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Dolutegravir-based combination antiretroviral therapy and central nervous system tolerability: a review of the literature

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ABSTRACT:

— ***Objective:*** Dolutegravir (DTG) is an integrase inhibitor (INI), nowadays widely used for the treatment of antiretroviral-naive and experienced HIV-affected patients, but there are some concerns about the risk of adverse events, especially regarding neuropsychiatric disorders and central nervous system (CNS) affections. We reviewed the safety of DTG in first- and second-line therapy.

— ***Materials and Methods:*** MEDLINE and Web-of-Science have been screened from 2013 until November 2017. Data from literature have been reviewed to identify randomized controlled trials, non-randomized controlled trials, cohort studies and observational studies on DTG-use in clinical practice. We focused our attention on the investigation of psychiatric and CNS-affecting drug-related adverse events (AEs).

— ***Results:*** DTG discontinuations due to AEs resulted to range from 1 and 4% in clinical trials and from 3 to 15% in real-life cohort studies. Among all AEs, CNS symptoms (mostly headache or insomnia) were the most represented, together with gastro-intestinal affections.

— ***Conclusions:*** CNS AEs can still be considered infrequent in patients submitted to DTG containing regimens, but these events become significantly higher when compared to other anti-retroviral regimens. These discontinuation rates should not discourage health-care providers from prescribing DTG-containing regimens, but they certainly should incite them to take into consideration the patient's antiretroviral history or any previous CNS event before the prescription.

— ***Keywords:*** Dolutegravir, Central nervous system, Tolerability, Combination antiretroviral therapy.

INTRODUCTION

Due to their safety and excellent efficacy profile, currently available integrase inhibitors (INIs) are nowadays the favorite regimes anchor drugs for HIV-affected antiretroviral therapy (ART)-naive patients, but they also consistently play a major role in the treatment of ART-experienced subjects[1,2]. Dolutegravir (DTG), a second-generation INI with once-daily dosing, has performed well in clinical trials, proving to have a high genetic barrier to resistance and a very good efficacy in both ART-naïve subjects[3-10] as well as experienced ones[11-13], even when affected by multiclass and/or first-generation INI resistance[14-16]. On the other hand, some safety concerns emerged from observational studies in real life about the risk of adverse events (AEs), especially regarding neuropsychiatric disorders and central nervous system (CNS) affections[17-27]. We reviewed the safety of DTG in first and second-line therapies, both in clinical trials and in real-life cohort studies.

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MATERIALS AND METHODS

MEDLINE and Web-of-Science were screened from January 2013 until November 2017. Data from literature were screened to identify randomized controlled trials, non-randomized controlled trials, cohort studies and observational studies in real life on DTG use in clinical practice. We aimed at investigating psychiatric and CNS-affecting drug-related AEs, comparing those reported in clinical trials, cohort and observational studies with AEs pointed out in real life.

RESULTS

Clinical trials

Results from clinical trials with DTG-based regimen therapies have been resumed in Table 1.

ART-naive patients

SPRING-1 is a phase IIb, 96-week, randomized, partially blinded, dose-ranging study of DTG 10, 25, or 50 mg qd *vs.* efavirenz (EFV) 600 mg qd, both used with a nucleoside reverse transcriptase inhibitor (NRTI) backbone of tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) in patients affected by HIV-1. The study design and details have been described elsewhere[3]. In this study, drug related AEs were observed in 47% of patients on DTG *vs.* 62% of on EFV at 96 weeks. Among CNS AEs, headache occurred more frequently with DTG (7% *vs.* 4%), whereas dizziness (3% *vs.* 18%) and insomnia (2% *vs.* 10%) occurred more frequently with EFV. In conclusion, DTG showed a safer profile compared to EFV regarding neuropsychiatric and CNS AEs.

