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Safety and efficacy of elvitegravir, dolutegravir, and raltegravir in a real-world cohort of treatment-naïve and -experienced patients

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Abstract

The aim of this retrospective cohort study was to compare safety, efficacy and rates and reasons of discontinuation of the 3 currently approved integrase strand transfer inhibitors (INSTIs) elvitegravir (EVG), dolutegravir (DTG), and raltegravir (RAL) in HIV-infected treatment-naïve and -experienced patients in a real-world cohort. One hundred four treatment-naïve patients were prescribed an INSTI-based combined antiretroviral therapy (cART)-regimen (first-line group) and 219 patients were switched to an INSTI-based cART-regimen from another treatment regimen (switch group) at our institution between May 2007 and December 2014. Twelve months after initiation of treatment, 92% of patients in the first-line group (EVG: 96%, n=22/23; DTG: 92%, n=34/37; RAL: 90%, n=28/31) and 88% of patients in the switch group (EVG: 94%, n=32/34; DTG: 90%, n=69/77; RAL: 85%, n=67/79) showed full virological suppression (viral load <50 copies/mL). Side effects of any kind occurred in 12% (n=12/104) of patients in the first-line group, and 10% (n=21/219) of patients in the switch group. In the switch group neuropsychiatric side effects (depression, vertigo, and sleep disturbances) occurred more frequently in patients treated with DTG (11%, n=10) compared to the 2 other INSTI-based cART-regimen (EVG: 2%, n=1; RAL: 1%, n=1). Side effects only rarely led to discontinuation of treatment (first-line-group: 2%, n=2/104; switch-group: 1%, n=3/219). In this real-world setting, INSTI-based ART-regimens were highly efficacious with no significant differences between any of the 3 INSTIs. Overall, side effects were only rarely observed and generally mild in all subgroups. In light of a slightly higher incidence of vertigo and sleep disturbances in patients switched to DTG, awareness of the potential onset of psychiatric symptoms is warranted during follow-up in those patients.

Abbreviations: 3TC = lamivudine, ABC = abacavir, ALT = alanine transaminase, AST = aspartate transaminase, ATV/r = atazanavir/ritonavir, cART = combined antiretroviral therapy, CI = confidence interval, CrP = C-reactive protein, DRV/r = darunavir/ritonavir, DTG = dolutegravir, EFV = efavirenz, EVG = elvitegravir, FTC = emtricitabine, HDL = high-density lipoprotein, INSTI = integrase strand transfer inhibitor, LDL = low-density lipoprotein, LPV = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RAL = raltegravir, RCT = randomized controlled trial, STR = single-tablet regimen, TDF = tenofovir disoproxyl fumarate.

Keywords: AIDS, cART, combined antiretroviral therapy, dolutegravir, elvitegravir, HIV, integrase inhibitors, integrase strand transfer inhibitor, raltegravir

1. Introduction

Current guidelines for treatment-naïve HIV-infected patients recommend combined antiretroviral therapy (cART) consisting of a "backbone" of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third antiretroviral drug.[1–3] Classes of antiviral agents recommended for combination treatment with NRTIs include non-nucleoside reverse transcriptase inhibitors (NNRTIs), boosted protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs). The latter have emerged as preferred anchor drugs for treatment-naïve patients in different international guidelines due to their excellent efficacy

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and favorable safety profile in comparison to NNRTIs[4–6] and PIs[7–9] in the respective randomized controlled trials (RCTs). INSTIs have shown high antiretroviral potency, a low risk of virologic failure as well as a high genetic barrier to resistance.

Raltegravir (RAL, Isentress) was the first approved INSTI. RAL was found to be noninferior to efavirenz (EFV) in treatment-naïve patients with a higher rate of viral suppression after 48 weeks (RAL: 86%, EVF: 82%, 95% confidence interval [CI]: −1.9 to 10.3) and fewer treatment-related severe adverse events (RAL: 44%, EVF: 77%, 95% CI: −40.2 to −25).[6] In comparison to the 2 other examined INSTI regimens, RAL required twice-daily dosing for many years, but the FDA recently also approved once daily dosing.

