Contents available at **PubMed**
www.aidsreviews.com

PERMANYER

AIDS Rev. 2019;21:4-10

Neuropsychiatric Adverse Events with Dolutegravir and Other Integrase Strand Transfer Inhibitors

Christian Hoffmann[1,2] and Josep M. Llibre[3]

[1]ICH Study Center Hamburg, Germany; [2]Department of Medicine II, University of Schleswig-Holstein, Campus Kiel, Germany; [3]Department of Infectious Diseases, University Hospital Germans Trias i Pujol; Fight AIDS Foundation, Badalona, Barcelona, Spain

Abstract

Neuropsychiatric adverse events (NPAEs) observed with the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) are usually mild to moderate. The most prevalent symptoms are insomnia and sleep disorders, but the spectrum also includes dizziness, anxiety, depression, headache, paraesthesia, muscle-skeletal pain, poor concentration, and slow thinking. In recent cohort studies involving >6400 patients in different countries, discontinuation rates due to NPAEs were observed in around 3.5% (range, 1.4-7.2%) of subjects treated with DTG. These rates have been higher than those seen in randomized clinical trials and were also higher than with other INSTIs such as elvitegravir or raltegravir. Elderly, female patients and those who initiate abacavir simultaneously appear to be more vulnerable in some cohorts. It remains unclear if NPAEs are driven by an increased DTG exposure. With heightened awareness of health-care providers and patients, reports of NPAEs will probably increase in the future. **(AIDS Rev. 2019;21:4-10)**

Corresponding author: Christian Hoffmann, hoffmann@ich-stadtmitte.de

Key words

Dolutegravir. Raltegravir. Elvitegravir. Bictegravir. Integrase strand transfer inhibitors. Psychiatric adverse events.

Introduction

During recent years, growing data from different cohort studies from European countries and Canada have suggested that the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) is associated with a heterogeneous pattern of neuropsychiatric adverse events (NPAEs). NPAEs were seen both in treatment-naïve and treatment-experienced HIV-infected patients[1-12]. The most prevalent symptoms were insomnia and sleep disorders, but the spectrum also included dizziness, anxiety, depression, headache, paraesthesia, muscle-skeletal pain, poor concentration, and slow thinking. Although usually reversible and non-serious, these NPAEs may lead to DTG discontinuation in a noticeable proportion of patients, contrasting the experiences made in randomized clinical trials (RCTs)[13]. It, therefore, seems prudent to summarize current knowledge on this phenomenon.

Correspondence to:
Christian Hoffmann
ICH Stadtmitte, Glockengiesserwall 1
20095 Hamburg, Germany
E-mail: hoffmann@ich-stadtmitte.de

Received in original form: 16-09-2018
Accepted in final form: 09-01-2019
DOI: 10.24875/AIDSRev.19000023

Table 1. Cohort studies focusing on dolutegravir tolerability in clinical practice, numbers indicate AEs and NPAEs, leading to dolutegravir discontinuation (D/C)

Country	n	FU, days	ART naïve (%)	All AEs D/C (%)	NPAE D/Cs (n) (%)	IR/100 PY	Risk factors associated with AE-related discontinuation
Italy[1]	295	258	18	5.4	1.4 (4)	n.s.	Older age, being naïve for ART
Italy[2]	173	189	0	9.2	3.5 (6)	n.s.	Female gender, abacavir use
France[3]	555	n.s.	n.s	7.0	3.1 (17)	n.s.	Abacavir use
France[4]	239	336	0	8.4	3.8 (9)	n.s.	n.s.
Spain[5]	275	288	13	10.2	7.2 (20)	9.8%	Abacavir use
Netherlands[6]	556	225	18	13.7	5.6[a] (31)	n.s.	Abacavir use
Switzerland[7]	1950	n.s.	17	3.8	1.7 (33)	1.8%	Female sex
Germany[8]	985	345	21	6.8	5.0 (49)	5.6%	Older age, female gender, abacavir use
Canada[9]	519	720	12	5.2	3.5 (18)	3.0%	Prior AE
France[10]	517	n.s.	6	10.6	5.4 (28)	n.s.	Older age (females), high BMI (males), high CD4 T-cells
UK[11]	129	165	n.s	2.3	2.3 (3)	n.s.	n.s.
Spain[12]	212	170	69	3.4	3.3 (7)	3.4%	Older age (any AE)
Total	6405				3.5 (225)		

