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

PERMANYER

AIDS Rev. 2018;20:13-25

Dolutegravir Neuropsychiatric Adverse Events: Specific Drug Effect or Class Effect

Jean Cyr Yombi

Department of Internal Medicine and Infectious Diseases, AIDS Reference Centre, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Belgium

Abstract

Integrase strand transfer inhibitors (INSTIs) are a newer class of antiretroviral treatment for HIV-infected patient. INSTIs currently available for use are raltegravir, elvitegravir, dolutegravir (DTG), and bictegravir. Clinical studies using INSTIs have demonstrated an 80-90% efficiency in treating HIV-positive antiretroviral therapy - naive patients. They are recommended by internatioal guidelines as the preferred agents for the first-line regimen. INSTIs have also been demonstrated as safe and tolerable. In clinical trials, the rate of adverse events (AEs) such as neuropsychiatric AEs (NPSAEs) leading to discontinuation is very low. However, recent published cohort studies show growing concerns on DTG induced NPSAEs. In this paper, we will review available evidence about DTG - NPSAEs and analyze whether the backbone (abacavir or tenofovir) matters as well as discussing the possible mechanism behind this toxicity. **(AIDS Rev. 2018;20:13-25)**

Corresponding author: Jean Cyr Yombi, jean.yombi@uclouvain.be

Key words

Dolutegravir. Integrase strand transfer inhibitors. Neuropsychiatric adverse events.

Introduction

There are several classes of antiretroviral drugs approved for the treatment of an HIV-infected patient including nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, and integrase strand transfer inhibitors (INSTIs)[1,2]. INSTIs currently approved and available for use are raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG)[3]. RAL (approved by Food and Drug Administration [FDA] in 2007) requires two daily doses (400 mg twice daily) and is now approved for once daily dose of 1200 mg. EVG (FDA approved in 2012) requires pharmacological boosting to be given once daily, and significant cross-resistance between RAL and EVG prevents sequential therapy with these two agents[4]. DTG was approved by FDA for treating-naive and experienced patients with HIV infection in August 2013[5]. DTG can be given once a day without boosting and can overcome some previous INSTIs failures. Bictegravir (BIC) is a novel INSTI with potent antiviral activity[6], given daily without the requirement for pharmacokinetic boosting, has a high genetic barrier to resistance and low potential for drug-drug interactions. BIctegravir is now approved by FDA in febrauary 2018. It is

Correspondence to:
Jean Cyr Yombi,
10 Avenue Hippocrate
1200 Brussels, Belgium.
E-mail: jean.yombi@uclouvain.be

Received in original form: 01/09/2017
Accepted in final form: 19/02/2018
DOI: 10.24875/AIDSRev.M17000013

submitted for FDA approbation[6]. Clinical studies using INSTIs have demonstrated an 80-90% efficiency in HIV-positive antiretroviral therapy (ART)-naive patients[7-16]. The INSTIs have been demonstrated as safe and tolerable[7-17] and are recommended as the preferred therapy option for patients initiating ART[18-21] and are often used in switch strategies for patients with tolerability issues[17,22]. They show similar rates of adverse events (AEs) such as nausea, diarrhea, and headaches commonly reported[22-24]. These AEs have been shown to be mild to moderate in severity and are not typically associated with treatment discontinuation. Neuropsychiatric AEs (NPSAEs) or psychiatric symptoms (PSs) have been reported in patients treated with INSTIs but typically occur less frequently than in patients treated with efavirenz[24,25]. Low occurrence of AEs leading to discontinuation, especially for DTG compared to ATV/r, EFV, and LPV/r, except RAL, and RPV[17] have been confirmed in two systematic reviews and network meta-analysis[26,27].

Since 2016, small case series[28,29] and a report from a Dutch cohort study[20] have raised concerns about the safety of DTG in real-life settings, especially in regard to NPSAEs. De Boer et al. reported in a small Dutch cohort that DTG treatment was discontinued in 55 of 387 (14.2%) patients after a median of 78 days because of side effects such as sleeping, gastrointestinal, and psychiatric problems[30]. Todd et al. reported that out of 157 naive and experience HIV patients on DTG, 56 (35%) reported side effects; 40 (25%) reported either low moods, anxiety, or sleep disorder. 16 (10%) discontinued DTG, out of which 13 (8%) due to intolerable side effects[31]. In 2017, major published real-life cohorts reported that 4-10% of discontinuation rates were due to DTG AEs[32-37]. These rates of AEs leading to DTG discontinuation were, however, higher than those reported in clinical trials, particularly in regard to NPSAEs[7-16].

In this article, we review randomized trials and cohort studies recently published concerning AEs and discontinuation of DTG especially in regard to NPSAEs. We also discuss if the backbone (tenofovir [TDF or TAF] or abacavir [ABC]) matters and finally we try to understand the mechanisms and risk factors behind these NPSAEs leading to discontinuation of therapy.

What summary of product characteristic (SmPC) tell us about the safety of INSTIs

The safety profile of RAL was based on the pooled safety data from two Phase III clinical studies in treatment-experienced adult patients and one Phase III clinical study in treatment-naïve adult patients[38]. The most frequently reported AEs during treatment were headache and nausea, occurring in 5% or more of patients. In the pooled analysis of treatment-experienced patients, the rates of discontinuation of therapy due to adverse reactions were 3.9% in patients receiving RAL + optimal background therapy (OBT) and 4.6% in patients receiving placebo + OBT. The rates of discontinuation of therapy in naïfs patients due to AEs were 5.0% in patients receiving RAL + emtricitabine (FTC) (+)TDF and 10.0% in patients receiving EFV + (FTC) (+) TDF. NPSAEs considered by investigators to be causally related to RAL (alone or in combination with other ART) are described as common or uncommon in table 1. The safety profile of DTG is based on pooled data from Phase IIb and III clinical studies in 1222 previously untreated patients, 357 previously treated patients unexposed to INSTIs and 264 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most commonly seen treatment-emergent adverse reactions were nausea (13%), diarrhea (18%), and headaches (13%). NPSAEs considered as least possibly related to DTG are listed in table 1 as very common, common, and uncommon[39]. The most frequently reported adverse reactions considered possibly or probably related to EVG/FTC/TDF/cobicistat (COBI) (stribild) in clinical studies of treatment-naïve (TN) patients were nausea (16%) and diarrhea (12%) (pooled data from Phase 3 clinical studies GS-US-236-0102 and GS-US-236-0103, through 144 weeks). The safety profile of stribild in virologically-suppressed patients derived from studies GS-US-236-0115, GS-US-236-0121, and GS-US-236-0123 is consistent with the safety profile of stribild in TN patients through week 48[37]. The most frequently reported AEs to stribild in clinical studies of virologically-suppressed patients were nausea (3% in study GS-US-236-0115 and 5% in study GS-US-236-0121) and fatigue (6% in study GS-US-236-0123). NPSAEs considered as least possibly related to EVG/FTC/TDF/COBI are listed in table 1 as very common, common, and uncommon[40]. For EVG/FTC/TAF/COBI (genvoya), assessment of adverse reactions is based on safety data from across all Phases 2 and 3 studies in which 2,396 patients received genvoya. The most frequently reported adverse reactions in clinical studies through 144 weeks were nausea (11%), diarrhea (7%), and headache (6%) (pooled data from Phase 3 clinical studies GS-US-292-0104 and GS-US-292-0111 in 866