Elvitegravir (EVG, Stribild as single-tablet regimen [STR] with cobicistat, tenofovir-disoproxylfumarat [TDF] and emtricitabine [FTC]) must be taken with food and requires pharmacological boosting which can lead to significant drug interactions.[10] In RCTs virological efficacy of EVG after 48 weeks was demonstrated to be noninferior to both EVF (EVG: 88% EVF: 84%, 95% CI: −1.6% to 8.8%)[11] and atazanavir/ritonavir (ATV/r) (EVG: 90% ATV/r: 87%, 95% CI: −1.9% to 7.8%).[8] After 96 weeks of treatment, patients treated with EVG showed neuropsychological side effects significantly less frequently than those treated with EVF (47% vs 66%, $P<.001$).[11]

Dolutegravir (DTG, Tivicay or Triumeq as STR with abacavir [ABC] and lamivudine [3TC]) has been shown to exhibit a higher barrier to resistance compared to EVG and RAL, can be dosed once daily, has a low interaction potential and there are no food restrictions.[12,13] DTG was associated with significantly more frequent virological suppression after 48 weeks compared to both EFV (DTG: 88%, EFV: 81%, 95% CI: 2%–12%, $P=.003$)[5] and darunavir/ritonavir (DRV/r) (DTG: 90%, DRV/r: 83%, 95% CI: 0.9%–13.2%).[7] In treatment-experienced patients, cART-regimens based on once-daily DTG showed greater virological effect when compared to twice-daily RAL (DTG: 71%, RAL: 64%, 95% CI 0.7%–14.2%).[14]

INSTIs have been demonstrated to be generally safe and tolerable. Discontinuation of treatment due to adverse events only occurred in 1% to 4% of patients treated with INSTIs in RCTs and no specific organ toxicity associated with INSTIs was identified.[15] However, recently several retrospective observational studies described relatively high frequencies of neuropsychiatric side effects in patients treated with DTG, especially amongst women and older patients.[16–20]

In this retrospective study we investigated efficacy and safety profiles of the 3 available INSTIs in a real-world cohort of HIV-infected individuals. Taking into account the virological, immunological, and clinical differences between these subgroups, we differentiated between treatment-naïve and -experienced patients. Of note, the most recent INSTI bictegravir, (Biktarvy as STR with tenofovir alafenamide and FTC) was not yet approved during the study period and was therefore not included into the analysis.[4]

2. Methods

We performed a retrospective analysis of HIV-infected patients who attended the infectious disease outpatient clinic of the University Medical Center Hamburg-Eppendorf and who initiated an INSTI-based cART-regimen between May 2007 and December 2014. The study protocol was approved by the local ethics committee of the Ärztekammer Hamburg (WF-72/18). Patients were identified by screening the electronic patient database for INSTI prescriptions. Both treatment-naïve and -experienced patients were included. Patients who received an INSTI-based cART-regimen within RCTs were excluded from further analysis. In order to be able to evaluate virological response to treatment with an INSTI-based cART-regimen, only patients who had an initial viral load taken within 3 months before to 1 week after starting an INSTI-based cART-regimen were included into further analysis. At our center, CD4+ T cell count and viral load is routinely measured at least every 3 to 6 months. If the respective virological and immunological data were available, also follow-up visits after 3 and 12 months were analyzed. Detectable viral load of >50 copies/mL after 12 months of treatment was considered virological failure. Demographic and clinical characteristics including viral load, CD4+ T cell count, creatinine, high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine transaminase (ALT), aspartate transaminase (AST), cholesterol, triglycerides, and C-reactive protein (CrP) were obtained from electronic health records. The treating physicians regularly document the reasons for discontinuation or switch of cART-regimen as well as side effects, and this information was extracted from the electronic medical records. The symptoms depression, vertigo, and sleep disturbances were all classified as neuropsychiatric side effects.