[a]Only sleep disturbances and insomnia. Total NPAE incidence was higher as multiple different NPAEs were reported in several patients. N.s: not stated, FU: median follow-up, NPAEs: neuropsychiatric adverse events

Incidence of NPAEs

In clinical cohort studies, the incidence rates of all drug-related AEs leading to DTG discontinuation varied between 2.3% and 13.7%. A considerable proportion was declared to be neuropsychiatric, leading to a total incidence of discontinuation due to NPAEs of 3.5% (range, 1.4-7.2%, Table 1). This high variability may derive not only from a lack of definition or diagnosis of every NPAE, different patient populations, or length of follow-up but also from differences in awareness and management of NPAEs. An Italian group recently showed that discontinuation rates due to sleep disturbances can be reduced when DTG is taken in the morning[14]. However, it can be assumed that the "true" incidence of both transient and persistent NPAEs in subjects receiving DTG is higher than 3.5%. In most clinical cohorts, the rates of NPAEs reported were limited to those disturbing enough to lead to drug discontinuation.

NPAEs with DTG may be unspecific, comprising vague feelings such as "foggy brained," "tetchy," or "prone to tears." Those events are often not written in electronic records or even considered drug related by the patients themselves and thus are commonly not captured with retrospective studies checking the electronic medical records or in prospective RCTs without specific questionnaires. With heightened awareness of health-care providers and patients, reports of NPAEs will probably increase in the future.

What is the reason for the discrepancy between RCTs and clinical routine?

In seven RCTs in treatment-naive (SPRING-1, SPRING-2, SINGLE, FLAMINGO, ARIA, GS-1489, and GS-1490) with 2117 subjects treated with DTG[15-21], the rates of NPAEs leading to DTG cessation were usually <1% within the 1st year. The evidence from RCTs in treatment-naïve patients is, therefore, robust. However, patients participating in RCTs may differ substantially from broader treated populations, as a consequence of explicit exclusion criteria and subtle recruitment biases. Limitations in access to health-care resources or limited treatment options may also motivate patients to continue an antiretroviral regimen in an RCT, even in

the presence of tolerable side effects. Predefined stopping criteria may also discourage premature discontinuations in cases of mild-to-moderate AEs. This may explain the discrepancy in the overall rates of AEs between RCTs and in the experiences made in clinical routine.

It should be noted that NPAEs not leading to discontinuation have been observed in all RCTs in a significant number of subjects. In a recent meta-analysis of all RCTs with DTG, there was a significantly higher risk of Grade 1-4 insomnia for DTG versus other antiretrovirals (6.1% vs. 4.5%, p = 0.02) but no differences with suicidality[22]. In SPRING-1, SPRING-2, and SINGLE, the rates of sleep disturbances were 2%, 5%, and 23%. The corresponding rates for dizziness of any grade were 3, 6, and 9%, respectively[23]. Not surprisingly, the higher prevalence of insomnia and dizziness observed in the SINGLE study was attributable to the double-blind design versus efavirenz, with a specific targeted questionnaire repeated at every visit that had not been used in other trials, leading patients and treating physicians to increased awareness to NPAEs[17,24].

Treatment-experienced patients: Higher rates of NPAEs

Compared to treatment-naïve patients, more AEs and NPAEs were reported in four open-label Phase III trials (SWORD1 and 2, STRIIVING, and NEAT022) evaluating the efficacy and safety of switching to DTG in patients with stable viral suppression on ART[25-27]. In the SWORD1 and 2 RCTs, the total rates of any drug-related AEs were 19% with DTG plus rilpivirine, compared to only 2% in the triple-drug continuation arms. The rates for NPAEs leading to withdrawal at 48 weeks were 1.6 versus 0.2%[25]. In the STRIIVING RCT, switch to DTG/abacavir/lamivudine was associated with a total drug-related AE rate at 24 weeks of 21%, compared to 1% in patients remaining on their regimen, and any NPAE in 13% versus 3%[26]. AEs leading to withdrawal were observed in 4% versus 0%, respectively. Finally, the NEAT022 RCT of switch from boosted protease inhibitor- to DTG-based regimens reported AEs, leading to withdrawal in 4.2% versus 1.4% in DTG and control arms, respectively. Mood disturbances or insomnia were the cause of DTG discontinuation in 3.1%[27]. In these four RCTs, a total of 29/1202 (2.8%) subjects have experienced NPAEs, leading to withdrawal of DTG during the 1st year of exposure.