Table 1. Frequencies of NPSAEs described as very common, common, and uncommon of dolutegravir, raltegravir, and elvitegravir in the SmPC[35,37]

NPSAEs	DTG	EVG	RAL
Psychiatric symptoms			
Insomnia	Common	Uncommon	Common
Abnormal dreams	Common	Not specified	Common
Nightmare	Not specified	Not specified	Common
Depression	Common	Uncommon	Common
Suicidality	Uncommon	Uncommon	Uncommon
Neurologic symptoms			
Headaches	Very common	Common	Common
Dizziness	Common	Uncommon	Common
Psychomotor hyperactivity	Not specified	Not specified	Common
Paresthesia	Not specified	Uncommon	Uncommon
Somnolence	Not specified	Uncommon	Uncommon

NPSAEs: Neuropsychiatric adverse events, DTG: Dolutegravir, EVG: Elvitegravir (stribild), RAL: Raltegravir, frequencies are defined as very common (≥ 1/10), common (≥ 1/100-< 1/10), uncommon (≥ 1/1,000-< 1/100), rare (≥ 1/10,000-< 1/1,000), very rare (< 1/10,000). SmPC: Summary of product characteristics.

treatment-naïve adult patients receiving genvoya). NPSAEs considered as least possibly related to EVG/FTC/TAF/COBI were considered as common and uncommon[41]. The SmPC of BIC is not yet available.

Randomized clinical trials

FDA conducted a meta-analysis of randomized, active-controlled Phase 3 trials in TN subjects comparing RAL, DTG, or EVG to: EFV, PIs (ATV, or darunavir [DRV])[42]. These trials were submitted by industry to FDA for support and approval of the INSTIs (STARMARK, SINGLE, FLAMINGO, SPRING 2, GS-US-236-0102, and GS-US-236-0103). Design details for each studies have been previously described[10-13,43,44]. The frequency of NPSAEs in each treatment group was assessed over 96 weeks. NPSAEs were identified using the Standardized MedDRA Query (SMQ) Version 18.0. A broad search in terms of depression and suicide/self-injury (DSS) SMQ and psychosis and psychotic disorders (PPD) SMQ was done. The event of highest toxicity grade was counted for each subject. The meta-analysis shows that the risk of NPSAEs in TN patients was similar for INSTIs versus EFV and INSTIs versus PIs. The risk difference (95% confidence interval [CI]) for DSS AEs and PPD AEs was: INSTIs versus EFV −3% (−5.0) and −1% (−2.1) and INSTIs versus PIs −1% (−2.4) and 0% (−2.1). Grade 3 and 4 events occurred in 1% of INSTIs and PIs subjects and 2% of EFV subjects. Subgroup analysis was not interpretable due to small sample size (Table 2). It is important to note that in two others randomized studies using INSTIs (once mark, ACTG 5257) rates of NPSAES were low[8,9].

Quercia et al.[45] analyzed safety data from Phase III/3b DTG trials involving treatment-naive patients to establish a clearer understanding of the frequency of NPSAEs: anxiety, depression (depression, bipolar depression, suicidal thoughts, and hypomania), insomnia, and nightmares, or abnormal dreams[45]. There were 4 studies included in the analysis: the 96 weeks SPRING-2, SINGLE and, FLAMINGO trials, and the 48-week all-women ARIA trial[10-13]. A total of 2634 participants were recruited into the 4 studies, 1315 of whom were treated with DTG. Low rates of NPSAEs were seen in all studies treatment arm, with most being mild or moderate (Grade 1-2). However, a higher incidence was observed in the SINGLE study compared to other trials, with 17% of DTG recipients reporting insomnia, 10% nightmares or abnormal dreams, 8% depression, and 7% anxiety. These rates were lower than those seen among patients taking the comparator drug, EFV (Table 3). Rates of NPSAEs leading to the withdrawal of treatment were below 5% in all trials. Depression led to the cessation of DTG therapy in 1 patient, with 6 RAL-treated, and 7 EFV-treated individuals stopping treatment because of this AE. Furthermore, 2 patients stopped taking DTG because of insomnia while 3 EFV-treated patients stopped treatment for this reason. Abnormal dreams or nightmares caused 2 DTG and 7 EFV patients to cease therapy. There were no cases of withdrawal of DTG because of anxiety, although 4 patients stopped EFV for this reason (Table 3). Fettiplace et al. in their review[46] completed the analysis of Quercia et al., four randomized studies in naive patient[45], including expe-

Table 2. FDA meta-analysis comparing NPSAEs of INSTI versus PI or EFV based on randomized, active-controlled Phase 3 trials submitted by industry to FDA to support approval of the INSTIs[38]

Pooled NPSAEs (all grade, all causes (n, %)	INSTI versus PI			INSTI versus EFV		
	INSTI (n=2447)	PI (n=597)	Risk difference (95% CI)	INSTI (n=2447)	EFV (n=1053)	Risk difference (95% CI)
Depression	174 (7.1%)	51 (8.5%)	−1.4% (−3.9%, 1%)	174 (7.1%)	101 (9.6%)	−2.5% (−4.5%, −0.5%)
Sleep disorders	10 (0.4%)	0	0.4% (0.2%, 0.7%)	10 (0.4%)	12 (1.1%)	−0.7% (−1.4%, 0%)
Suicidal thoughts and behaviors	14 (0.6%)	1 (0.2)	0.4 (0%, 0.8%)	14 (0.6%)	2 (0.2%)	0.4% (0%, 0.8%)
Memory impairment	13 (0.5%)	5 (0.8%)	−0.3 (−1.1%, 0.5%)	13 (0.5%)	3 (0.3%)	0.2% (−0.2%, 0.7%)

FDA: Food Drug and Administration; INSTI: integrase strand transfer inhibitors; PI: protease inhibitors; EFV: efavirenz; NPSAEs: neuropsychiatric adverse events; CI: confidence interval.

rienced treated patient from SAILING[14] concluded that insomnia was the most commonly reported NPSAEs. They draw the same conclusions in regard to NPSAEs.

Recent data of two Phase III randomized clinical trials involving naive patient treated with DTG and BIC have been published[15,16]. The first study was a comparison between DTG/ABC/3TC and BIC/FTC/TAF in single tablet[15]. Comparing BIC/FTC/TAF to DTG/ABC/3TC, the most common AEs were diarrhea (13%, 13%), headaches (11%, 14%), and nausea (10%, 23%). Nausea was significantly more frequent in the DTG arm. AEs leading to study drug discontinuation were uncommon and occurred in four (1%) participants in the DTG arm due to nausea and generalized rash (n = 1), thrombocytopenia (n = 1), chronic pancreatitis, steatorrhea (n = 1), and depression (n = 1), all of which were deemed by the investigator to be related to study drugs. Overall, NPSAEs were equally distributed between treatment groups, 14/314 (4%) of patient experienced insomnia in BIC arm versus 20/325 (6%) in DTG arm. During the study, patients tended to use more medication to sleep in DTG arm[15].