2.1. Statistical analysis

Continuous data were assessed for normal distribution and means or medians presented and compared by the Students *t* test or Wilcoxon rank-sum test, respectively. The Chi-square test or Fischer exact test, where appropriate, were used for analysis of categorical data. Statistical descriptive analysis was performed using Stata v. 14.2 (StataCorp, College Station, TX)

3. Results

3.1. Study population

A total of 411 HIV-infected patients initiated an INSTI-based cART-regimen at our center during the study period. Of those, 88 patients were not eligible for further analysis: 34 patients took part in other clinical studies and for 39 patients not all required laboratory tests had been performed at the time of initiation of an INSTI-based cART-regimen (Fig. 1). Fifteen patients had a switch of cART-regimen twice and were therefore only included once in the study after the first switch. Three hundred twenty-three patients were included in the subsequent analysis, of which 104 patients were treatment-naïve and 219 patients were patients who were switched to an INSTI-based cART-regimen from another treatment regimen. Baseline characteristics of the study population subdivided in the respective subgroups are presented in Table 1. The majority of patients were male (79%, n=254/321). While the percentage of male patients was higher in the subgroup of treatment-naïve patients for patients who received EVG compared to those who received DTG or RAL ($P=.04$), there were no significant differences in gender distribution between the 3 INSTIs in the switch group. Median age of the entire study cohort was 43 years (range 17–76). In the switch group, patients treated with EVG were significantly younger than those who received DTG or RAL ($P=.007$), but no significant difference of median age was observed in treatment-naïve patients. The median follow-up after initiation of INSTI-based

