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ORIGINAL RESEARCH

Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients

C Hoffmann,[1,2] T Welz,[3] M Sabranski,[1] M Kolb,[3,4] E Wolf,[5] H-J Stellbrink[1] and C Wyen[3,4]

[1]ICH Study Center Hamburg, Hamburg, Germany, [2]Department of Medicine II, University of Schleswig-Holstein, Kiel, Germany, [3]Praxis am Ebertplatz, Cologne, Germany, [4]Department I of Internal Medicine, University Hospital Cologne, Cologne, Germany and [5]MUC Research GmbH, Munich, Germany

Objectives

Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor (INSTI), is now among the most frequently used antiretroviral agents. However, recent reports have raised concerns about potential neurotoxicity.

Methods

We performed a retrospective analysis of a cohort of HIV-infected patients who had initiated an INSTI in two large German out-patient clinics between 2007 and 2016. We compared discontinuation rates because of adverse events (AEs) within 2 years of starting treatment with dolutegravir, raltegravir or elvitegravir/cobicistat. We also evaluated factors associated with dolutegravir discontinuation.

Results

A total of 1950 INSTI-based therapies were initiated in 1704 patients eligible for analysis within the observation period. The estimated rates of any AE and of neuropsychiatric AEs leading to discontinuation within 12 months were 7.6% and 5.6%, respectively, for dolutegravir (n = 985), 7.6% and 0.7%, respectively, for elvitegravir (n = 287), and 3.3% and 1.9%, respectively, for raltegravir (n = 678). Neuropsychiatric AEs leading to dolutegravir discontinuation were observed more frequently in women [hazard ratio (HR) 2.64; 95% confidence interval (CI) 1.23–5.65; P = 0.012], in patients older than 60 years (HR: 2.86; 95% CI: 1.42–5.77; P = 0.003) and in human leucocyte antigen (HLA)-B*5701-negative patients who initiated abacavir at the same time (HR: 2.42; 95% CI: 1.38–4.24; P = 0.002).

Conclusions

In this large cohort, the rate of discontinuation of dolutegravir because of neuropsychiatric adverse events was significantly higher than for other INSTIs, at almost 6% within 12 months. Despite the limitations of this retrospective study, the almost three-fold higher discontinuation rates observed amongst women and older patients underscore the need for further investigation, especially in patient populations usually underrepresented in clinical trials.

Keywords: antiretroviral therapy, dolutegravir, HIV infection, integrase inhibitors, side effects, adverse events

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Introduction

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) developed by ViiV Healthcare (Brentford, Greater London, UK). Dolutegravir showed a high antiviral potency and a good safety profile in four large randomized clinical trials (RCTs) in treatment-naïve patients and in one RCT in treatment-experienced patients. Among 1579 trial subjects, only 2% experienced an adverse event (AE) leading to discontinuation [1,3,10,11,15]. Dolutegravir has an improved pharmacokinetic and resistance profile compared with the other INSTIs, with the higher resistance barrier probably attributable to prolonged binding with integrase complexes [5]. In addition to its excellent efficacy, dolutegravir has a low interaction potential and is available in two different once-daily formulations, including a single-tablet

Correspondence: Dr Christian Hoffmann, ICH Stadtmitte, Glockengiesserwall 1, 20095 Hamburg, Germany. Tel: +49 40 2800 4200; fax: +49 40 2800 42020; e-mail: hoffmann@ich-hamburg.de

regimen (STR) co-formulated with abacavir and lamivudine. Consequently, since its approval in 2014, dolutegravir has rapidly gained an important place in the management of HIV infection. However, in recent months, a small case series [6] and a report from a Dutch cohort study [14] have raised concerns about the safety of dolutegravir in real-life settings, especially with regard to neuropsychiatric AEs. This led us to review data on INSTI use in our own cohort with a specific focus on neuropsychiatric AEs leading to INSTI discontinuation.

Methods

We performed a retrospective analysis using the anonymized data for all HIV-infected patients under routine clinical care in two large German HIV treatment centres, who initiated an INSTI-based therapy between January 2007 and April 2016. In both centres, antiretroviral therapy (ART) is prescribed by physicians specialized in HIV care who are also responsible for the patients' general medical care.