SPRING-2 is a phase III, 96-week, randomized, double-blind non-inferiority study which compared DTG 50 mg once-daily *vs.* RAL 400 mg b.i.d. in HIV-1 affected patients, each combined with a fixed-dose dual NRTI backbone of TDF/FTC or ABC/3TC. The study design and details have been described elsewhere[4]. Briefly, tolerability and safety of DTG *vs.* RAL showed comparable results up to 96 weeks, with similar rates of AEs and low occurrence of AEs leading to discontinuation, in both groups (2% for both). Among CNS AEs, headache resulted to be more common with DTG than with RAL (14% *vs.* 13%).

SINGLE is a phase III, randomized, double-blind study comparing DTG 50 mg plus ABC/3TC once daily *vs.* EFV/TDF/FTC once daily among HIV-1 infected patients, as described before[5]. Not only DTG 50 mg + ABC/3TC proved to be superior than EFV based-regimen, but it also showed better safety and tolerability, with lower number of interruptions due to drug related AEs both at 48 weeks (2% *vs.* 10%) and at 96 and 144 weeks (3% *vs.* 11%). In the EFV/TDF/FTC arm, dizziness (33% *vs.* 7% with DTG) and abnormal dreams (16% *vs.* 7% with DTG) played a major role, but insomnia was more commonly reported in the DTG arm (10% *vs.* 7% with EFV). This study corroborated the results obtained in SPRING-1, concluding that DTG-based regimen showed lower rates of neuropsychiatric and CNS AEs compared to an EFV-based one.

FLAMINGO is a phase IIIb, randomized, open-label study, in which HIV-1 affected subjects receiving DTG 50 mg qd were compared to others receiving DRV/r 800 mg/100 mg qd, each administered with TDF/FTC or ABC/3TC. The study design and details have been described elsewhere[6]. DTG-based regimen proved to be superior to darunavir/ritonavir (DRV/r)-based one, this superiority also being driven by a lower number of interruptions for any reasons (AEs leading to discontinuation being 3% in DTG arm *vs.* 6% in DRV/r arm at 96 weeks). Among CNS/psychiatric side effects, headache was shown in 15% and 10%, insomnia in 7% and 6%, dizziness in 6% and 5% and depression in 5% and 2%, respectively, at 48 weeks.

ARIA is a randomized, open-label, non-inferiority phase III-b study in which a fixed-dose combination of DTG/ABC/3TC was compared with ritonavir-boosted atazanavir (ATV/r) plus TDF/FTC in previously untreated women with HIV-1 infection (ARIA). The study design and details have been described elsewhere[7]. Non-inferiority of DTG/ABC/3TC regimen was proved and general AEs were assessed to be similar between the two groups. Headache more frequently resulted in ATV (6%) than in DTG-treated group (2%), as well as psychiatric AEs such as insomnia, anxiety, depression or depressed mood and suicidal ideation. Discontinuation rate due to AEs resulted to be lower for DTG (4%) than for ATV (7%) group.

GS-US-380-1489 is a double-blind, active-controlled, phase III, randomized non-inferiority trial in which patients were assigned to receive either co-formulated bictegravir (BIC) 50 mg, FTC 200 mg, and tenofovir alafenamide (TAF) 25 mg (B/F/TAF) or co-formulated DTG/ABC/3TC, each combined with placebo[8]. With regards to efficacy, non-inferiority of B/F/TAF was confirmed and no resistances occurred in any of the two arms. General AEs rate leading to discontinuation were lower in B/F/TAF arm (0% *vs.* 1%). Overall, CNS and psychiatric AEs resulted to be similar between treatment groups, with minor differences: headache 11% *vs.* 14% and insomnia 4% *vs.* 6%.