The second study was a comparison between BIC/FTC/TAF in single tablet versus DTG plus FTC/TAF. The most frequent AEs (BIC vs. DTG) were headaches (12.5/12.3%), diarrhea (11.8/12.0%), and nausea (7.8/9.5%). Comparing BIC to DTG, NPSAEs reported were insomnia (6 vs. 1), dizziness (6 vs. 2), depressed mood (3 vs. 0), drowsiness (2 vs. 2), sleep disorders (2 vs. 0), and abnormal dreams (1 vs. 2). AEs leading to study drug discontinuation were uncommon, occurring in five (2%) of 320 participants in the BIC arm, and one (<1%) of 325 in the DTG arm. No individual AEs leading to study drug discontinuation occurred in more than one participant. AEs led to five participants in the BIC arm discontinuing study medication (cardiac arrest [n = 1], paranoia [n = 1], chest pain [n = 1], abdominal distension [n = 1], and sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia [n = 1]); all except for the events of cardiac arrest and paranoia were considered by the investigators to be related to study drugs. AEs leading to study drug discontinuation in the DTG arm included erythema and pruritus (n = 1 had both events); neither event was considered related to study drugs[16].

Switch studies have also been published with DTG. In Phase III SWORD 1 and 2 studies, an open-label switch to DTG (50 mg) plus RPV (25 mg) once daily was not inferior at week 48 versus continued three- or four-drug ART, with efficiency rates of 95% in both arms[47]. As might be expected with a switch regimen including one or two new drugs administered to all participants, slightly more AEs leading to discontinuation occurred with DTG plus RPV than with the continued three- or four-drug ART (3% vs. 1%, respectively), with 2% on DTG plus RPV discontinuing because of NPSAEs (anxiety [4], depression [3], insomnia [2], depressed mood [2] headache [1], and suicidal ideation [1]). In the Phase III STRIIVING study, 551 experienced patients were randomized to switch from a variety of ART regimens to the single-tablet regimen (STR) Triumeq or remain in their prior regimen. 10 patients (4%) in the switch arm discontinued because of AEs versus none in the continuation arm[48].

Table 3. NPSAEs in 4 randomized phase 3b clinical trial were DTG compared to PI (DRV/r or ATV/r), RAL or EFV[41]

Cases, n (%)	SPRING-2 (96 weeks)		FLAMINGO (96 weeks)		SINGLE* (144 weeks)		ARIA (48 weeks)	
	DTG (n=411)	RAL (n=411)	DTG (n=242)	DRV/r (n=242)	DTG (n=414)	EFV (n=419)	DTG (n=248)	ATV/r (n=247)
Insomnia								
Overall	25 (6)	20 (5)	20 (8)	16 (7)	71 (17)	52 (12)	10 (4)	8 (3)
Drug-related	6/25 (24)	3/20 (15)	4/20 (20)	5/16 (31)	43/71 (61)	28/52 (54)	5/10 (50)	1/8 (13)
Severe/grade 3/4	0	0	0	0	3/71 (4)	0	1/10 (10)	0
Led to withdrawal	0	0	0	0	1/71 (1)	4/52 (8)	1/10 (10)	0
Anxiety								
Overall	17 (4)	23 (6)	13 (5)	9 (4)	28 (7)	30 (7)	5 (2)	8 (3)
Drug-related	1/17 (6)	2/23 (9)	1/13 (8)	0	4/28 (14)	11/30 (37)	0	1/8 (13)
Severe/grade 3/4	1/17 (6)	0	0	0	0	3/30 (10)	0	2/8 (25)
Led to withdrawal	0	0	0	0	0	4/30 (13)	0	0
Depression								
Overall	29 (7)	21 (5)	16 (7)	12 (5)	35 (8)	44 (11)	9 (4)	11 (4)
Drug-related	1/29 (3)	2/21 (10)	0	0	13/35 (37)	19/44 (43)	1/9 (11)	1/11 (9)
Severe/grade 3/4	1/29 (3)	1/21 (5)	3/16 (19%)	1/12 (8)	5/35 (14)	8/44 (18)	0	1/11 (9)
Led to withdrawal	0	0	0	0	1/35 (3)	6/44 (14)	0	0
Suicidality								
Overall	4 (<1)	6 (1)	4 (2)	1 (<1)	3 (<1)	7 (2)	3 (1)	4 (2)
Drug-related	0	0	1/4 (25)	0	0	4/7 (57)	1/3 (33)	0
Severe/grade 3/4	3/4 (75)	5/6 (83)	3/4 (75)	0	2/3 (67)	5/7 (71)	0	1/4 (25)
Led to withdrawal	0	2/6 (33)	1/4 (25)	0	0	1/7 (14)	0	0

PI: protease inhibitors; DTG: dolutegravir; RAL: raltegravir; EFV: efavirenz; DRV/r: darunavir boosted by ritonavir; ATV/r: atazanavir boosted by ritonavir.

Real life cohorts studies, a german cohort

Hoffmann et al.[32] performed a retrospective analysis using anonymized data for all HIV-infected patients under routine clinical care in two large German HIV treatment centers, who initiated an INSTI-based therapy between January 2007 and April 2016. They compared discontinuation rates because of AEs within 2 years of starting treatment with DTG, RAL, or EVG/COBI and also evaluated factors associated with DTG discontinuation. A total of 1950 INSTI-based therapies were initiated in 1704 patients eligible for analysis within the observation period. 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 INSTIs as first-line therapy was higher for EVG (23%) and DTG (21%), compared with RAL (13%). Among treatment-experienced patients, the proportion of patients switching their regimen to an INSTI therapy because of NPSAEs (almost exclusively caused by EFV) was similar for RAL (9%) and DTG (8%) but higher for EVG (23%). In total, an AE leading to discontinuation was observed in 122 of 1950 INSTIs 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 EVG (n = 287), 7.6% and 9.3% for DTG (n = 985), and 3.3% and 3.9% for RAL (n = 578).

Discontinuation rates were the highest for EVG (as Stribild©), mainly because of renal AEs, probably attributable to TDF/COBI. NPSAEs leading to discontinuation were reported more frequently with DTG. The estimated rates of NPSAEs leading to discontinuation within 12 and 24 months were 5.6% and 6.7% for DTG, 0.7% and 1.5% for EVG, and 1.9% and 2.3% for RAL, respectively (Table 4). NPSAEs leading to discontinuation among 49 of 985 patients started on DTG were further analyzed. The median time between the beginning of DTG and discontinuation was 3.1 months and 38 of 49 (78%) patients had stopped DTG 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 DTG. In 32 of 37 (86%) patients followed for at least 3 months after DTG discontinuation, the subsequent antiretroviral regime was tolerated and effective. In six patients who had interrupted DTG, NPSAEs recurred in all six cases on re-exposure. It is to be noted that, three of these patients were also simultaneously re-exposed to ABC. In the multivariate Cox regression model, female gender, age > 60 years, simultaneous initiation of ABC, and DTG initiation in 2016 remained significantly associated with DTG discontinuation. These associations remained consistent when patients starting DTG in 2016 were excluded. There was no association between DTG discontinuation and treatment center, ethnicity, treatment line (first-line vs. treatment-experienced), prior regimen, reason for switch, or CD4 T-cell count.