Patients were identified by screening electronic patient databases at both centres for all INSTI prescriptions issued. INSTIs were raltegravir as Isentress© (MSD, Kenilworth, New Jersey, USA), elvitegravir as the STR Stribild© (Gilead Sciences, Foster City, California, USA) including cobicistat, tenofovir disoproxil fumarate (TDF) and emtricitabine (two patients who initiated Genvoya© (Gilead Sciences, Foster City, California, USA) instead of Stribild© after licensing in January 2016 were also included), and dolutegravir as Tivicay© (ViiV Healthcare) or as the STR Triumeq© (ViiV Healthcare) which includes abacavir and lamivudine. Elvitegravir was only available as STR in Germany during the study period.

Patients receiving INSTIs within RCTs or who initiated their INSTI-based ART elsewhere were excluded from the analysis, as were patients without a follow-up visit after starting an INSTI. Both treatment-naïve and treatment-experienced patients were included. Patients who had received more than one INSTI at different times during the observation period contributed exposure time to each drug separately. Intermittent treatment interruptions were not accounted for if the patient was on INSTI at the last follow-up.

The treating physicians in both centres routinely document the main reason for any ART discontinuation or modification. The start and stop dates and all documented reasons or symptoms for discontinuation of each INSTI were extracted from the electronic database. We also recorded whether or not the subsequent ART regimen was tolerated for at least 3 months. The following symptoms were classified as neuropsychiatric AEs: insomnia, sleep disturbances, dizziness, nervousness, restlessness, depression, poor concentration, slow thinking and otherwise unexplained pain or paraesthesia.

In patients treated with dolutegravir, other co-variables potentially associated with drug discontinuation were evaluated. These included whether dolutegravir was initiated as first-line treatment or in treatment-experienced patients and whether abacavir or other antiretroviral agents were initiated simultaneously, as well as age, gender, ethnicity (Caucasian *vs*. other), CD4 T-cell count (> 500, 200–500 or < 200 cells/μl) and calendar period at INSTI initiation. Among treatment-experienced patients, we documented the regimen preceding dolutegravir initiation and the reason for the switch to a dolutegravir-containing regimen (neuropsychiatric AEs, nonneuropsychiatric AEs, treatment failure or treatment simplification).

We used the Mann-Whitney U or Kruskal-Wallis test and Chi-square test respectively for comparison of continuous and categorical data between two or more groups. Kaplan–Meier analysis including log-rank testing was used to compare exposure times for specific INSTIs with respect to the above co-variables. Discontinuations for reasons other than AEs (e.g. simplification) were censored. In the dolutegravir subgroup, a multivariate Cox regression analysis was used to identify risk factors for discontinuation because of any AE and because of neuropsychiatric AEs. All variables were initially included in the full model. Using stepwise backward selection, variables with $P \geq 0.05$ were excluded from the model.

Results

We identified 1704 patients who had initiated 1950 INSTI-based therapies. A total of 228 patients had received two INSTIs and nine had received three INSTIs. In total, 21% (208) of patients were started on an INSTI as first-line therapy. The proportion of patients starting INSTI first-line therapy was higher for elvitegravir (23%) and dolutegravir (21%), compared with raltegravir (13%). Among treatment-experienced patients, the proportion of patients switching their regimen to an INSTI therapy because of neuropsychiatric AEs (almost exclusively caused by efavirenz) was similar for raltegravir (9%) and dolutegravir (8%) but higher for elvitegravir (23%).

Duration of follow-up and reasons for discontinuation are shown in Table 1. As expected, follow-up for raltegravir (European licensing 2007) was longer than for elvitegravir (2013) or dolutegravir (January 2014) and more patients died while on raltegravir ($n = 32$). No deaths were considered to be drug-related. Discontinuation

because of virological failure was very low for all INSTIs. Of patients exposed to raltegravir, almost a third switched to other regimens for simplification.