GS-US-380-1490 was a phase 3, randomized, double-blind, active-controlled study in which patients were assigned to receive either co-formulated B/F/TAF regimen or DTG plus F/TAF, each regimen combined with placebo[9]. B/F/TAF proved non-inferiority *vs.* DTG + F/TAF. Rates of AEs were comparable between the two arms, with similar rates of headache (12.5% *vs.* 12.3%), insomnia (5% *vs.* 4.3%), and general psychiatric events as sleep disorder/insomnia/dyspepsis/tension headache/depressed mood (0.3% *vs.* 0%). Overall, rate of discontinuation due to AEs was low, higher in B/F/TAF group (2%) than in DTG group (<1%).

ACTG A5353 is a phase II, single-arm, 52-week, pilot study of DTG 50 mg plus 3TC 300 mg in treatment-naïve subjects with viral load (VL) ≥ 1000 and < 500,000 copies per ml, as described before[10]. DTG plus 3TC demonstrated potent virologic efficacy, with no AEs leading to discontinuation.

Table 1. Clinical trials with Dolutegravir.

Name of the study	INI (n=)	CTR (n=)	Regimen	w	Summary: efficacy and AEs
			ART-naïve HIV-affected patients		
SPRING-1[3]	155	50	DTG 10, 25 or 50 mg + TDF/FTC or ABC/3TC vs. EFV + TDF/FTC or ABC/3TC	96	Drug related AEs were observed in 47% of patients on DTG vs. 62% on EFV. Among CNS/psychiatric AEs, headache occurred more frequently with DTG whereas dizziness and insomnia were more common with EFV.
SPRING-2[4]	411	411	DTG (50 mg QD) + RAL placebo (BID) + 2 NRTIs vs. RAL (400 mg BID)+DTG placebo (QD)+2 NRTIs	96	Similar rates of AEs and low occurrence of AEs leading to discontinuation in both groups (2%). Among CNS AEs, headache was more common.
SINGLE[5]	414	419	DTG 50 mg + ABC/3TC vs. EFV/TDF/FTC or EVG/COBI/ FTC/TDF	144	DTG showed a better safety and tolerability, with lower number of interruptions due to drug related AEs (2% vs. 10%). Dizziness and abnormal dreams were more common with EFV, insomnia was more commonly reported with DTG.
FLAMINGO[6]	242	242	DTG (50 mg QD) + 2 NRTIs vs. DRV/r (800/100 mg QD) + 2 NRTIs	96	Low rates of discontinuation due to AEs were registered (2% and 4% respectively). CNS/psychiatric AEs were more frequent in DTG arm, mostly headache, while insomnia, dizziness and depression rates were similar.
ARIA[7]	250	249	DTG/ABC/3TC vs. ATV/r + TDF/FTC in naïve women	144	Discontinuation rate due to AEs resulted to be lower for DTG than for ATV group. General AEs were similar between the two groups, as well as psychiatric ones, with low rates of insomnia, anxiety, depression or depressed mood and suicidal ideation.
GS-US[8] -380-1489	315	314	B/F/TAF vs. DTG/ABC/3TC	144	General AEs rate leading to discontinuation was lower in B/F/TAF arm, with CNS symptoms as follows: headache 11% vs. 14% and insomnia 4% vs. 6%
GS-US[9] -380–1490	325	320	B/F/TAF vs. DTG + F/TAF	144	Rates of AEs were comparable between the two arms, with similar rates of headache, insomnia, and general psychiatric events.
ACTG[10] 5353	37/83	N	DTG (50 mg QD) + 3TC (300 mg QD) in ART-naïve patients with HIV-1 RNA <500,000 c/mL (> or < 100.000 c/ml)	52	No AEs leading to discontinuation were registered.
			ART-experienced HIV-affected patients		
SAILING[11]	354	361	DTG (50 mg QD)+BR vs. RAL (400 mg BID)+BR	48	Discontinuation rates due to AEs were comparable with DTG and with RAL, with the same rate of CNS affection (headache: 9%).
VIKING[14] (Cohort-1)	27	N	DTG (50 mg QD)+OBR	24	The safety profile of DTG was comparable in the two cohorts. AEs (grade ≥2) were reported in 48% and 67% patients in cohorts 1 and 2, respectively. It is to be noted that insomnia was reported in 11% of patients in cohort-1 vs. - 0% in cohort-2.
VIKING (Cohort-2)	24	N	DTG (50 mg BID)+ OBR: functional mono-therapy phase (replace RAL with DTG or add DTG if RAL already stopped)	11d-24	
VIKING-3[15]	183	N	DTG (50 mg BID)+ OBR (not incl. RAL) in subjects with INI resistances	48	Discontinuation due to AE was of 4%. Any AEs (grade ≥2) were registered in 55% of patients, with 27% as drug-related AEs. Among those, 2% of headache and no insomnia events were registered.