A spanish cohort

This is a retrospective, Penafiel et al.,[33] analysis of a prospectively followed cohort including all antiretroviral-naive and all virologically suppressed antiretroviral-experienced patients prescribed a first regimen containing RAL, EVG, or DTG with at least one follow-up visit. Major outcomes were early discontinuation (1 year) due to any reason and more specifically due to toxicity. Incidence was calculated as a number of episodes per 1000 person-years. There were 557 patients treated with RAL, 322 patients treated with EVG, and 212 patients treated with DTG meeting criteria for inclusion in this analysis. Patients treated with RAL were also treated with emtricitabine (FTC)/TDF disoproxil fumarate (TDF) (n=390, 70%), lamivudine (3TC)/abacavir (n = 139, 25%), or with other agents (n = 28, 5%). All patients treated with EVG in this cohort had received it as the STR containing EVG/COBI/FTC/TDF. Patients treated with DTG were taking it either as the STR containing DTG/3TC/ABC (n = 93, 44%) or as individual DTG tablets together with other antiretroviral agents (n = 119, 56%); 36 of those taking individual DTG tablets were also taking the fixed-dose combination 3TC/ABC. There was a trend to a lower incidence of early discontinuation for any reason with EVG (168 episodes per 1000 patient-years [PY]) than with RAL (271 episodes per 1000 PY) or with DTG (264 episodes per 1000 PY) ($p < 0.0821$). The incidence of early discontinuation not attributed to toxicity was lower in patients taking EVG (64 episodes per 1000 PY) than in patients taking RAL (191 episodes per 1000 PY) or DTG (182 episodes per 1000 PY) ($p < 0.0003$). The incidence of overall early discontinuation not due to toxicity was not significantly different between antiretroviral-naive (137 episodes per 1000 PY) and antiretroviral-experienced patients with undetectable viral load (180 episodes per 1000 PY) ($p < 0.2508$). Although the incidence of early discontinuation due to AEs was the highest for EVG and the lowest for RAL, there were no significant differences among the three drugs. The rate of early DTG discontinuation due to AEs was double when DTG was combined with 3TC/ABC than when it was not, although this difference was not significant. Overall, the incidence of early discontinuation due to AEs was higher in naive (103 episodes per 1000 PY) than inexperienced (48 episodes per 1000 PY) patients ($p < 0.0308$). The most common AEs were NPSAEs (n = 17), followed by osteomuscular (n = 12) and digestive (n = 12). NPSAEs and systemic effects were significantly more common with DTG than with RAL or EVG. Almost all patients discontinuing DTG due to toxicity had experienced NPSAEs (n = 7, 88%) in contrast to those discontinuing RAL (n = 7, 35%) or EVG (n = 3, 19%) due to toxicity ($p < 0.0046$) (Table 4). Clinical manifestations of NPSAEs leading to early discontinuation, as reported in the medical database, were heterogeneous but did not substantially differ among INSTIs. The most common clinical NPSAEs leading to early discontinuation were insomnia (n = 5 in DTG), dizziness, or headaches (Table 4).

PICSIS cohort

Llibre et al.[34] reported their experience of discontinuation of DTG, EVG/COBI, and RAL due to toxicity in a prospective cohort. The PISCIS Cohort is an ongoing observational cohort that includes about 21000 HIV-infected patients aged ≥ 16 years from 10 hospitals in Catalonia and 2 in the Balearic Islands (Spain). All subjects having started one of these 5 regimens including DTG with ABC/3TC or TDF/FTC (Regimens A and B, respectively), RAL with ABC/3TC (C) or TDF/FTC (D), or the coformulation EVG/COBI/TDF/FTC (E) since July 2013 as their initial regimen or a switch with plasma HIV-1 RNA < 50 copies/mL were included. The incidence rate and 95% confidence interval (IR [95% CI]) of discontinuation due to toxicity is estimated as the ratio of the number of discontinuation by 100 pa-

tients/year of follow-up. Out of 13066 patients on follow-up in July 2016, 2096 subjects were included (90% naives), receiving Regimens A (n = 859), B (n = 108), C (n = 208), D (n = 280), and E (n = 641). Out of them, 430 stopped prematurely their regimen, and 74 due to AEs. The corresponding IR (95% CI) for DTG, RAL and EVG/COBI were 5.1 (3.6-7.0), 3.0 (1.8-4.5), and 2.8 (1.7-4.1), respectively. Among those receiving DTG, the IR with ABC/3TC or TDF/FTC were 4.9 (3.3-6.9) and 6.3 (2.0-12.9), respectively, with no significant differences between them. The aHR of discontinuation due to AEs with DTG versus RAL was 1.1 (0.6-2.1), DTG versus EVG/COBI 1.6 (0.8-2.9), and EVG/COBI versus RAL 0.8 (0.4-1.6). In subjects starting an initial therapy or a switch regimen with an undetectable viral load, there was no significant difference in the discontinuation rates due to AEs among those receiving DTG, RAL, or EVG/COBI. For those receiving DTG, there is no significant difference between those receiving ABC/3TC or TDF/FTC. This prospective analysis showed that there was a significantly higher rate of discontinuation due to NPSAEs with DTG versus either RAL or EVG/COBI. EVG/COBI/TDF/FTC and DTG + TDF/FTC showed lower rates of discontinuation due to NPSAEs. Rates of discontinuation due the AEs were low, but most subjects are discontinuing DTG/ABC/3TC did so due to NPSAEs (Table 4).

OPERA database

The OPERA database and research network (Observational Pharmacoepidemiology Research and Analysis), Hsue et al., is a multi-site observational database built from the complete patient health records managed by an Electronic Health Record systems gathering more than 400 participating caregivers across more than 51 US cities[49]. Using data from the OPERA database, 11539 HIV-positive patients were identified who initiated DTG, EFV, RAL, DRV, EVG, and RPV-based regimens (commonly prescribed anchor drugs) regardless of previous ART treatment from January 1, 2013 (the 1st year DTG was marketed) through August, 2016[49]. Patients exposed to any of the drugs of interest before the observation period were excluded. Patients were observed from the start of these regimens until the first of the following censoring events: discontinuation of the agent of interest, cessation of continuous clinical activity, death, or study end. NPSAEs included diagnoses of the following psychiatric conditions during the observation period: anxiety, depression, insomnia, and suicidality. Discontinuations within 14 days of a NPSAEs were also analyzed. Patients receiving DTG were more likely to have a history of anxiety at baseline than patients receiving EFV, DRV, or RPV (all $p < 0.001$). History of depression was more common in patients receiving DTG than in patients receiving EFV, RPV, or EVG (all $p < 0.0001$). Patients taking DTG were also more likely to have a history of insomnia than patients taking EFV, DRV, RPV, or EVG (all $p < 0.0001$). When considering NPSAEs, depression was the most common for all drugs. Patients prescribed RAL-containing regimens experienced more prevalent depression ($p = 0.006$) and anxiety diagnoses ($p = 0.01$) than patients taking DTG-containing regimens. Patients taking EVG-containing regimens had a higher prevalence of being diagnosed with anxiety ($p = 0.006$) than patients taking DTG. The incidence of new NPSAEs (excluding those with a history of the psychiatric condition) resulted in fewer events for all conditions except suicidality which was rare even without considering history. There was no significant difference in NPSAEs incident between patients receiving DTG and patients receiving any of the other anchor drugs. In summary, DTG use was not associated with an increased risk of NPSAEs or drug discontinuation due to NPSAEs, despite more patients with a history of psychiatric disorders being prescribed DTG treatment. Patients receiving DTG were the least likely to experience a discontinuation within 14 days of a prevalent NPSAEs (DTG: 0.8%; EFV: 3.0%, $p < 0.0001$; RAL: 3.7%, $p < 0.0001$; DRV: 2.0%, $p = 0.0009$; RPV: 1.5%, $p = 0.04$; EVG: 1.2%, $p = 0.1$), or an incident NPSAEs (DTG: 0.3%; EFV: 2.2%, $p < 0.0001$; RAL: 1.7%, $p < 0.0001$; DRV: 1.0%, $p = 0.006$; RPV: 1.0%, $p = 0.006$; EVG: 0.8%, $p = 0.04$).