In total, an AE leading to discontinuation was observed in 122 of 1950 INSTI exposures (6.3%). The estimated rates of any AEs leading to discontinuation within 12 and 24 months, respectively, were 7.6% and 12.3% for elvitegravir (n = 287), 7.6% and 9.3% for dolutegravir (n = 985), and 3.3% and 3.9% for raltegravir (n = 578). Discontinuation rates were highest for elvitegravir (as Stribild©), mainly because of renal AEs, probably attributable to TDF/cobicistat. Neuropsychiatric AEs leading to discontinuation were reported more frequently with dolutegravir. The estimated rates of neuropsychiatric AEs leading to discontinuation within 12 and 24 months were 5.6% and 6.7% for dolutegravir, 0.7% and 1.5% for elvitegravir, and 1.9% and 2.3% for raltegravir, respectively. The Kaplan–Meier curves for INSTI exposure and discontinuations because of neuropsychiatric events are shown in Figure 1.

Table 1 Outcome and adverse events (AEs) for individuals who received prescriptions of integrase strand transfer inhibitors (INSTIs) between January 2007 and April 2016 in both centres

	Dolutegravir	Elvitegravir	Raltegravir
Total INSTI therapies (*n*)	1073	342	776
INSTI started within RCT (*n*)	13	14	17
INSTI started elsewhere (*n*)	48	21	66
Insufficient data, lack of follow-up (*n*)	27	20	15
Follow-up per exposure (months) [median (range)]	11.5 (0–25.4)	16.0 (0.4–33.4)	36.3 (0.2–107.3)
Exposures on INSTI analysed (*n*)	985	287	678
Alive and on INSTI at time of data cut [% (*n*)]	91.0 (896)	83.3 (239)	54.0 (366)
Death while on INSTI [% (*n*)]	0.9 (9)	0.3 (1)	4.7 (32)
Reasons for discontinuation of INSTI (per exposure) over entire follow-up period			
ART simplification [% (*n*)]	1.0 (10)	2.8 (8)	31.3 (212)
Virological failure [% (*n*)]	0.1 (1)	1.7 (5)	4.7 (32)
Other reasons [% (*n*)]	0.2 (2)	2.4 (7)	1.5 (8)
Discontinuation because of AEs (any) [% (*n*)]	6.8 (67)	9.4 (27)	4.1 (28)
All AEs leading to discontinuation over entire follow-up period			
Renal [% (*n*)]	0.2 (2)	3.5 (10)	0.0 (0)
Gastrointestinal [% (*n*)]	0.7 (7)	2.8 (8)	0.9 (6)
Hepatic [% (*n*)]	0.1 (1)	0.0 (0)	0.1 (1)
Skin [% (*n*)]	0.3 (3)	0.7 (2)	0.1 (1)
Other [% (*n*)]	0.5 (5)	1.4 (4)	0.9 (6)
Neuropsychiatric [% (*n*)]	5.0 (49)	1.0 (3)	2.1 (14)
Neuropsychiatric adverse events*			
Insomnia, sleep disturbances	36	2	4
Poor concentration, slow thinking	8	0	0
Dizzyness	13	1	3
Headache, paraesthesia	16	1	6
Depression	7	0	1

ART, antiretroviral therapy; RCT, randomized clinical trial.
*More than one symptom possible, as documented.

Neuropsychiatric AEs leading to discontinuation among 49 of 985 patients started on dolutegravir were further analysed. The median time between dolutegravir start and discontinuation was 3.1 months and 38 of 49 (78%) patients had stopped dolutegravir within 6 months. The most frequent symptoms (multiple symptoms possible but no temporal sequence documented) included insomnia and sleep disturbances as well as dizziness and painful paraesthesia. No symptoms were life-threatening or led to hospitalization and most symptoms disappeared quickly after discontinuation of dolutegravir. In 32 of 37 (86%) patients followed for at least 3 months after dolutegravir discontinuation, the subsequent antiretroviral regime was tolerated and effective. In six patients who had interrupted dolutegravir, neuropsychiatric AEs recurred in all six cases upon re-exposure. Of note, three of these patients were also simultaneously re-exposed to abacavir.