Continued

Table 1 *Continued.* Clinical trials with Dolutegravir.

Name of the study	INI (n=)	CTR (n=)	Regimen	w	Summary: efficacy and AEs
			ART-experienced HIV-affected patients		
VIKING-4[16]	14	16	DTG (50 mg BID) + remaining components of FR vs. Placebo + remaining components of FR	8d- 48	Safety and tolerability data (median follow-up of 55 weeks) were consistent with the other larger DTG studies, with most frequent drug-related CNS AE registered being dizziness (7%).
DAWNING[12]	312	312	DTG + 2 NRTIs vs. LPV/r + 2 NRTIs in patients failing first-line therapy of an NNRTI + 2 NRTIs	48	Discontinuations due to AEs or death were of 1 and 4%, respectively. Among the most common AEs affecting CNS, headache was registered in 7 and 5% respectively.
STRIIVING[13]	275	278	Switch to DTG/ABC/3TC from current cART regimen: immediate and deferred (after 24w) switch	48	AEs resulted to be more frequent in the DTG arm than with current ART both at 24 and at 48 weeks. DTG group was more affected by psychiatric disorder AEs. Insomnia happened more frequently on DTG at week 24, as well as headache, while resulting comparable between DTG arm and late switch arm at week 48.
SWORD[17] **1 and 2**	53	49	Switch to DTG + RPV from TDF containing regimen in ART-experienced subjects: immediate vs. deferred (after 48w) switch	148	Among AEs leading to withdrawal (>1 AE), headache, anxiety, depression, insomnia, panic attack and suicidal ideation were all registered each in <1% of patients on DTG+RPV regimen.
			Pilot retrospective studies		
PADDLE[19] (Cohort 1 and 2)	10+ 10	N	DTG (50 mg QD) + 3TC (300 mg QD) in ART-naïve patients	96	No discontinuations, 30% of patients had AEs (mostly headache).
DOLULAM[18]	27	N	Switch to DTG 50 mg + 3TC 300 mg QD	96	11.1% discontinuation, 66.7% of these due to drug AEs (mostly fatigue)

(c)ART= (combination) antiretroviral treatment; INI= integrase inhibitor; CTR= control arm; w= weeks; vs. = versus; QD= once a day; BID= twice a day; VL<50c/ml= viral load or HIV-RNA<50 copies/ml; N= not applicable; FR= failing regimen; mITT= modified intention-to-treat; ITT-e= intention-to-treat exposed; RAL= raltegravir; EFV= efavirenz; EVG= elvitegravir; COBI= cobicistat; DTG= dolutegravir; ATV= atazanavir; DRV= darunavir; TDF/FTC= tenofovir disoproxil/ emtricitabine; ABC/3TC= abacavir/lamivudine; LPV= lopinavir; r= ritonavir; B= bictegravir; F= emtricitabine; TAF= tenofovir alafenamide fumarate; (N)NRTI= (non-)nucleoside reverse; CNS= central nervous system; BMD= bone mineral density

ART-experienced patients

SAILING is a phase III, 48-week, randomized, double-blind study that compared ART- experienced and INI-naive patients who were receiving either DTG 50 mg qd or RAL 400 mg bid, both associated with a background therapy. The study design and details have been described elsewhere[11]. In this study, discontinuation rates due to AEs resulted to be comparable between DTG (1%) and RAL (3%), with the same rate of CNS affection (headache: 9%).