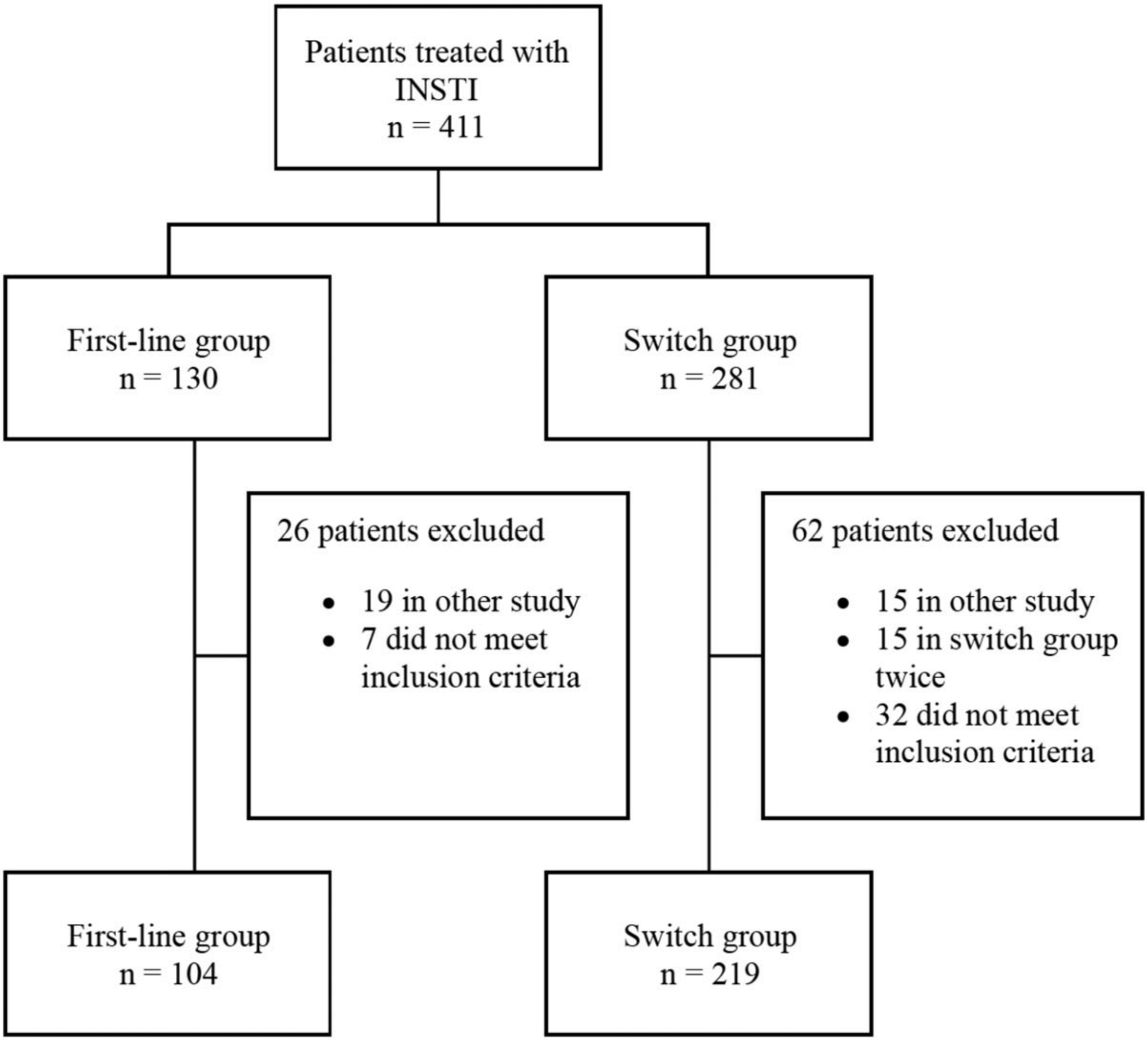

Figure 1. Patient selection.

Table 1

Baseline characteristics of the study population.

	First-line group (treatment-naïve)					Switch group (treatment-experienced)				
	EVG	DTG	RAL	total	*P*	EVG	DTG	RAL	total	*P*
Patients, n	29	41	34	104		45	89	85	219	
Gender, n (%)					.04					.17
Male	28 (97)	35 (85)	25 (74)	88 (85)		30 (67)	74 (83)	62 (73)	166 (76)	
Female	1 (3)	6 (15)	9 (26)	16 (15)		15 (33)	15 (17)	22 (26)	52 (24)	
Transgender	0	0	0	0		0	0	1 (1)	1 (0)	
Age, median (range)	39 (22–74)	36 (17–65)	44 (18–72)	39 (17–74)	.37	43 (26–73)	50 (20–76)	46 (18–76)	47 18–76)	.007
cART-backbone, n (%)					<.001					<.001
TDF/FTC	29 (100)	22 (54)	29 (85)	80 (77)		44 (98)	37 (42)	39 (46)	120 (55)	
ABC/3TC	0	16 (39)	3 (9)	19 (18)		0	32 (36)	5 (6)	37 (17)	
DRV/r	0	0	1 (3)	1 (1)		0	0	6 (7)	6 (3)	
LPV/r	0	0	0	0		0	0	4 (5)	4 (2)	
Several	0	3 (7)	0	3 (3)		0	17 (19)	4 (5)	21 (10)	
Other	0	0	1 (3)	1 (1)		1 (2)	3 (3)	27 (32)	31 (14)	

3TC = lamivudine, ABC = abacavir, cART = combined antiretroviral therapy, DRV/r = darunavir/ritonavir, DTG = dolutegravir, EVG = elvitegravir, FTC = emtricitabine, LPV = lopinavir/ritonavir, RAL = raltegravir, TDF = tenofovir disoproxyl fumarate.

cART-regimen was 360 days both for patients in the first-line and the switch-group with no difference between the treatment regimens. The antiretroviral drugs patients received in addition to the respective INSTI varied between the 3 subgroups. Patients treated with RAL also received a “backbone” of TDF/FTC (first-line group: 85%, n=29/34; switch group: 46%, n=39/84) or ABC/3TC (first-line group: 9%, n=3/34; switch group: 6%, n=5/84). Fewer patients received combination treatment with DRV/r or other combinations. All patients treated with EVG received a STR with Stribild including cobicistat/TDF/FTC, 1 patient in the switch group additionally received DRV/r. Patients treated with DTG either received the STR Triumeq containing DTG/ABC/3TC (first-line group: 39%, n=16/41; switch group: 36%, n=32/89) or single DTG tablets in combination with TDF/FTC (first-line group: 54%, n=22/41; switch group: 42%, n=37/88).