Table 2 shows the main characteristics of patients on dolutegravir and those discontinuing dolutegravir because of AEs. Considering the entire observation period, 6.8%

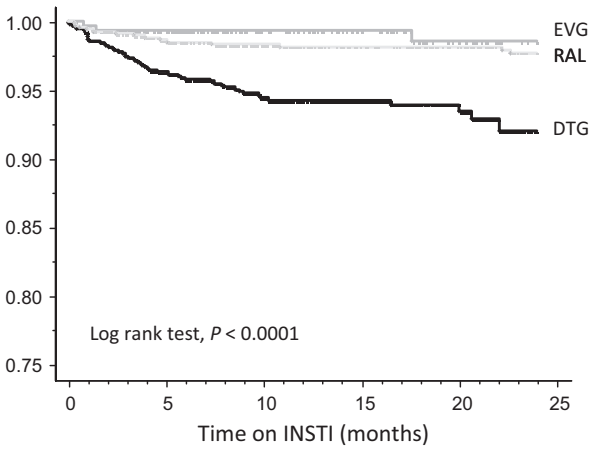

Fig. 1 Discontinuation because of neuropsychiatric adverse events for all integrase strand transfer inhibitors (INSTIs) within 24 months of initiation (all other events censored). EVG, elvitegravir; RAL, raltegravir; DTG, dolutegravir.

Table 2 Numbers and characteristics of patients initiating dolutegravir (DTG)-based antiretroviral therapy (ART) and the proportion of patients with any or with neuropsychiatric adverse events (AEs) leading to DTG discontinuation over the entire follow-up period

	All patients initiating DTG	Discontinuation of DTG because of	
		Any AE	Neuropsychiatric AEs
All patients [% (*n*)]	985	6.8 (67)	5.0 (49)
Hamburg [% (*n*)]	658	6.4 (42)	4.6 (30)
Cologne [% (*n*)]	327	7.6 (25)	5.8 (19)
Male gender [% (*n*)]	909	6.3 (56)	4.6 (42)
Female gender [% (*n*)]	70	15.7 (11)	10.0 (7)
Transgender [% (*n*)]	6	0.0 (0)	0.0 (0)
Caucasian origin [% (*n*)]	887	7.1 (63)	5.2 (46)
Age at DTG initiation			
Age (years) [median (range)]	46.2 (17.9–89.7)	50.6 (25.4–81.6)	51.1 (26.5–76.0)
Older age, > 60 years [% (*n*)]	91	14.3 (13)	11.0 (10)
50–60 years [% (*n*)]	254	8.7 (22)	5.9 (15)
40–50 years [% (*n*)]	348	5.2 (18)	3.2 (11)
30–40 years [% (*n*)]	208	4.8 (10)	4.8 (10)
Younger age, < 30 years [% (*n*)]	84	4.8 (4)	3.6 (3)
CD4 count at DTG initiation			
CD4 count (cells/μl) [median (range)]	591.5 (5–1678)	630 (46–1608)	647 (250–1608)
CD4 count > 500 cells/μl [% (*n*)]	626	6.9 (43)	5.4 (34)
CD4 count 200–500 cells/μl [% (*n*)]	296	7.4 (22)	5.1 (15)
CD4 count < 200 cells/μl [% (*n*)]	62	3.2 (2)	0.0 (0)
Antiretroviral therapy with DTG			
First-line, plus ABC+3TC [% (*n*)]	113	9.7 (11)	6.2 (7)
First-line, plus TDF+FTC [% (*n*)]	95	3.2 (3)	2.1 (2)
ART experienced, DTG the only new drug [% (*n*)]	550	5.8 (32)	4.4 (24)
ART experienced, plus ABC initiated [% (*n*)]	165	11.5 (19)	9.1 (15)
ART experienced, plus other ARVs [% (*n*)]	62	3.2 (2)	1.6 (1)
Calendar period of DTG initiation			
2014	482	6.0 (29)	4.1 (20)
2015	453	6.8 (31)	5.1 (23)
1–4/2016	50	14.0 (7)	12.0 (6)