DAWNING was an international, multicenter, non-inferiority study conducted in limited-resource settings[12]. Its aim was to compare DTG plus 2 NRTIs to ritonavir-boosted lopinavir (LPV/r) during second-line therapy in patients who had previously failed NNRTI-based first-line ART. LPV/r arm had been stopped early because of the superiority proved by DTG arm. Drug-related AEs resulted to be lower in the DTG arm (2% DTG discontinuations *vs.* 5% LPV/r ones), while CNS events resulted comparable in both arms.

STRIIVING is a Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study were ART-experienced patients were randomized to switch from different ART regimens to the single-tablet-regimen (STR) DTG/ABC/3TC or to remain on their prior regimen[13]. The results of the study demonstrated the non-inferiority of switching to DTG/ABC/3TC *vs.* continuing current ART, with a better outcome with the early switch. AEs resulted to be more frequent in the DTG arm than with current ART both at 24 (66% *vs.* 47%) and at 48 weeks (75% *vs.* 60%). DTG/ABC/3TC group was more affected by psychiatric disorder AEs compared with the current ART group through week 24 (13% *vs.* 3%), while the percentage of psychiatric AEs after the late switch (through week 48)

was 9%. Insomnia happened more frequently on DTG/ABC/3TC arm than with current ART (4% *vs.* <1%) at week 24, as well as headache (5% *vs.* 1%), while the results were comparable between DTG/ABC/3TC arm and late switch arm at week 48 (5% *vs.* 4% for insomnia, 6% *vs.* 4% for headache).

VIKING is a phase IIb, multicenter, open-label, single-arm, and pilot study with 2 sequential cohorts of HIV-affected patients having evidence of RAL resistance. Patients were submitted to receive DTG 50 mg once daily (cohort I) or 50 mg twice daily (cohort II) continuing their failing regimen (excluding RAL) until the 10th day, after which the background regimen was optimized[14]. The study design and details have been described elsewhere. The safety profile of DTG was comparable in the two cohorts. AEs (grade ≥2) were reported in 48% and 67% patients in cohorts 1 and 2, respectively. Of note, insomnia was reported in 11% of patients in cohort -1 *vs.*- 0% in cohort-2.

VIKING-3 is a single-arm, open-label phase III study among ART-experienced patients with evidence of INI-resistance, submitted to DTG 50 mg BID while continuing their failing regimen (excluding RAL or elvitegravir - EVG) through day 7, after which the regimen was optimized, as previously described[15]. As regards AEs, discontinuation rate at 48 weeks was 4%. Any AE (grade ≥ 2) was registered in 55% of patients, with 27% as drug-related. Among those, 2% of headache and 0% of insomnia events were registered.

VIKING-4 is a phase III, randomized, double blind and placebo-controlled superiority study, as it has been described previously[16]. Patients underwent to DTG 50 mg twice daily or placebo (PCB) regimen with their previous failing regimen for 7 days, followed by a single-arm, open-label DTG 50 mg twice-daily regimen, together with an optimized ART regimen. Safety and tolerability data (median follow-up of 55 weeks) were consistent with the other larger DTG studies, with most frequent drug-related CNS AE registered being dizziness (7%).

SWORD 1 and 2 are two identically designed phase III, randomized, multicenter, open-label, parallel-group, non-inferiority switch studies from TDF containing regimen to DTG plus rilpivirine (RPV) regimens among ART-experienced subjects. Immediate switch was compared with deferred (after 48 weeks) switch; the study design and details have been described elsewhere[17]. Among AEs leading to withdrawal (>1 AE), headache, anxiety, depression, insomnia, panic attack and suicidal ideation were all registered each in <1% of patients on DTG+RPV regimen.

