of bias. DGV may have been used selectively to treat more vulnerable patient groups because of the favorable information that reached physicians through the registral studies or marketing activities. Obviously, the strict selection criteria for some of the trials were not applied to our patient population prior to initiation of DGV. Also, other factors like comedication or unrecognized passing illnesses due to, for example infectious agents may have contributed to the high rate of DGV interruption and confounded the results by misclassification. Furthermore, because many alternative antiretroviral drugs are currently available, the threshold for changing cART may be lower compared with the setting of the randomized trials that used DGV in one of the study arms. In both centers though, similar effects were observed, in which daily work was performed and supervised by experienced HIV physicians and specialized nurses. Overall, we conclude that although DGV performed well in most patients, side effects induced more treatment discontinuations than expected. Prospects raised by the randomized trials and published literature reviews [10,11] were not fully met in our clinical practices. As guidelines have moved to INSTI-based cART for initial antiretroviral treatment, larger cohort studies on a national or international level are needed to precisely define the overall performance of the individual INSTI in clinical practice with regard to adverse effects and tolerability [12].

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Conflicts of interest
There are no conflicts of interest.

References