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

of patients discontinued dolutegravir due to any AE and 5.0% due to neuropsychiatric AEs. Female patients and patients older than 60 years had an increased risk of dolutegravir discontinuation: 15.7% and 14.3% discontinued for any AE, and 10.0% and 11.0% for neuropsychiatric AEs, respectively. Treatment-experienced patients initiating abacavir at the same time had a higher risk of discontinuation because of any AE (11.5% of patients) or because of neuropsychiatric AEs (9.1% of patients) than patients who did not initiate abacavir simultaneously ($P = 0.014$ and $P = 0.016$, respectively). A similar but nonsignificant trend was also seen in treatment-naïve patients. Of note, human leucocyte antigen (HLA)-B*57 testing had been performed in all patients prior to abacavir initiation. In the multivariate Cox regression model, female gender, age > 60 years, simultaneous initiation of abacavir, and dolutegravir initiation in 2016 remained significantly associated with dolutegravir discontinuation (Table 3). These associations remained consistent when patients starting dolutegravir in 2016 were excluded. There were no statistically significant interactions between any of the variables in the final model. There was no association between dolutegravir discontinuation and treatment centre, ethnicity, treatment line (first-line *vs.* treatment experienced), prior regimen, reason for switch or CD4 T-cell count. Figures 2a–c show the Kaplan–Meier curves reflecting the time on dolutegravir stratified by gender, age group, concomitant initiation of abacavir and treatment line.

Discussion

In this large cohort of 1704 HIV-infected patients treated with at least one INSTI, the estimated overall discontinuation rate because of any AEs was around 6% within the first year of initiation. By far the commonest reason for discontinuation of dolutegravir was neuropsychiatric AEs (6%), which occurred less frequently in patients on raltegravir or elvitegravir (as Stribild©). These discontinuation rates are markedly lower than those recently reported in a smaller Dutch cohort where dolutegravir treatment was discontinued in 55 of 387 (14.2%) patients after a median of 78 days because of side effects, in particular sleeping, gastrointestinal and psychiatric problems [14]. Unfortunately, the authors did not provide details of ethnicity (only about one-third of the patients were of Dutch origin) or of other potential risk factors.

Our rates of AEs leading to dolutegravir discontinuation were, however, higher than those reported in clinical trials, particularly with regard to neuropsychiatric AEs. In four RCTs in treatment-naïve patients (SPRING-1, SPRING-2, SINGLE and FLAMINGO) and in one RCT in treatment-experienced patients (SAILING), all AEs ascribed to dolutegravir led to drug cessation in 1.2–2.5% of patients within the first year, comparable to rates of AEs leading to discontinuation of raltegravir and lower than those leading to discontinuation of efavirenz and darunavir/ritonavir [1,3,10,11,15]. However, although discontinuation rates were low, significant numbers of

Table 3 Relative hazards (RHs) of variables significantly associated with dolutegravir (DTG) discontinuation [because of any adverse event (AE) or neuropsychiatric AEs] and remaining in the final Cox model

	RH	95% CI	*P*
Any AE			
Female, *vs.* male gender	2.81	1.46–5.41	0.002
Older age (> 60 years), *vs.* younger age	2.88	1.56–5.34	< 0.001
ABC with DTG initiated, *vs.* no ABC	2.63	1.61–4.29	0.0001
DTG start in 2016, *vs.* in 2014/2015	8.93	3.76–21.28	< 0.0001
Neuropsychiatric AEs			
Female, *vs.* male gender	2.64	1.23–5.65	0.01
Older age (> 60 years), *vs.* younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, *vs.* no ABC	2.42	1.38–4.24	0.002
DTG start in 2016, *vs.* in 2014/2015	11.36	4.31–29.41	< 0.0001

ABC, abacavir; CI, confidence interval.

neuropsychiatric AEs, although usually mild, were observed in all the RCTs. For example, in SPRING-1, SPRING-2 and SINGLE, the rates for dizziness of any grade were 3, 6 and 9%, respectively. The corresponding rates for sleep disturbances were 2, 5 and 23% [4]. It has been speculated that the higher prevalence of insomnia observed in the SINGLE study was attributable to the specific study questionnaire that had not been used in other trials [15,16]. In a meta-analysis funded by ViiV Healthcare, the odds of discontinuation because of AEs were significantly lower with dolutegravir than with all treatments except raltegravir and rilpivirine [9]. In the phase III STRIIVING study, 551 experienced patients were randomized to switch from a variety of ART regimens to the STR Triumeq© or remain on their prior regimen. Ten patients (4%) in the switch arm discontinued because of AEs *vs.* none in the continuation arm [12].