Undoubtedly, open-label switch studies are exposed to physician awareness bias and are expected to reveal higher numbers of AEs due to the inclusion of a control arm that maintains the current stable regimen that has been presumably well tolerated. However, the rates of NPAEs in these open-label RCTs come close to the experiences made in clinical cohorts.

Potential risk factors

In a German cohort of almost 1000 patients exposed to DTG, a significantly higher incidence of NPAEs was found in older and female patients[8]. This has also been observed by some but not all cohort studies (Table 1). An RCT specifically done in females did not identify higher rates of NPAEs[19]. Female and older patients may be associated with disparities in pharmacokinetics/pharmacodynamics. In elderly patients, reductions in renal and hepatic clearance may lead to an increase in volume of the distribution of lipid-soluble drugs. There is no evidence that other factors such as a specific ethnicity or the presence of psychiatric disorders are associated with a higher risk for NPAEs.

In a single-center study of 861 patients who had initiated DTG outside RCTs since 2014, there were 155 patients (18.0%) with preexisting depressive disorders and 55 patients (6.4%) with other neuropsychiatric diagnoses. These patients were not at higher risk for DTG discontinuation due to NPAEs than patients without neuropsychiatric diagnoses[28]. In a US cohort, subjects receiving DTG or raltegravir were more likely to have a history of psychiatric diagnosis at baseline but were not more likely to experience NPAEs[13].

Is there a genetic predisposition?

It is still unclear whether a genetic predisposition could modulate an individual's susceptibility to experience NPAEs with DTG or other INSTIs. In a Japanese study, subjects carrying specific UGT1A1 gene polymorphisms such as UGT1A1*6, UGT1A1*28, or both alleles showed a positive association between DTG exposure and cumulative incidence of selected NPAEs[29]. Up to now, this is the only study reporting on an association between specific gene polymorphisms and the incidence of NPAEs seen with DTG.

Are NPAEs associated with higher drug exposure?

There is disagreement over whether this a higher DTG exposure correlates with NPAEs. During recent years, several studies observed an association

between pharmacogenetic variants linked to DTG metabolism and increased plasma concentrations[29-31]. The above-cited study from Japan reported on an association between DTG plasma trough concentrations and NPAEs[30]. At least one "central nervous system (CNS) side effect" was observed in 41 of 162 patients (25%) including dizziness, headache, insomnia, restlessness, and anxiety. Patients with NPAEs showed higher trough DTG plasma concentrations. However, the number of patients with NPAEs was relatively low in this study and it remained unclear how NPAEs had been assessed. In another small study from France, DTG trough levels were significantly higher in patients with NPAEs[10]. These preliminary findings would suggest that NPAEs are driven by increased drug exposure.

A recent pharmacokinetic study found higher drug exposure for DTG in older patients[32] which may explain the higher event rate in elderly patients. Older people (>60 years) had significantly higher DTG plasma Cmax levels but not C24, AUC0-24, or t1/2[32]. However, PK DTG parameters were not associated with sleep or cognition changes in this study. More recently, a case report showed that therapeutic drug monitoring might be useful in individuals expressing unusual DTG pharmacokinetics[33]. However, a retrospective analysis of DTG plasma levels from frozen samples found no association between plasma levels and risk of discontinuation due to NPAEs[28]. Finally, an open-label Phase III study using a double dose of DTG (50 mg BID) did not report a higher rate of NPAEs, suggesting a lack of association between higher exposure to DTG and development of NPAEs[34].

Coadministration of other drugs

There are conflicting data whether a higher NPAE rate is seen with the coadministration of other drugs. In the German cohort, the risk for DTG discontinuation was 2-fold higher when abacavir was initiated simultaneously. This has been confirmed by some, but not all cohort studies (Table 1). It remains debatable whether the current data are sufficient to exclude a drug-to-drug interaction between abacavir and DTG[35,36]. Beside interactions, nucleoside reverse transcriptase inhibitors, particularly zidovudine and abacavir, may also cause CNS manifestations including mania and psychosis[37].

Other drugs than abacavir must also be considered. For example, atazanavir significantly inhibits DTG metabolism by inhibition of the UDP-glucuronosyltransferase, resulting in a 2-–4-fold increase in drug disposition compared with other antiretroviral drugs[38]. Cobicistat also significantly increases DTG trough concentrations, possibly by a higher degree of inhibition of the intestinal efflux transporter P-glycoprotein, ultimately resulting in increased DTG absorption[39]. However, there are no data that coadministration of agents such as atazanavir or cobicistat could influence the risk of NPAEs with DTG.