Pilot prospective studies

DOLULAM was a pilot, prospective, monocentric, cohort study conducted among 27 HIV-affected experienced patients, with no mutations of resistance for INIs, who were switched to DTG plus 3TC once daily for tolerability reasons, as previously described[18]. This study showed impressive results, supporting the concept of maintenance regimen combining DTG plus 3TC. Three discontinuation events were registered, 2 of them due to drug related AEs (mostly fatigue).

PADDLE was a proof-of-concept pilot study, designed to evaluate the antiviral efficacy, safety and tolerability of a two-drug regimen with DTG plus 3TC as initial ART regimen in naïve patients. The study design and details have been described elsewhere[19]. Briefly, the study drugs were well tolerated. A total of 8 drug-related AEs were reported in 6 out of 20 patients: among those, 3 had headache (appearing to be the most frequent drug-related AE) and 1 reported somnolence, with no AEs leading to discontinuation.

Cohort studies

Observational retrospective studies

Results from cohort studies with DTG-based regimen therapies have been resumed in Table 2.

In 2016, an observational Dutch Cohort showed a particularly and unexpectedly high rate of neuropsychiatric disorders affecting ART-experienced patients on DTG regimens. The cohort design and characteristics have been discussed elsewere[20]. Briefly, among 556 patients submitted to DTG-containing regimens, either as a first therapy or as a switch one, 85 (15.3%) discontinuations were recorded, 13.7% (76 patients) being due to drug-related AEs. In particular, insomnia and sleep disorders were found in 5.6% of patients presenting DTG- intolerance; NPs (such as anxiety, psychosis and depression) were found in 4.3% of patients, thus representing the main reasons for switching DTG.

Another Dutch cohort, ATHENA, later took into consideration 3416 HIV-patients submitted either to DTG or to EVG based regimens (31% as a first-line regimen). As previously described[21], in this 3416-person analysis they focused on treatment discontinuations with DTG or EVG, which proved to be rare and with no differences between the two treatments, but significantly higher among ART-experienced than naive patients. Discontinuations resulted to be mostly due to toxicity, also including CNS adverse events.

The OPERA cohort is an observational retrospective study of 11539 patients, in routine U.S. practice, identified to have been submitted to DTG- (19%), EVG- (29%), RAL- (8%) or other antiretroviral (44%)-based regimens (within 5 clinical trials, OPERA cohort and spontaneously reported cases). The objective of this cohort, as described before[22], was to investigate the incidence of CNS AEs depending on the drug regimen choice. Briefly, DTG and RAL prescriptions included a higher proportion of patients with CNS disorders at baseline. CNS disorders during treatment resulted to be more common with RAL than DTG, while the frequency of "new" CNS AEs (subject with no prior history of that disorder) was similar across all regimens. Specifically, among the 6347 patients in the OPERA cohort, selected PSs (insomnia, anxiety, depression, and suicidality) resulted to be comparable between DTG-,

Table 2. Observational studies with Dolutegravir.