Clinical trials are, however, designed to provide evidence of efficacy and safety under ideal conditions. Although a large amount deal of information on a product's safety and efficacy is gathered during clinical development, it is not possible to fully describe the safety profile of a product in pre-marketing clinical trials. Post-marketing studies are the only sources of information that allow the assessment of the real-life effectiveness and safety of a new drug [17].

It is well known that patients participating in RCTs are highly selected and may differ substantially from broader populations treated in different clinical settings, as a consequence of explicit exclusion criteria and subtle recruitment biases. Predefined stopping criteria for study drugs may discourage premature discontinuations in cases of mild to moderate AEs. Moreover, limitations in health care resources or limited treatment options may motivate patients to continue an antiretroviral regimen, even in the presence of side effects. For example, in SAILING, 49% of patients came from centres outside of Europe and North America [1]. Given the limited treatment options for patients in these settings, it is plausible that continuation of INSTI was a higher priority for them than for our patients. This may be illustrated by the high numbers of mild or moderate neuropsychiatric symptoms reported compared with the low discontinuation rates seen in the RCTs.

The two RCTs comparing dolutegravir with efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI) with well-recognized neuropsychiatric side effects, suggest a possible signal for the frequency of neuropsychiatric AEs seen with dolutegravir in 'real-life'. In SINGLE, there were significantly more discontinuations of Atripla® than of DTG with ABC + lamivudine because of psychiatric and nervous system disorders but the incidence of insomnia was significantly greater in the Triumeq® group and the incidences of headache, fatigue and depression were similar. Dizziness, abnormal dreams, anxiety and somnolence were more common with Atripla® [15]. In the SPRING-1 dose-finding study, headache occurred more frequently in the dolutegravir 50 mg/day group than in the efavirenz group (10 *vs.* 4%, respectively), with dizziness (6 *vs.* 18%, respectively) and insomnia (6 *vs.* 10%, respectively) less common with dolutegravir but still occurring at similar frequencies to those found in our study [11].

More recently, preliminary data have been reported from the phase IIIb randomized, open-label ARIA study designed to demonstrate noninferior antiviral activity of the STR Triumeq® compared with atazanavir boosted with ritonavir plus TDF and emtricitabine in 495 treatment-naïve adult women [8]. ARIA, conducted by ViiV Healthcare, enrolled women (41% of the study participants were of African heritage) in 12 countries, with the USA and South Africa contributing the two largest groups of participants. There were fewer dolutegravir AEs leading to discontinuation compared with those in the atazanavir arm (4 *vs.* 7%, respectively) and none of the AEs seen with dolutegravir was neuropsychiatric. The reasons for the conflicting results between this trial and our data remain unclear, but the facts that most women were enrolled in settings with restricted ART access and that the RCT was open-label may have influenced the outcome.

The pattern of neuropsychiatric AEs leading to dolutegravir discontinuation in our cohort was heterogeneous. The most frequent (but not universal) events were insomnia and sleep disturbances, but also dizziness and painful paraesthesia which could not be explained otherwise. Of note, in almost all patients, the symptoms occurred during the first few weeks on dolutegravir, were not life-threatening, did not lead to hospitalization and