The different cART-regimen patients had received before the switch primarily included regimen based on PIs, NNRTIs, and INSTIs with significant differences between the 3 subgroups (Supplemental Table 1, http://links.lww.com/MD/D170). Patients treated with DTG were most often switched from EFV (34%, n=30) or other NNRTIs (9%, n=8), less often from PIs (31%, n=28). The subgroup that was switched to RAL frequently had earlier received a PI-based regimen (51%, n=43). The majority of 40% (n=18) of patients treated with EVG were switched from another INSTI-based cART-regimen, less often from a PI-based (31%, n=14) or EFV-based regimen (24%, n=11).

The reasons for a change of the cART-regimen also varied between the 3 subgroups. Overall, the most frequent reasons were neuropsychiatric side effects to the previous regimen (18%, n=38), the wish for a reduction of the number of tablets (16%, n=34) and laboratory side effects (10%, n=22). Patients with neuropsychiatric side effects were most often switched to DTG (n=24), patients with a wish for a reduction of the number of tablets most often to EVG. When the patients were further stratified by the respective cART-regimen used before the switch, neuropsychiatric symptoms mainly led to a switch of treatment in patient that had received EFV (n=19) (Supplemental Table 2, http://links.lww.com/MD/D170). Patients previously treated with a PI-based cART-regimen were most frequently switched due to gastrointestinal complaints (n=10) or the which for a reduction of the number of tablets (n=11). The main reason why patients were switched from one INSTI to another INSTI was the whish for a reduction of the number of tablets (n=21).

3.2. Efficacy

Data for 189 patients were available for the 3 months follow-up visit and for 281 patients for the 12 months follow-up visit. A total of 19 patients were lost to follow-up during the 12 months after initiation of the INSTI-based cART-regimen (first-line group: n=6, switch group: n=13) (Supplemental Table 3, http://links.lww.com/MD/D170). All treatment-naïve patients and 31% of all patients in the switch group had a detectable viral load $>10^5$ c/mL at baseline (Table 2). Of the 189 patients for whom a 3 month follow-up visit was recorded, 73% of treatment-naïve patients and 86% of treatment-experienced patients had an undetectable viral load defined as HIV-RNA <50 copies/mL by this point, altogether showing a slightly higher rate of viral suppression in patients receiving DTG. However, no significant difference in efficacy was observed between the 3 INSTIs after 12 months of treatment with a generally high rate of virological suppression rate of 92% (EVG: 96%, n=22/23; DTG: 92%, n=34/37; RAL: 90%, n=28/31, *P*=.97) in the first-line group and a lower rate of 88% (EVG: 94%, n=32/34; DTG:

Table 2

Virological and immunological data.

	First-line group (treatment-naïve)											
	Baseline				3 mo				12 mo			
	EVG	DTG	RAL	*P*	EVG	DTG	RAL	*P*	EVG	DTG	RAL	*P*
n	29	41	34		22	19	22		23	37	31	
HIV-RNA												
median, 10^3 copies/mL	73	65	70	.27	0.01	0	0.01	.2	0	0	0	.7
range, 10^3 copies/mL	0.7–600	0.5–7000	0.1–1400		0–19	0–0.06	0–0.3		0–8.8	0–722	0–25	
<50 copies/mL, n (%)	0 (0)	0 (0)	0 (0)	N/A	16 (80)	17 (90)	13 (59)	.08	22 (96)	34 (92)	28 (90)	.97
CD4+ T cells												
median, cells/μL	306	258	201	.13	377	345	287	.4	502	465	386	.13
range, cells/μL	6–1127	2–647	5–650		137–644	53–1175	2–824		70–1296	2–1683	55–1100	
<200 cells/μL, n (%)	9 (31)	17 (43)	16 (49)	.37	1(5)	3 (16)	4 (19)	.4	3 (13)	6 (16)	3 (10)	.80
	Switch group (treatment-experienced)											
	Baseline				**3 mo**				**12 mo**			
	EVG	**DTG**	**RAL**	***P***	**EVG**	**DTG**	**RAL**	***P***	**EVG**	**DTG**	**RAL**	***P***
n	45	89	85		24	53	49		34	77	79	
HIV-RNA												
median, 10^3 copies/mL	0	0	72	<.01	0	0	0	0	0	0	0	.33
range, 10^3 copies/mL	0–970	0–420	0–6800		0–9.4	0–0.26	0–6.4		0–0.2	0–5.1	0–170	
<50 copies/mL, n (%)	31 (69)	70 (80)	41 (49)	<.01	19 (79)	50 (94)	39 (80)	.05	32 (94)	69 (90)	67 (85)	.38
CD4+ T cells												
median, cells/μL	443	429	399	.16	511	545	399	.06	583	561	464	<.01
range, cells/μL	21–1843	2–1341	14–1064		25–903	52–1287	73–1050		27-1171	86–1537	27–1247	
<200 cells/μL, n (%)	4 (9)	8 (9)	16 (19)	.10	2 (8)	4 (8)	12 (26)	.02	1 (3)	2 (3)	11 (14)	.02