Could physician awareness play a role in the claim of NPAEs to DTG?

In people living with HIV, psychiatric symptoms and disorders are more prevalent than in the general population. Psychiatric diseases represent a risk for HIV acquisition and HIV infection itself may not only increase the risk of developing but also aggravate several psychiatric conditions[40]. Clinicians must be vigilant and familiar with these NPAEs and try to attribute them to DTG or the background personality traits.

Once a warning is launched regarding a potential association between a drug and NPAEs, physicians prejudice to associate frequent NPAEs with that given drug may facilitate discontinuation of that drug. This may occur at a physician or at a center level, and it is difficult to explore. This bias by treating center has been identified by Llibre et al. (in press) but not by Hoffmann et al. However, the later cohort included only two centers and a lower number of subjects and events[8].

Possible mechanisms of NPAEs

What are the precise mechanisms underpinning the neurotoxicity associated with DTG, whether or not associated with higher drug levels? As integrase functions are unique to retroviruses, its inhibition should not hamper the normal operations in human cells. INSTIs do not inhibit any human DNA polymerase significantly nor do they inhibit any tested enzyme activity, transporter, or receptor-ligand assays. Thus, a precise mechanism can be only speculated at this time.

For efavirenz, several potential mechanisms may explain the well-known neurotoxicity of this antiretroviral agent. These include altered calcium homeostasis, decreases in brain creatine kinase, mitochondrial damage, increases in brain proinflammatory cytokines, and involvement of the cannabinoid system[41]. However, the observation made in a small pilot study that almost all patients experiencing efavirenz-associated NPAEs showed improvement after switching from efavirenz to

DTG, argue against similar pathogenic pathways[42]. It remains unclear if there is a direct neuronal toxicity of DTG and other INSTIs and if this toxicity, if existent, results in NPAEs, and/or neurological impairment.

Are NPAEs a class effect of INSTIs?

Based on the current data, it cannot be excluded that NPAEs represent a class effect of all INSTIs. Compared to elvitegravir and raltegravir, DTG exhibits a lower intersubject pharmacokinetic variability[26] and a slower dissociation from integrase DNA complexes[43]. Moreover, the current data suggest a free passage across the blood–brain barrier[44]. It is unknown if a lower CNS drug exposure with elvitegravir or raltegravir mitigates potential neurotoxicity of these INSTIs. In a German cohort study, some NPAEs have also been attributed to elvitegravir and raltegravir, though to a lesser extent compared to DTG[8]. Cohort studies from France, Spain, and Canada which compared the NPAE incidence rates of DTG and other INSTIs have found similar results. NPAEs were highest with DTG but were also seen with elvitegravir or raltegravir[4,5,9,12]. For raltegravir, a small case series on exacerbation of depression with raltegravir exposure has been reported 1 year after marketing approval[45]. The French pharmacovigilance network found a significant association between raltegravir and depression[46]. Another case series suggested an association between severe insomnia and high concentrations of raltegravir[47]. However, results from a large ongoing RCT in treatment-naïve patients did not yield any safety signal regarding AEs or NPAEs with 1200 mg once daily versus 400 mg twice daily of raltegravir[48].

Bictegravir, a new INSTI with structural similarity to DTG, is coformulated with tenofovir alafenamide and emtricitabine. It has gained marketing approval in Europe in June 2018. In three large double-blinded RCTs in both treatment-naïve and treatment-experienced patients, the rates of AEs leading to discontinuation and the rates of NPAEs such as insomnia were comparable between bictegravir and DTG[20,21,49]. Data from clinical cohorts are lacking.

Dolutegravir during pregnancy

Data on DTG during pregnancy remain limited. Dolutegravir crosses the placenta easily, resulting in infant concentrations comparable to maternal plasma concentrations. However, a small PK study has recently shown that maternal exposure to DTG is lower in pregnancy. Paired data demonstrated a 29% decrease in AUC 0-24 in the third trimester compared with postpartum[50]. Of note, the significant differences seen between pregnancy and postpartum were in part due to the higher than expected DTG exposures postpartum. It remains unclear if mood changes postpartum are aggravated with DTG exposure.