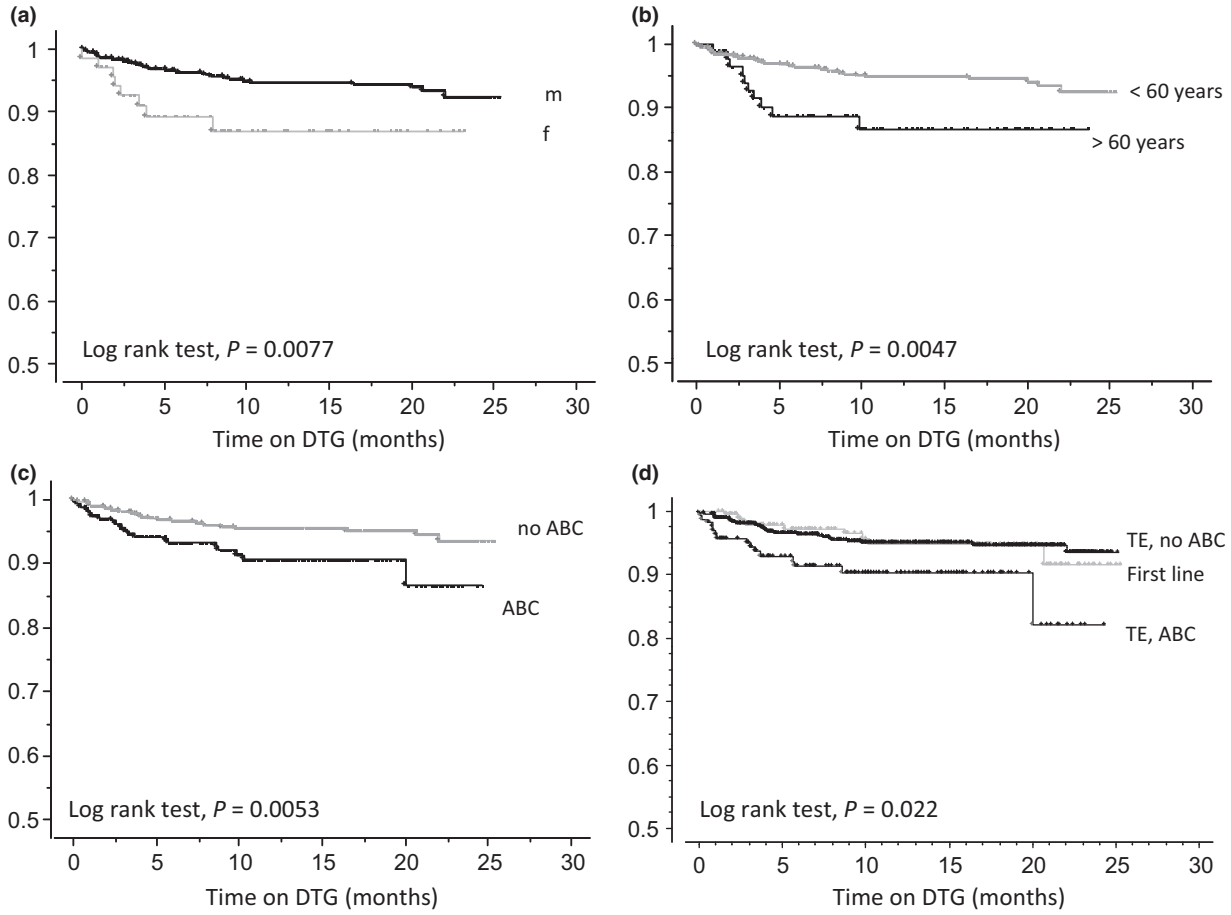

Fig. 2 Relationship between neuropsychiatric adverse events (all other events censored) and time on dolutegravir for (a) female (f) *vs.* male (m) patients, (b) older (> 60 years old) *vs.* younger patients, (c) patients on abacavir (ABC) *vs.* those not initiating ABC with dolutegravir, and (d) first-line *vs.* treatment-experienced (TE) patients (ABC *vs.* no ABC initiated with dolutegravir). DTG, dolutegravir.

disappeared quickly after discontinuation of dolutegravir, which was usually the only action taken.

Of concern was the fact that the rate of dolutegravir discontinuation because of AEs was almost threefold higher in women and in patients older than 60 years. Further studies evaluating the effect of sex, age, body mass index and race on dolutegravir pharmacokinetics (PK) are warranted. RCTs to date have primarily enrolled white and normal weight men between the ages of 19 and 54 years, leaving important sections of the HIV-infected population underrepresented [4]. In the four trials evaluating dolutegravir as first-line therapy, the median age was 34–37 years and only 13–16% of patients were female. It is possible that different PK may have contributed to the higher rate of dolutegravir-related AEs in these groups. Although the pathways of metabolism and transport suggest that the drug should be relatively unaffected by such differences, no study has specifically assessed the effects of demographic diversity on dolutegravir PK parameters. This also applies to patients with hepatic comorbidity, in which the unbound fraction of dolutegravir in plasma is higher than in healthy volunteers. Finally, it remains to be investigated whether neuropsychiatric events represent a direct neurotoxic effect. Dolutegravir achieves high therapeutic concentrations in the central nervous system (CNS), mainly by passive diffusion with a low possibility of active transporter involvement [7].