DTG=dolutegravir, EVG=elvitegravir, RAL=raltegravir.

Table 3

Side effects.

	First-line group (treatment-naïve)				Switch group (treatment-experienced)			
	EVG	DTG	RAL	Total	EVG	DTG	RAL	Total
None, n (%)	23 (79)	40 (98)	28 (85)	91 (88)	42 (95)	73 (82)	82 (96)	197 (90)
Depression, n (%)	2 (7)	1 (2)	2 (6)	5 (5)	0	1 (1)	0	1 (0)
Vertigo, n (%)	0	0	0	0	1 (2)	7 (8)	0	8 (4)
Sleep disturbances, n (%)	0	0	0	0	0	2 (2)	1 (1)	3 (1)
Flu-like, n (%)	1 (3)	0	2 (6)	3 (3)	1 (2)	2 (2)	0	3 (1)
Laboratory values, n (%)	2 (7)	0	1 (3)	3 (3)	0	1 (1)	0	1 (0)
Gastrointestinal, n (%)	0	0	0	0	0	1 (1)	2 (2)	3 (1)
Rash/itching, n (%)	1 (3)	0	0	1 (1)	0	1 (1)	0	1 (0)
General weakness, n (%)	0	0	0	0	0	1 (1)	0	1 (0)

DTG = dolutegravir, EVG = elvitegravir, RAL = raltegravir.

90%, n = 69/77; RAL: 85%, n = 67/79, P = .38) in the switch group.

In treatment-naïve patients the median CD4+ T cell count was 255/μL at baseline, 336/μL after 3 months and 463/μL after 12 months. In treatment-experienced patients, the median CD4+ T cell count at baseline was generally higher with a mean of 424/μL, 478/μL after 3 months and 536/μL after 12 months with significantly lower levels in patients treated with RAL (EVG: 583/μL, DTG: 561/μL, RAL: 464/μL, P < .01). After 12 months of treatment, only few patients showed a CD4+ T cell count <200/μL in the first-line group (EVG: n = 3, DTG: n = 6, RAL: n = 3, P = .8). In the switch-group, significantly more patients treated with RAL had low CD4+ T cell counts <200/μL (EVG: n = 1, DTG: n = 2, RAL: n = 11, P = .02).

3.3. Adverse events

Overall, adverse events occurred in 12% of treatment-naïve and in 10% of treatment-experienced patients (Table 3). The most commonly reported adverse events were vertigo (switch group: 4%, n = 8), depression (first-line group: 5%, n = 5; switch group: 0.4%, n = 1) and flu-like symptoms (first-line group: 1%, n = 3; switch group: 3%, n = 3). In the first-line group, depression occurred in 2 patients treated with EVG and RAL, respectively and 1 patient who received DTG without significant differences between the subgroups (P = .62). Vertigo and sleep disturbances did not occur in the first-line group. In the switch group; however, the incidence of neuropsychiatric complaints (depression, vertigo, and sleep disturbances) occurred significantly more frequently (P = .01) in patients treated with DTG (11%, n = 10) compared to EVG (2%, n = 1) and RAL (1%, n = 1). Patients in this subgroup receiving DTG suffered from vertigo (8%, n = 7), sleep disturbances (2%, n = 2), and depression (1%, n = 1), while 1 patient treated with EVG reported vertigo and 1 patient treated with RAL had sleep disturbances.