In April 2018, a potential early signal for an increased prevalence of neural tube defects in association with DTG-based regimens from the time of conception came from the Tsepamo trial, a 4-year surveillance program from Botswana[51]. An unscheduled preliminary analysis revealed that among 426 infants born to HIV-positive women who had been taking DTG-based antiretroviral therapy from the time of conception, four (0.94%; 95% CI 0.37%, 2.4%) had a neural tube defect, compared to 14 (0.12%; 95% CI 0.07%, 0.21%) of 11,300 infants born to women who had been exposed to any non-DTG antiretroviral therapy from the time of conception. The last updated prevalence of neural tube defects associated with DTG exposure at conception is 4/596 (0.67%, 95% CI 0.26% - 1.7%). Although clearly more data are needed to confirm or refute this signal (further data of the Tsepamo programme are expected to be reported in March 2019), these observations have already changed DTG policy and recommendations in several African countries and developed countries[52].

What are the next steps?

Cohort studies should evaluate other INSTIs such as raltegravir, elvitegravir but also newer INSTIs such as bictegravir or cabotegravir. Patients who have discontinued DTG or other INSTIs due to NPAEs should be described more accurately, especially with respect to concomitant therapies, previous psychiatric conditions, time association with the start of the INSTI, and improvement after INSTI discontinuation. Sleep architecture in PLWH and neuropsychological validated tests would illustrate minor sleep disorders and subclinical cognitive changes in asymptomatic patients on INSTIs.

A high background rate of many psychiatric conditions among PLWH may hinder the detection of a potential association between NPAEs and a given drug. In our experience, many patients with NPAEs had no prior psychiatric condition. Moreover, the vast majority of the patients who switched away from DTG due to NPAEs had no tolerability problems with the subsequent antiretroviral regimen[28].

Conclusion

NPAEs with DTG seen in clinical routine care are usually mild to moderate and rarely necessitate drug withdrawal but could require drug discontinuation more frequently than expected from RCTs, particularly those with a double-blind design. Many questions remain unresolved and should be addressed both by the manufacturers and independent researchers. In the time of modern ART regimens where patients can expect a normal life expectancy in quantity and quality, patient's tolerability demands are increasing. Consequently, even reversible and non-serious side effects deserve further research, especially in an aging population that faces an anticipated decade-long exposure to INSTIs.

Conflicts of interest

Christian Hoffmann: Abbvie, Boehringer-Ingelheim, Bristol Myers-Squibb, Gilead Sciences, HEXAL, Hormosan, Merck Sharp Dohme, Theratech and ViiV Healthcare.

Josep M Llibre: Boehringer-Ingelheim, Bristol Myers-Squibb, Gilead Sciences, Merck Sharp Dohme, and ViiV Healthcare.