Others cohorts studies

Lepik et al.[50] reported their postmarketing experience of adverse drug reactions associated with INSTIs. This observational study compares Aes reported with RAL, EVG/COBI (in a fixed-dose combination) and DTG during routine clinical use in British Columbia Canada initiated as a component of the antiretroviral regimen between January 1st, 2012 and December 31, 2014. The primary outcome was any AEs resulting in INSTIs discontinuation, excluding suspected AEs with causality classification assessed as "unlikely." In this large cohort of 1467 naive and experienced treated HIV-patients (DTG = 519, EVG = 395, and RAL = 553), the overall proportion of AEs leading to discontinuation was greater in patients on EVG/COBI 26/301 (8.64%) versus RAL

24/522 (4.60%), and DTG 9/299 (3.01%). However, the proportion of NPSAEs was greater in patients on DTG than the other two INSTIs by around 2.7%[46].

Fettiplace et al.[46] reported spontaneously postmarketing cases of NPSAEs in patients treated with either DTG or ABC/3TC/DTG which were identified from the ViiV Healthcare Global Safety Database (OASIS, based on Oracle Argus Safety 2013; Oracle Corporation, Redwood Shores, CA) through February 29, 2016. The same MedDRA preferred terms applied to the clinical trial data were used, and cases were grouped into 4 NPSAEs (insomnia, anxiety, depression, and suicidality) for analysis. The time to outcome (TTO) for the event, drug action taken, and event outcome were examined for cases in which this information was available. For patients with depression or suicidality, a case review was performed to assess characteristics such as history of depression/suicidality and presence of other ongoing risk factors. Because it is not possible to estimate the true incidence of an event from spontaneous data, reporting rates were calculated for the 4 NPSAEs using estimated exposure to DTG and ABC/3TC/DTG sales data, which provide an indication of reporting frequencies. Rates were calculated as the number of spontaneously reported cases during an estimated 124,737 PY of exposure to DTG and 62,045 PY of exposure to ABC/3TC/DTG and are expressed as the number of cases per 1000 PY. Most spontaneously reported cases were reported by health-care providers (> 85%). Reporting rates for all NPSAEs in patients treated with DTG or ABC/3TC/DTG were 3.09 and 2.79/1000 PY, respectively. Reporting rates for the 4 specific NPSAEs were low and comparable between DTG and ABC/3TC/DTG with insomnia being the most commonly reported (approximately 1 event per 1000 PY for both DTG and ABC/3TC/DTG). Cases of suicidality were reported at 0.25 cases per 1000 PY. The TTO was reported for approximately one-third of patients with insomnia, anxiety, and depression and was generally < 28 days after starting treatment with DTG or ABC/3TC/DTG, although TTO for depression with DTG was typically > 28 days. Action taken with the drug was reported in 71-80% of cases for all 4 NPSAEs and was most often discontinuation (60-93%), where event outcome was available (39-60% of cases), the majority resolved or improved.

Bonfanti et al.[51] reported discontinuation of DTG due to AEs in a cohort of 295 patients from the frame of surveillance cohort long-term toxicity antiretrovirals/antivirals project, an online reporting system for adverse reactions to antiretroviral drugs, designed by the Italian coordination for the study of allergy and HIV infection group. In this observational cohort, 32 patients (10.8%) withdrew their DTG-containing regimen. 16 patients (5.4% of patients and 50% of those who stopped their treatment) interrupted DTG because of an AE. The AEs list included one hypersensitivity reaction in a patient on ABC/3TC/DTG, two cases of muscle-skeletal pain and two of abdominal pain, renal impairment in three patients, vomiting (one) and diarrhea (one), one liver enzymes increase, two skin rash, one ischemic ictus, and two NPSAEs (one drowsiness and one headache). Median time to interruption due to an AE was 180 days (IQR 106-353). The overall rate of discontinuation of DTG due to NPSAEs was 1%.

Menard et al.[35] performed a retrospective analysis in patients who had initiated DTG between January 1, 2014, and November 30,2016, monitored in the infectious diseases unit in public hospitals of Marseille, Southeastern France. A total of 517 DTG-based ART were initiated during the observation period, and 55 AEs (10.6%) led to their discontinuation, with 28 (51%) of these AEs being NPSAEs (overall rate 5, 4%). Irritability and sleep disturbances were the most frequently observed NPSAEs. They did not observe any association between ABC administration and NPSAEs. In multivariate analysis, they found that women with NPSAEs were significantly older (median age, 51 years; range, 44-66) than women who discontinued DTG because of non-NPSAEs (p = 0.03).

Does the backbone matter (ABC vs. TDF or TAF)

There have been a debate about the fact that when DTG is associated to ABC, patients discontinue more their ART due to side effect especially NPSAEs. Two Phase III randomized clinical trials used either ABC/3TC or FTC/TDF with DTG in the same study. The FLAMINGO and SPRING 2 trial[11,12]. In the Flamingo[12], the most common drug-related AEs were diarrhea (23/242 [10%] in the DTG group vs. 57/242 [24%] in the DRV plus ritonavir group), nausea (31/242 [13%] vs. 34/242 [14%]), and headaches (17/242 [7%] vs. 12/242 [5%]). More patients in the DRV plus ritonavir group than in the DTG group discontinued because of AEs (15/242 [6%] vs. 7/242 [3%]). No differences were seen between ABC/3TC and FTC/TDF plus DTG. However, from the baseline to 48 weeks, three patients in the DTG group attempted suicide (ABC/3TC = 1, FTC/TDF = 2) with one of these events considered possibly related to the study drug (ABC/3TC); no suicide attempts

Table 4. Major cohort studies published in 2017 comparing NPSAES of DTG to EVG or RAL[22,24]