Within the observation period of 12 months a total of 6 treatment-naïve patients (6%) and 11 treatment-experienced patients (5%) discontinued treatment, 5 of them due to side effects (Supplemental Table 3, http://links.lww.com/MD/D170): 2 patients who received EVG as first-line therapy discontinued treatment due to rash/itching and laboratory reasons, respectively and 3 patients in the switch-group who received DTG discontinued treatment due to neuropsychiatric, flu-like and gastrointestinal complaints, respectively.

None of the patients died during the observation period. In total, 6 patients (5%) in the first-line group (EVG: n = 2, DTG: n = 3, RAL: n = 1) and 13 patients (6%) in the switch-group (EVG: n = 4, DTG: n = 6, RAL: n = 3) were lost to follow-up. Since we have no further information on the reasons for the loss of follow-up in these patients, we cannot exclude the possibility that these patients experienced side effects, which might have led to a possible selection bias.

Further data on selected laboratory parameters at initiation of INSTI-based cART-regimen and after 12 months of treatment are shown in Supplemental Table 4, http://links.lww.com/MD/D170. At baseline, no differences were seen between all subgroups. After 12 months, the median creatinine value was significantly higher for patients in the switch group treated with DTG compared to those that received EVG or RAL. In the first-line group EVG and DTG both led to a higher increase of creatinine levels than RAL. Median changes of HDL, LDL, AST, ALT, cholesterol, and triglycerides between the subgroups were only minimal yet sometimes significant.

4. Discussion

A total of 321 patients were analyzed in this retrospective study of HIV-infected patients who were prescribed an INSTI-based cART-regimen with EVG, DTG, or RAL at our infectious disease outpatient clinic from May 2007 until December 2014 with a follow-up period of 12 months. Of note, this small single-center cohort was further stratified into treatment-naïve and -experienced patients who switched from other regimens so that virologic efficacy, side effects, and safety profiles could be assessed for each individual patient subgroup. This is in contrast to several recent other real-world studies that either

(1) did not compare all 3 available INSTIs[15,17,21]
(2) did not differentiate between treatment-naïve or -experienced patients[17] or
(3) that focused on only certain aspects like reasons for discontinuation.[15–17,22]

As a main result of our study, cART based on any of the 3 INSTIs was highly efficient, especially in treatment-naïve patients, of which a total of 92% had an undetectable viral load defined as HIV-RNA <50 copies/mL after 12 months of treatment. In the switch group the proportion of virologic suppression was slightly lower (88%). This is in line with data from registration trials[5–7,10–12,14,23], real-world studies[21,24,25] as well as meta-analyses[26,27] that demonstrate that INSTI-based regimens are highly efficacious and suggest that they are superior to NNRTI- and PI-based therapy with respect to viral suppression and discontinuation rates in cART-naïve as well as cART-experienced patients. Virologic failure defined as >50 copies/mL after 48 weeks of INSTI-based cART-regimen was 10% to 14% in treatment-naïve patients[5–8,11] and 29% to 36% in treatment-experienced patients in the respective RCTs.[14,24]

Of note, in our study cohort, patients treated with RAL also had generally lower median CD4+ T cell counts after both 3 and 12 months of treatment, in both the first-line and the switch group. However, patients treated with RAL also had lower, yet not significant, median CD4+ T cell counts at baseline in both subgroups and, in the switch-group, a higher median viral load at baseline. This, as well as the slightly lower proportion of virologic suppression after in patients who received RAL (85%), compared to DTG (90%), or EVG (94%), could be due to the fact that RAL was the first approved INSTI in 2007, when treatment guidelines did not generally recommend initiation of cART in asymptomatic patients with CD4+ T cell counts >350/μL.[28]