Name of the study	Patients on INI (n=)	Regimen	w	Summary: efficacy and AEs
		Observational retrospective studies		
DUTCH[20] COHORT	556	Experienced and naïve patients submitted to DTG-based regimens	N	15.3% discontinuations, 13.7% due to drug-related AEs: among these, NPs in 4.3%, insomnia and sleep disorders in 5.6%
ATHENA[21] COHORT	3416	Experienced and naïve patients submitted to DTG- or EVG-based regimens	N	Discontinuation rate was rare for both of the regimens, mostly due to toxicity, especially CNS disorders.
OPERA[22] COHORT	6437	Experienced and naïve patients submitted to DTG-, RAL-, EVG-, or other ARV- based regimens	N	Comparable rates of insomnia, anxiety, depression, and suicidality between the 4 regimens. Higher prevalence of anxiety and depression in RAL-submitted patients.
FRENCH[23] COHORT	2260	Mostly pretreated and naïve patients submitted to DTG-based regimens	N	Discontinuation rate 10.6%, with 50% of these due to NP AEs.
CISAI/SCOLTA[24] COHORT	437	Pretreated and naïve patients submitted to DTG-based regimens	N	10.8% total discontinuation events, 50% of these due to AEs. Only 2 patients reporting CNS symptoms.
SWISS[25] COHORT	4041	Experienced and naïve patients submitted to DTG- or RAL- based regimens	N	14.1% discontinued their treatment for any reasons, with toxicity or intolerance occurring in 1/3 of them. NP events were recorded in less than 2% of the patients, being more represented in the DTG group.
GERMAN[26] COHORT	1704	Experienced and naïve patients submitted to DTG-, RAL- or EVG-based regimens	N	Discontinuation rate due to any AEs related to the use of DTG was 7.6%. The DTG discontinuation rate due to NP events was 5.6%, higher than the same rate for EVG (0.7%) or RAL (1.9%) treated patients
LONDON[27] COHORT	181	Pretreated and naïve patients submitted to DTG-based regimens	N	Discontinuation rates comparable with Phase III studies, mostly due to dizziness and insomnia. No discontinuation among pregnant women.
ITALIAN[27] COHORT	132	Experienced patients switched to DTG + RPV	N	Discontinuation due to toxicity happened in 34.8% of patients with 3% rate of NP AEs.
DAT'AIDS[29] COHORT	152	Experienced patients switched to DTG + RPV	N	13% discontinuation events, mostly (63%) due to AEs with neurological disorders being the most frequent AEs (58%).

TivEdO study

INI= integrase inhibitor; w= weeks; N= not applicable; DTG= dolutegravir; NP(s)= neuro-psychiatric symptoms; AEs= adverse events; RAL= raltegravir; EVG= elvitegravir; DRV= darunavir; RPV= rilpivirine; ARV= anti-retroviral; ART= anti-retroviral therapy; CNS= central nervous system.

EVG-, RAL- and DRV- based regimens, with the exception of a higher prevalence of anxiety and depression in RAL-submitted patients. Also, treatment interruptions due to PSs proved to be generally low, with DTG-treated patients showing the lowest rates (range 0.1-0.6%).

The analysis of a French Cohort of 2260 HIV-affected and mostly pretreated subjects also focused the interest on NP AEs related to the use of DTG. As better-described elsewhere[23], the discontinuation rate resulted to be 10.6%, with 50% of these due to neuro-psychiatric AEs (rate of discontinuation due to NPs was 5.4%), accordingly to most of the other real-life studies.

In the frame of the Italian SCOLTA (Surveillance Cohort of Long-term Toxicity of Antiretrovirals) project, the CISAI (Italian Coordination for the Study of Allergy and HIV Infection) group evaluated a cohort of 437 HIV-affected patients submitted to DTG-regimens[24]. Briefly, 32 (10.8%) total discontinuation events were registered, of which 50% (16) were due to AEs. More precisely, only 2 patients reported CNS symptoms (one somnolence and one headache), while the rest of them reported other systems to have been affected (gastro-intestinal, renal, muscle-skeletal, skin). These results, with a rate of discontinuation due to NP events of 1%, corroborated the data from clinical trials and were partly in contrast with other observational cohorts in real life where the rates resulted to be higher.

The SHCS (Swiss HIV Cohort Study), a large Swiss cohort of HIV-affected patients, was studied in order to analyze subjects starting a RAL- or DTG- based ARV regimen. The design and details of the study have been described elsewere[25]. Out of 4041 patients included in the study, 568 (14.1%) discontinued their treatment for any reasons within the first year, with toxicity or intolerance occurring in one third of them (181 patients, 4.5% of the total number of patients). Moreover, NP events were recorded in less than 2% of the patients (still being the most commonly reported AEs) and they were more represented in the DTG group.