NPSAEs	Hoffmann et al (German cohort) Drug exposure			Penafiel et al (Spanish cohort) Drug exposure			LLibre et al (PICSIS cohort) Drug exposure		
n (%)	DTG (985)	RAL (678)	EVG (287)	DTG (212)	RAL (557)	EVG (322)	DTG (873)	RAL (566)	EVG (582)
All aes (%)	6.8 (67)	4.1 (28)	9.4 (27)	3.8 (8)	3.6 (20)	5 (16)	3 (26)	5.1 (29)	3.4 (20)
Neuropsychiatric side effect	5.0 (49)	2.1 (14)	1.0 (3)	3.3 (7)	1.2 (7)	0.9 (3)	2.1 (17)	1.6 (9)	0.7 (4)
Insomnia, sleep disturbance	3.6 (36)	0.6 (4)	0.7 (2)	3.3 (7)	0.8 (5)	1.2 (4)	NA	NA	NA
Poor concentration, slow thinking	0.8 (8)	0	0	NA	NA	NA	NA	NA	NA
Dizziness	1.3 (13)	0.4 (3)	0.3 (1)	0.9 (2)	0.5 (3)	0.3 (1)	NA	NA	NA
Headache, paresthesia	1.6 (16)	0.8 (6)	0.3 (1)	1.4 (3)	0.5 (3)	0.3 (1)	NA	NA	NA
Depression	0.7 (7)	0.1 (1)	0	NA	NA				

NPSAEs: neuropsychiatric adverses events; DTG: dolutegravir; RAL: raltegravir; EVG: elvitegravir; NA: not available.

occurred in the DRV plus ritonavir group. All of these patients had a history of suicidal ideation, a fourth participant in the DTG group died by committing suicide after 48 weeks (FTC/TDF). This patient had a history of previous suicide attempt and bipolar depression. In SPRING 2 trial[11], there was a low occurrence of AEs leading to discontinuation in both groups (10 patients [2%] in each group). The most common clinical AEs were nausea (DTG 15% and RAL 14%), nasopharyngitis (13% and 14%), diarrhea (14% and 13%), and headaches (14% and 13%); however, specific data on NPSAEs for patient on ABC/3TC versus TDF/FTC plus DTG were not available, but there was no difference in term of AEs leading to discontinuation between ABC/3TC plus DTG or FTC/TDF plus DTG. In Phase 3 of two randomized trials comparing BIC to DTG, DTG was combined to ABC/3TC [15] in one trial and FTC/TAF in another[16]. Rates of NPSAEs were comparable in the two trials for DTG arm irrespective of the backbone, headache (14%/12.3%) and insomnia (6.5%/5%) for ABC/3TC versus FTC/TAF respectively. In cohorts studies, some have shown that the risk of discontinuation due to NPSAEs was higher in DTG arm when combined with ABC/3TC[30,32,34,37]. Cid-silva shows that the discontinuations rates due to NPSAEs were significantly higher among patients receiving DTG compared with those on EVG/COBI (6.9% vs. 1.5%). Thus, a patient under a DTG-based regimen had 5.9 times more risk of discontinuation due to a NPSAEs than a patient receiving EVG/COBI, especially if DTG was administered in combination with ABC/3TC. The most frequent patterns of NPSAEs were abnormal dreams, mood changes, sleep disturbances, anxiety, depression, and suicidal ideation. All of them quickly disappeared after discontinuation of DTG[37]. Boer *et al.* found that DTG was switched more frequently in regimens that include ABC[30]. However, others cohorts[35,51] did not find the same association with ABC.

In our opinion, it is not possible now to draw definitive conclusions, in regard to this debate.

What can be the mechanism and risk factors behind this NPSAEs or central nervous system (CNS)

The mechanisms leading to NPSAEs induced by integrase inhibitors especially DTG are not yet understood. Probably it is multifactorial. It must be highlighted that most antiretrovirals have a well-described toxicity in the peripheral nervous system while little is known of their toxicity profile on CNS neurons[52].

Some *in vitro* data (immortalized cell lines and peripheral dorsal root ganglia neurons) showed the potential for antiretrovirals to produce neuronal damage: using primary cultures of rat forebrain, Robertson et al.[53-55] showed that several antiretrovirals achieved toxic concentrations in the CSF without any additive effect. Hinckley et al.[56] screened 10 ART drugs (ABC, ATV, COBI, DRV, DTG, EFV, EVG, RPV, RTV, and TDF) and generated a neurotoxicity profile based on mitochondrial membrane potential, reactive oxygen species, cell health, and neurite growth. The majority of tested drugs demonstrated neurotoxicity: 7 caused mitochondrial toxicity and 3 affected neurite growth. DTG and EFV resulted in minor but significant neurite growth. In clinical studies, however, despite coincidence of a common NPSAEs profile between EFV and DTG, studies switching from EFV to DTG in virologically suppressed patients with ongoing efavirenz-associated NPSAEs was associated with significant improvement in NPSAEs, with a reduction in overall CNS score and improvement in depression, dizziness and quality of sleep, without affecting antiretroviral efficacy. These data showed that the mechanism beyond CNS toxicity can involve different and multiple pathways depending on the drug[57,58]. It is to be noted that neurite outgrowth or inhibition could contribute to CNS pathology[56]. Drug penetration in CNS depends on multiple factors such as plasma concentration, drug-drug interactions, inflammation, advanced age, drugs characteristics, transporters, and pharmacogenetic[52]. In older patients, the absorption of drugs by the CNS may be affected by the reduced blood efflux, a permissive blood-brain barrier, and altered CSF flow.

Older age has been found to be a risk factor for NPSAEs induced by DTG in some cohorts studies[32,33,35,51] but not in all cohorts[34,37]. Elliot et al.[59] studied whether DTG exposure at 50 mg once a day correlated with sleep problems in the elderlies versus the younger individuals. The analysis involved people aged 60 or over switching from a suppressive antiretroviral regimen to coformulated ABC/3TC/DTG (Triumeq). DTG area under the curve (AUC) and trough concentration (Ctrough) did not differ significantly between the older group and younger control group (geometric mean [GM] 51,799 vs. 48,068 ng*h/mL, p = 0.56, for AUC; GM 1052 vs. 942 ng/mL, p = 0.77, for Ctrough). However, DTG Cmax was significantly higher in older people than in the younger control group (GM 4246 vs. 3402 ng/mL) (p = 0.00496). 28 days after the switch to Triumeq, global scores and individual domains on the Pittsburgh sleep quality index (PSQI) did not differ significantly from prestwich measures in people 60 and over. However, higher DTG Cmax and AUC were associated with shortened sleep on the PSQI (p = 0.05 and p = 0.03). Yagura et al.[60] examined the association between DTG plasma trough concentration and NPSAEs in 162 Japanese HIV-1-infected patients who had undergone antiretroviral treatment, including DTG treatment. DTG plasma trough concentration was measured, and the association between DTG concentration and NPSAEs was statistically analyzed within 6 months of DTG introduction. At least one of the following NPSAEs was observed in 41 patients (25%), these included dizziness (14/41, 34%), headaches (11/41, 27%), insomnia (11/41, 27%), restlessness (4/41, 10%), and anxiety (3/41, 7%). Patients with NPSAEs showed higher trough DTG plasma concentrations compared with subjects without symptoms (median, 1.34 µg/mL vs. 1.03 µg/mL, p = 0.003 by univariate Mann-Whitney U-test). A positive correlation was observed between DTG concentrations and the frequency of NPSAEs (p = 0.002 by Cochran-Armitage test). No significant difference in DTG concentration was observed among NPSAEs (p = 0.56 by Kruskal-Wallis test). Menard et al. also found that a supratherapeutic DTG Ctrough and greater median value of 1340 ng/ml found by Yagura et al.[56] and was significantly higher in patients with than without NPSAEs which suggested a relationship between DTG exposure and toxicity[35]. The difference between these studies is probably the profile of patients recruited and the study design; for example, Japanese patient has different genetic background such as cytochrome, drug transporters, and low BMI[52]. Menard et al.[35] reported in their study, among male patients who discontinued DTG because of AEs, that the BMI was significantly higher in those with NPSAEs than non-NPSAEs (24 vs. 20; p = 0.03).