We did not find any impact of CD4 T-cell counts or ethnicity on AE rates. Correlations between tolerability or PK and race, sex and immune status are well described for NNRTIs such as nevirapine and efavirenz [13]. There was also no evidence for any cross-drug effect. Eighty-six per cent of patients who switched away from an INSTI because of AEs had no tolerability problems with the subsequent antiretroviral regimen

which contained other INSTIs, protease inhibitors or NNRTIs.

Our study has several important limitations.

Firstly, because of the retrospective design, we were unable to account for confounding and bias resulting from patient selection. However, potential sources of bias and confounding related to patient selection for INSTI initiation are likely to be fewer in Germany than in most other settings as, unlike in most settings worldwide, there are no financial restrictions to ART (in particular INSTI) prescribing. While the treatment histories of our patients did indeed show some differences in the context in which the INSTI was initiated (i.e. salvage therapy, treatment simplification, or prior intolerability of efavirenz or other regimens), these reflect the availability of more INSTI alternatives over time. For example, the fact that more treatment-experienced patients switched to raltegravir can be explained by the fact that raltegravir had been the only INSTI available in 2007–2012.

Patients initiating raltegravir before 2013 were likely to have had fewer ART options and therefore a higher motivation to remain on therapy despite side effects. However, the discontinuation rates for raltegravir remained relatively stable over time. One might also hypothesize that previous neuropsychiatric AEs on efavirenz may have influenced the reporting of neuropsychiatric symptoms and/or patients' willingness to persevere with a subsequent regimen in the presence of such symptoms. We found no association between neuropsychiatric events on INSTIs and previous treatment history or reason for switch among experienced patients, and our findings on the tolerability of various INSTIs are not explained by differences in the reason for INSTI initiation.

The high rates of discontinuation of dolutegravir in 2016 are difficult to explain other than by an enhanced awareness of the treating physicians of the possibility of dolutegravir being the drug responsible for neuropsychiatric AEs. Of note, our results and conclusions remained consistent when patients initiating dolutegravir in 2016 were excluded.

It has been shown that patients' beliefs and satisfaction with therapy modulate the impact of mild AEs [2]. However, in most patients (including women and older patients) who discontinued dolutegravir, the subsequent ART regime was well tolerated. Neuropsychiatric AEs recurred in six patients who were re-exposed to dolutegravir after stopping it once.

It was not possible to determine whether the AEs were solely related to dolutegravir. Discontinuation rates were markedly higher in patients initiating abacavir at the same time, despite prior HLA testing. This was seen in both naïve and treatment-experienced patients, and it remains unclear whether some of these events were directly related to abacavir. We found no difference between dolutegravir neuropsychiatric AEs for patients on abacavir as STR and those on a two or three tablet regimen (data not shown). Data for the dolutegravir/abacavir combination remain relatively limited as, except for the SINGLE trial, the majority of patients did not receive abacavir in the RCTs.

As we only had data on AEs leading to discontinuation, the true rate of AEs related to dolutegravir may be higher, even in the setting of a broad range of antiretroviral options and a lower threshold to modify a regimen. Indeed, anecdotally several patients complained of neuropsychiatric AEs during the first few weeks on dolutegravir which disappeared thereafter despite continuing dolutegravir.

Finally, because this was a retrospective observational cohort study, it was not possible to characterize neuropsychiatric AEs in detail and we also did not have information on the timing of dolutegravir administration. As these AEs were also, to a lesser extent, seen with other INSTIs, it remains unclear whether they represent a class effect with variable incidence between different INSTIs.

In this retrospective analysis of more than 1700 patients treated with INSTIs, almost 6% of therapies with dolutegravir were discontinued because of neuropsychiatric side effects within a year of initiation. The discontinuation rate for dolutegravir because of these AEs was higher than that reported in clinical trials and higher than for raltegravir and elvitegravir. Neuropsychiatric AEs were seen especially in women, in older patients and in patients who initiated abacavir at the same time. As dolutegravir is likely to remain among the preferred antiretroviral options for HIV-infected patients, it is vital that post-marketing surveillance and further research be done on the safety of dolutegravir outside of RCTs and on mechanisms for potential neurotoxicity, especially in populations underrepresented in the RCTs.

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