References

1. Bonfanti P, Madeddu G, Gulminetti R, et al. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. AIDS. 2017;31:455-7.
2. Borghetti A, Baldin G, Capetti A, et al. Efficacy and tolerability of dolutegravir and two nucleos(t)ide reverse transcriptase inhibitors in HIV-1-positive, virologically suppressed patients. AIDS. 2017;31:457-9.
3. Cailhol J, Rouyer C, Alloui C, Jeantils V. Dolutegravir and neuropsychiatric adverse events: a continuing debate. AIDS. 2017;31:2023-4.
4. Charpentier C, Peytavin G, Lê MP, et al. High virological suppression regardless of the genotypic susceptibility score after switching to a dolutegravir-based regimen: week 48 results in an observational cohort. J Antimicrob Chemother. 2018;73:1665-71.
5. Cid-Silva P, Llibre JM, Fernández-Bargiela N, et al. Clinical experience with the integrase inhibitors dolutegravir and elvitegravir in HIV-infected patients: efficacy, safety and tolerance. Basic Clin Pharmacol Toxicol. 2017;121:442-6.
6. De Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS. 2016;30:2831-4.
7. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. AIDS. 2017;31:1853-8.
8. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18:56-63.
9. Lepik KJ, Yip B, Ulloa AC, et al. Adverse drug reactions to integrase strand transfer inhibitors. AIDS. 2018;32:903-12.
10. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS. 2017; 31:1201-3.
11. Negedu O, Kim SH, Weston R, et al. Retrospective review of routine clinical patient experiences with dolutegravir; Virological suppression, immunological recovery and adverse events. HIV Med. 2017;18:709-10.
12. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother. 2017;72:1752-9.
13. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. J Acquir Immune Defic Syndr. 2017;74:423-31.
14. Capetti AF, Di Giambenedetto S, Latini A, et al. Morning dosing for dolutegravir-related insomnia and sleep disorders. HIV Med. 2018; 19:e62-3.
15. van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis. 2012;12:111-8.
16. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381:735-43.
17. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013; 369:1807-18.
18. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;383:2222-31.
19. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV. 2017;4:e536-46.
20. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet. 2017;390:2073-82.
21. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017; 390:2063-72.
22. Hill AM, Mitchell N, Hughes S, Pozniak AL. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials. Curr Opin HIV AIDS. 2018;13:102-11.
23. Cottrell ML, Hadzic T, Kashuba AD. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. Clin Pharmacokinet. 2013;52:981-94.
24. Kandel CE, Walmsley SL. Dolutegravir-a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther. 2015; 9:3547-55.
25. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018;391:839-49.
26. Trottier B, Lake JE, Logue K, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, phase IIIb study. Antivir Ther. 2017;22:295-305.
27. Gatell JM, Assoumou L, Moyle G, et al. Immediate vs. deferred switching from a boosted protease inhibitor (PI/r) based regimen to a dolutegravir (DTG) based regimen in virologically suppressed patients with high cardiovascular risk or age ≥50 years: final 96 weeks results of NEAT 022 study. Clin Infect Dis. 2019;68:597-606.
28. Hoffmann C, Wolf E, Schewe K, et al. CNS Toxicity of Dolutegravir is not Associated with Psychiatric Conditions or Higher Plasma Exposure. Abstract 424. Boston, Massachusetts: 25th CROI; 2018.
29. Yagura H, Watanabe D, Kushida H, et al. Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse events in Japanese individuals infected with HIV-1. BMC Infect Dis. 2017;17:622.
30. Chen S, St Jean P, Borland J, et al. Evaluation of the effect of UGT1A1 polymorphisms on dolutegravir pharmacokinetics. Pharmacogenomics. 2014;15:9-16.
31. Elliot ER, Neary M, Else L, et al. NR1I2 RS2472677 and ABCG2 RS2231142 Influence Dolutegravir Concentrations in Plasma. Abstract 467. Boston, Massachussetts: 25th CROI; 2018.
32. Elliot ER, Wang X, Singh S, et al. Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition. Clin Infect Dis. 2019;68:87-95.
33. Parant F, Miailhes P, Brunel F, Gagnieu MC. Dolutegravir-related neurological adverse events: a case report of successful management with therapeutic drug monitoring. Curr Drug Saf. 2018;13:69-71.
34. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir-and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014;210:354-62.
35. De Boer MG, Brinkman K. Recent observations on intolerance of dolutegravir: differential causes and consequences. AIDS. 2017;31:868-70.
36. Cattaneo D, Rizzardini G, Gervasoni C. Intolerance of dolutegravir-containing combination antiretroviral therapy: not just a pharmacokinetic drug interaction. AIDS. 2017;31:867-8.
37. Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. CNS Drugs. 2014;28:131-45.

38. Cattaneo D, Minisci D, Cozzi V, et al. Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect? Antivir Ther. 2017;22:353-6.
39. Gervasoni C, Riva A, Cozzi V, et al. Effects of ritonavir and cobicistat on dolutegravir exposure: when the booster can make the difference. J Antimicrob Chemother. 2017;72:1842-4.
40. Dubé B, Benton T, Cruess DG, Evans DL. Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci. 2005;30:237-46.
41. Decloedt EH, Maartens G. Neuronal toxicity of efavirenz: a systematic review. Expert Opin Drug Saf. 2013;12:841-6.
42. Bracchi M, Pagani N, Clarke A, et al. Multicentre open-label pilot study of switching from efavirenz to dolutegravir for central nervous system (CNS) toxicity. J Int AIDS Soc. 2016;19 Suppl 7:154-5.
43. Hightower KE, Wang R, Deanda F, et al. Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. Antimicrob Agents Chemother. 2011;55:4552-9.
44. Letendre SL, Mills AM, Tashima KT, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. Clin Infect Dis. 2014;59:1032-7.
45. Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS. 2008;22:1890-2.
46. Lafay-Chebassier C, Chavant F, Favrelière S, et al. Drug-induced depression: a case/non case study in the French pharmacovigilance database. Therapie. 2015;70:425-32.
47. Eiden C, Peyriere H, Peytavin G, Reynes J. Severe insomnia related to high concentrations of raltegravir. AIDS. 2011;25:725-7.
48. Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV. 2017;4:e486-94.
49. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV. 2018;5:e357-65.
50. Mulligan N, Best BM, Wang J, et al. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. AIDS. 2018; 32:729-37.
51. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med. 2018;379:979-81.
52. Nakkazi E. Changes to dolutegravir policy in several African countries. Lancet. 2018;392:199.