Higher rates of NP AEs leading to DTG discontinuation in women and older patients were recorded in a German Cohort of 1704 patients[26]. Discontinuation rate due to any AEs related to the use of DTG was 7.6%. The DTG discontinuation rate due to NP events was 5.6%, resulting to be higher than the same rate for EVG (0.7%) or RAL (1.9%) treated patients.

The London Cohort analyzed 181 HIV-affected naïve and experienced patients submitted to DTG-containing regimens; among these, 9 out of 54 women were pregnant. The cohort details and characteristics have been described elsewhere[27]. Briefly, both virological efficacy and discontinuation rates resulted comparable to phase 3 studies. As regards PSs or CNS effects, dizziness (22%) and insomnia (33%) appeared to be the most frequent toxicity related AEs bringing to discontinuation. Among pregnant women, DTG was well tolerated and no discontinuation events were registered.

The safety of the combination DTG plus RPV was assessed in an Italian Cohort of 132 HIV-affected patients enrolled in 8 different centers. As thoroughly described elsewhere[28], discontinuations due to toxicity happened in 34.8% of patients with 3% rate of NP AEs (higher than in clinical trials: <1%).

The same ARV combination real-life performance was also evaluated in a French Cohort, the DAT'AIDS, with the main focus of monitoring the viral efficacy[29]. Nineteen out of 152 patients (13%) discontinued the treatment, mostly (63%) due to AEs: among these, neurological disorders resulted to be the most frequent AEs (58%).

DISCUSSION

To date, discontinuation rates of DTG due to AEs, reported in clinical trials, appear to be low, especially in treatment-naïve patients: 2% in SPRING-2, 3% in SINGLE and FLAMINGO, 4% in ARIA[4-7]. Among these, the most frequent NP AE resulted to be insomnia, but only in SINGLE this event had a rate higher than 5%[5]; this might be justified by the fact that only in this trial, patients had to fill in a specific questionnaire for CNS events. Discontinuation rates due to AEs resulted to be low also in experienced patients (2-4%), even though NP symptoms were reported more frequently compared to naïve-patients[11-17]. One possibility to interpret this result might be that experienced patients had, by definition, already been treated before with other regimens and this fact might have already influenced their tolerability. For instance, subjects coming from another INI might be subjected to some class-related side effects (such as headache and dizziness), as pointed out by Capetti et al[28] in their observational cohort. Also, a proportion of patients presenting NP symptoms might suffer from some CNS disorders independently from the ARV regimen, and this has not been always taken into consideration when assessing the AEs rate.

On the other hand, when looking at 'real-life' cohort studies, variable rates of discontinuation due to AEs has been reported, generally higher compared to those from clinical trials, going from 3 to 15%[20-29]. More specifically, DTG discontinuations due to CNS events resulted to be more relevant (0.3-5%) compared to the other INI regimens (0.7-3%)[21-22,25-26].

Among all AEs, gathered data through clinical trials and real-life studies confirmed that neuro-psychiatric symptoms are the most common events happening during DTG-containing regimens compared to the other regimens, but CNS AEs can be still considered infrequent.

Some authors tried to correlate the incidence of NP disorders with high DTG dosages in cerebrospinal fluid, which were identified in some symptomatic patients' samples[30] but not confirmed in others[31]. For this reason, further studies on this field might be interesting, leading to some possible new insights, in order to investigate the eventual role of higher concentrations of DTG in the CNS [30,31].

CONCLUSIONS

DTG-containing regimens play a major role in the treatment of both ART-experienced and naïve HIV-infected subjects. CNS AEs can be still considered infrequent in patients submitted to DTG containing regimens, but it has to be highlighted that these events have higher frequency when compared to other INI-based antiretroviral regimens in most studies. Therefore, a careful clinical evaluation of previous CNS events and psychiatric comorbidity should be performed in order to reduce the risk of the most severe events in patients starting INI especially if DTG is prescribed.

Conflict of Interest:
The Authors declare that they have no conflict of interests.

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