There is an ongoing controversy on the tolerability of DTG in real-world settings since recently several cohort studies reported unexpectedly high discontinuation rates of DTG due to mainly neuropsychiatric side effects. In a Dutch cohort treatment with DTG was discontinued in 4% (n=24/387) of patients after a median of 78 days because of neuropsychiatric side effects.[17] A retrospective analysis of a German cohort demonstrated a discontinuation rate of almost 6% (n=55/985) within the first year of initiation due to neuropsychiatric adverse events in patients treated with DTG.[16] In a real-world cohort from France, 5% (n=28/517) of HIV-infected patients treated with DTG discontinued treatment due to neuropsychiatric adverse events.[18] These high rates of discontinuation due to neuropsychiatric symptoms are in contrast to data of preceding RCTs on DTG in which discontinuing due to adverse events were reported for less than 2% of patients according to a meta-analysis.[29] However, in those RCTs dizziness was observed in 3% to 9% and sleep disturbances in 2% to 23% of patients.[5,12,30] While DTG achieves high concentrations in the central nervous system, the pathophysiological mechanism involved in the onset of neuropsychiatric symptoms in patients treated with DTG has not yet been described.[31]

Clinical trials remain the most effective form of evaluating safety and efficacy in drug development and approval. However, the enforcement of strict inclusion and exclusion criteria may lead to selection bias and a highly selective study population. In contrast, real-world studies refer to data collected from daily life of broader populations treated in different clinical settings outside the scope of tightly controlled RCTs. Thus, it remains important to conduct post-marketing surveillance and collect data from real-world cohorts on the safety of DTG. This is especially the case for patient groups not represented in the respective RCTs. In our study cohort, 11% (n=10) of patients who were switched to DTG suffered from neuropsychiatric side effects (depression, vertigo, and sleep disturbances), which was significantly higher compared to the other INSTI-based cART-regimens (EVG: 2%, n=1; RAL: 1%, n=1). These symptoms led to discontinuation of treatment in only 1 patient. However, neuropsychiatric side effects had also occurred frequently in these patients when treated with their previous cART-regimen and led to the switch of treatment in 16 patients (EVG: n=4, RAL: n=3) (Supplemental Table 1, http://links.lww.com/MD/D170). This may be at least partly explained by the fact that this subgroup had received an EFV-based cART-regimen more often than patients that were switched to EVG or RAL, since EFV is associated with causing neuropsychiatric side-effects: out of 23 patients that were switched to an INSTI-based cART-regimen due to neuropsychiatric symptoms, 19 had been treated with EVG (Supplemental Table 2, http://links.lww.com/MD/D170). On the other hand, a certain subset of patients might have a general predisposition for developing neuropsychiatric side-effects and therefore may have developed these symptoms, both when they were on their previous cART-regimen and on the DTG-based cART-regimen. In the first-line-group no significant differences in neuropsychiatric side effects between the 3 INSTIs were observed. In summary, our data generally support the notion that in patients with a history of neuropsychiatric symptoms or side effects to a cART-regimen, awareness of the potential onset of neuropsychiatric symptoms is crucial during follow-up in particular when they are switched to therapy with DTG.[32]

Liver toxicity and metabolic abnormalities are important adverse events in patients on cART, even though newer antiretroviral drugs like INSTIs are generally well tolerated. In our analysis, INSTI-based cART-regimens did not cause clinically significant elevation of liver enzymes, lipoproteins, cholesterol, triglycerides, or CrP. After 12 months of treatment patients that received DTG showed a significant increase of creatinine levels. However, DTG is known to decrease tubular section of creatinine without affecting glomerular filtration, which is why cystatin C has been suggested to be a more reliable marker for estimation of glomerular filtration rate.[33]

Our study has several important limitations inherent with the retrospective study design. Most patients in our study were white males which is not representative of people living with HIV globally. In the light of reports of higher rates of neuropsychiatric adverse events leading to discontinuation of DTG in women and older patients[16] additional studies are needed to examine efficacy and safety profiles in a broader demographic, especially in populations underrepresented in the registration trials.

In summary, in this retrospective real-world study we confirm that INSTI-based cART-regimens are highly efficacious with few differences between EVG, RAL, and DTG. We observed a slightly higher incidence of vertigo and sleep disturbances in patients switched to DTG, so awareness of the potential onset of neuropsychiatric symptoms is warranted during follow-up in those patients.

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