Other risk factors such as being a female and having a history of a psychiatric condition have been described. Hoffmann et al.[32] described high rates of discontinuation due to NPSAEs in women (3 fold). Other cohorts studies did not find this correlation[33,34,37]. Randomized Phase III clinical trials using INSTIs[7-16] did not find this correlation. It can be argued that there was a small percentage of women in these randomized trials. However, the ARIA study – which evaluated the efficiency of ABC/3TC/DTG compared to TDF/FTC in combination with ATV/ritonavir in women (n = 495) – did not observe higher rates of discontinuation due to NPSAEs related to DTG in women[13].

Patients with a history of psychiatric conditions were also at a higher risk. In randomized clinical trials, among DTG-treated patients who experienced NPSAEs, few were considered of grade 3-4 intensity or reported as serious, and most DTG-treated patients (95%) who experienced suicidality had a history of psychiatric conditions[10-16]. Fettiplace et al.[46] reported that the NPSAEs with the highest incidence in clinical trials were also the most common in spontaneously reported cases. Most insomnia, anxiety, and depression cases were not serious. The serious cases of depression and suicidality shared similar characteristics to those observed in clinical trials including a history of depression or other NPSAEs in 80% of cases for which this information was reported.

Conclusions and perspectives

INSTIs are a major antiretroviral class in the HIV treatment armamentarium[3]. They are very effective, convenient, and well tolerated[7-16,43,44]. DTG and BIC are second-generation orale INSTI, actually, DTG is the only with FDA approval (2013). Approval process of BIC by FDA is ongoing. BIC is also approved by FDA in February 2018.

They have potential advantages in comparison to first-generation INSTIs, including unboosted daily dosing, limited cross-resistance with RAL and EVG, and a high barrier to resistance; the INSTIs are associated with very few AEs and low rates of discontinuation due to AEs[26,27]. In two meta-analysis and systematic reviews[26,27] the mean odds ratio for AEs or discontinuation due to AEs were very low and did not differ between drugs. In RCTs[10-16] in treatment-naïve patients, all AEs attributed to DTG led to drug cessation in 1.2-2.5% of patients within the 1st year, on the contrary in real-life cohorts study[32-37] the estimated overall discontinuation rate because of any AEs was around 4-10% within the 1st year of initiation. The reasons for the conflicting results observed between trials and some cohorts remains 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. Clinical trials are, however, designed to provide evidence of efficiency and safety under ideal conditions. Although a large amount of a product's efficiency and safety is gathered during clinical development, it is not possible to fully describe the safety profile of a product in pre-marketing clinical trials. Postmarketing studies are the only source of information that allows the assessment of the real-life efficiency and safety of a new drug[61]. It is well known that patients participating in RCTs are highly selected and may differ substantially from the broader population treated in different clinical settings, as a consequence of explicit exclusion criteria and subtle recruitment biases. Predefined criteria for studying drugs may discourage premature discontinuation in cases of mild to moderate AEs. Nevertheless, concerning NPSAEs, by far the most common reason for discontinuation of DTG was NPSAEs, which occurred less frequently in patients on RAL or EVG (as Stribild©). The mechanism behind these NPSAEs remains misunderstood and is probably multifactorial. Efforts need to be made to understand the potential mechanisms leading to these NPSAEs. Clinicians should remember that patients can complain about these NPSAEs in daily practice, classically they are mild to moderate in the majority of cases, not life-threatening except in patients with a history of severe psychiatric conditions. In Cohort studies, the median time of discontinuation of DTG due NPSAEs was 3 or 6 months[32,37]. When these symptoms worsen the quality of life of the patient, clinicians should stop DTG and change to other drugs or INSTIs and maintain follow-up because other INSTIs or ARV drugs can also lead to NPSAEs although in lesser proportions. If the choice is to switch, most symptoms disappear quickly after discontinuation of DTG. But before stopping any medications, other causes of NPSAEs should be excluded (alcohol abuse, recreative drug, and drug-drug interaction). NPSAEs are substantially more frequent among people living with HIV (PLWHIV) (anxiety 28%, depression up to 48%, and insomnia 29-73%) compared with the general population (anxiety 7.3%, depression 5-10%, and insomnia 3.6-18%)[25,62]. Despite these AEs (mild to moderate), INSTIs especially DTG are very good antiretroviral that improves our arsenal in treating HIV-infected patients and are recommended by all international guidelines as first-line therapy of cART[3,18,19].

Conflict of interest

Dr. Jean Cyr Yombi has nothing to disclose.

References

1. Grinsztejn B, Coelho LE, Luz PM, Veloso VG. Towards an ideal antiretroviral regimen for the global HIV epidemic. J Virus Erad. 2017;3:111-6.
2. 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.
3. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the international antiviral society-USA panel. JAMA. 2016;316:191-210.

4. Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. Clin Infect Dis. 2014;59:265-71.
5. Gu WG. Newly approved integrase inhibitors for clinical treatment of AIDS. Biomed Pharmacother. 2014;68:917-21.
6. Gallant JE, Thompson M, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics of bictegravir as 10-day monotherapy in HIV-1-infected adults. J Acquir Immune Defic Syndr. 2017;75:61-6.
7. Blanco JL, Whitlock G, Milinkovic A, Moyle G. HIV integrase inhibitors: a new era in the treatment of HIV. Expert Opin Pharmacother. 2015; 16:1313-24.
8. 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.
9. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med. 2014;161:461-71.
10. Walmsley S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. J Acquir Immune Defic Syndr. 2015;70:515-9.
11. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;13:927-35.
12. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV. 2015;2:e127-36.
13. Orrell CH, Belonosova E, Porteiro N, et al. Superior Efficacy of Dolutegravir/Abacavir/Lamivudine (DTG/ABC/3TC) Fixed Dose Combination (FDC) Compared with Ritonavir (RTV) Boosted Atazanavir (ATV) Plus Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) in Treatment-Naive Women with HIV-1 Infection (ARIA Study) Abstract 10215. Durban, South Africa: presented at: 21st International AIDS Conference; 2016. p. 18-22.
14. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382:700-8.
15. Gallant J, Lazzarin A, Mills A, et al. A Phase 3 Randomized Controlled Clinical Trial of Bictegravir in a Fixed Dose Combination, B/F/TAF, vs ABC/DTG/3TC in Treatment-naïve Adults at Week 48. Paris: IAS, Late Breaker Oral Abstract MOAB0105LB; 2017.
16. Sax P, Pozniak A, Arribas J, et al. Phase 3 Randomized, Controlled Clinical Trial of Bictegravir Coformulated with FTC/TAF in a Fixed-dose Combination (B/F/TAF) vs Dolutegravir (DTG) + F/TAF in Treatment-Naïve HIV-1 Positive Adults: week 48 Results. Paris: IAS, Late Breaker Poster Abstract TUPDB0201LB; 2017.
17. Gutierrez Mdel M, Mateo MG, Vidal F, Domingo P. Drug safety profile of integrase strand transfer inhibitors. Expert Opin Drug Saf. 2014; 13:431-45.
18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents; 2015. Available from: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. [Last accessed on 2016 Jun 28].
19. European AIDS Clinical Society (EACS) Guidelines. Version 8.0. 2015. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. [Last accessed on 2016 Feb 15].
20. Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the international antiviral society-USA panel. JAMA. 2014;312:410-25.
21. Policy Brief: consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: what's New; 2015. Available from: http://www.apps.who.int/iris/bitstream/10665/198064/1/9789241509893_eng.pdf. [Last accessed on 2016 Aug 15].
22. Rokas KE, Bookstaver PB, Shamroe CL, et al. Role of raltegravir in HIV-1 management. Ann Pharmacother. 2012;46:578-89.
23. Curtis L, Nichols G, Stainsby C, et al. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naive patients. HIV Clin Trials. 2014;15:199-208.
24. Park TE, Mohamed A, Kalabalik J, Sharma R. Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection. Expert Rev Anti Infect Ther. 2015;13:1195-212.
25. Dubé B, Benton T, Cruess DG, Evans DL. Neuropsychiatric manifestations of HIV infection and AIDS. J Psychiatry Neurosci. 2005;30:237-46.
26. Kanters S, Vitoria M, Doherty M, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016;3:e510-20.
27. Patel DA, Snedecor SJ, Tang WY, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One. 2014;9:e105653.
28. Kheloufi F, Allemand J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. AIDS. 2015;29:1723-5.
29. 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.
30. 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.
31. Waqas S, O'Connor M, Levey C, et al. Experience of dolutegravir in HIV-infected treatment-naive patients from a tertiary care university hospital in ireland. SAGE Open Med. 2016;4:2050312116675813.
32. 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.
33. 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.
34. Llibre JM, Esteve A, Miro JM. Discontinuation of DTG, EVG/c, and RAL due to Toxicity in a Prospective Cohort. Poster 651. Seattle WA (USA): conference on Retroviruses and Opportunistic Infections (CROI); 2017. p. 13-6.
35. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in europe. AIDS. 2017; 31:1201-3.
36. Todd S, Rafferty P, Walker E, et al. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. Int J STD AIDS. 2017;28:1074-81.
37. 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.
38. Isentress 400mg Film-Coated Tablets. Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000860/WC500037405.pdf. [Last accessed on 2018 Jan 18].
39. Tivicay 50mg Film-Coated Tablets. Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002753/WC500160680.pdf. [Last accessed on 2014 Jan 20].
40. Vitekta EU SmPC, March; 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002577/WC500155576.pdf. [Last accessed 2013 Nov 13].
41. Genvoya. Summary of Product Characteristics. 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004042/WC500197861.pdf. [Last accessed on 2015 Nov 19].
42. Viswanathan P, Baro E, Soon G, et al. Neuropsychiatric Adverse Events Associated With Integrase Strand Transfer Inhibitors. Seattle WA (USA): conference on Retroviruses and Opportunistic Infections (CROI); 2017. p. 13-6.
43. Zolopa A, Sax PE, DeJesus E, et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr. 2013;63:96-100.
44. Rockstroh JK, DeJesus E, Henry K, et al. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr. 2013;62:483-6.
45. Quercia R, Roberts J, Murungi A, et al. Psychiatric Adverse Events from the DTG ART-naiive Phase 3 Clinical Trials. HIV Drug Therapy. Glasgow, Abstract; 2016. p. 210, 23-6.
46. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. J Acquir Immune Defic Syndr. 2017; 74:423-31.
47. Llibre JM, Hung CC, Brinson C, et al. Phase III SWORD 1 and 2: switch to DTG + RPV Maintains Virologic Suppression Thorugh 48 wks. CROI, O-4 Abstract 44LB; 2017. p. 13-6.
48. 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.
49. Hsu R, Fusco J, Henegar C, et al. Psychiatric Disorders Observed in HIV + Patients Using 6 Common 3rd Agents in OPERA. Abstract 664. Seattle, Washington, USA: presented at: conference on Retroviruses and Opportunistic Infections; 2017. p. 13-6.
50. Lepik KJ, Nohpal A, Yip B, et al. Adverse Drug Reactions Associated with Integrase Strand Transfer Inhibitors in Clinical Practice: post-marketing Experience with Raltegravir, Elvitegravir-cobicistat and Dolutegravir. Toronto: IAS, Poster Abstract Tupeb; 2015. p. 258.

51. 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.
52. Calcagno A, Di Perri G, Bonora S. Pharmacokinetics and pharmacodynamics of antiretrovirals in the central nervous system. Clin Pharmacokinet. 2014;53:891-906.
53. Cui L, Locatelli L, Xie MY, Sommadossi JP. Effect of nucleoside analogs on neurite regeneration and mitochondrial DNA synthesis in PC-12 cells. J Pharmacol Exp Ther. 1997;280:1228-34.
54. Werth JL, Zhou B, Nutter LM, Thayer SA. 2', 3'-Dideoxycytidine alters calcium buffering in cultured dorsal root ganglion neurons. Mol Pharmacol. 1994;45:1119-2.
55. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. J Neurovirol. 2012;18:388-99.
56. Hinckley S, Sherman S, Best BM. Neurotoxicity Screening of Antiretroviral Drugs With Human iPSC-Derived Neurons. Abstract 395. Boston, Massachusetts: conference on Retroviruses and Opportunistic Infections (CROI); 2016. p. 22-5.
57. Bracchi M, Pagani N, Clarke A, et al. Multicentre open-label pilot study of switching from efavienz to dolutegravir for central nervous system (CNS) toxicity. J Int AIDS Soc. 2016;19 Suppl 7:154-5.
58. Keegan M, Winston A, Higgs C, et al. Tryptophanmetabolism and its relationship with central nervous system toxicity in subjects switching from efavirenz to dolutegravir. J Int AIDS Soc. 2016;19 Suppl 7:153-4.
59. Elliot E, Wang X, Simmons B, et al. Relationship between Dolutegravir Plasma Exposure, Quality of Sleep and its Functional Outcome in Patients Living with HIV over the Age of 60 Years. Abstract O_08. Chicago: 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; 2017. p. 14-7.
60. Yagura H, Watanabe DD, Nakauchi T. Effect of Dolutegravir Plasma Concentration on Central Nervous System side Effects. Abstact 426. Seattle WA(USA): retroviruses and Opportunistic Infections (CROI); 2017. p. 13-6.
61. Sharrar RG, Dieck GS. Monitoring product safety in the postmarketing environment. Ther Adv Drug Saf. 2013;4:211-9.
62. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep 2008;5:163-71.