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Vergleich der Sicherheit und Wirksamkeit der Integraseinhibitoren Elvitegravir, Dolutegravir und Raltegravir bei therapienaiven und vorbehandelten HIV-Patienten

Dissertation

zur Erlangung des Grades eines Doktors der Zahnmedizin an der Medizinischen Fakultät der Universität Hamburg.

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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

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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

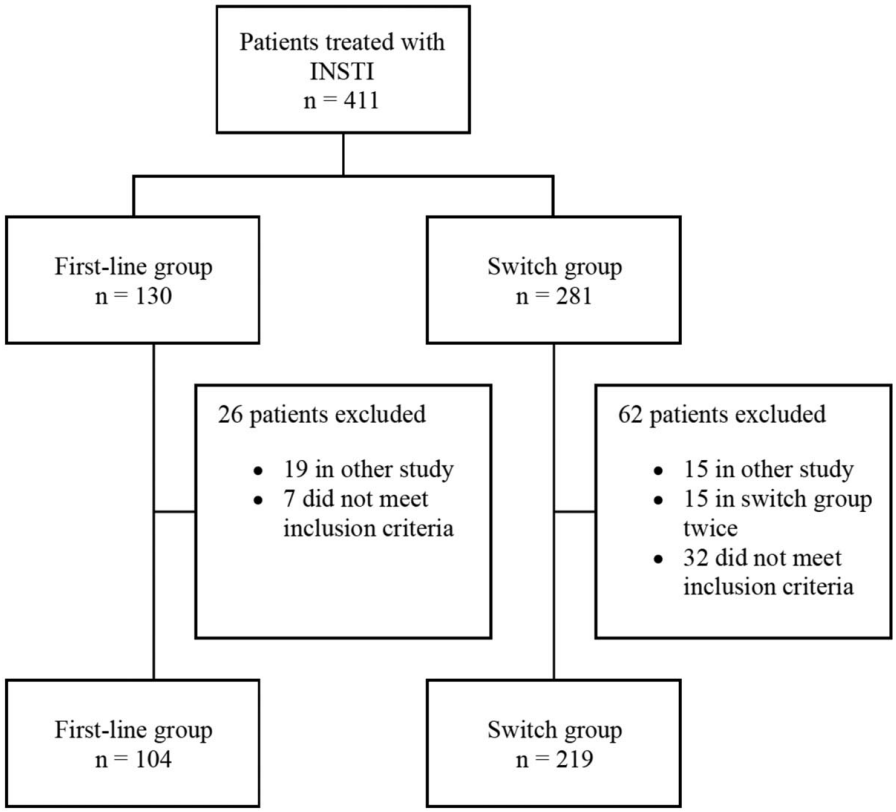

Figure 1. Patient selection.

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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References

[1] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed July 29, 2019.

[2] Gunthard 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.

[3] Ryom L, Boesecke C, Gisler V, et al. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. HIV Med 2016;17:83–8.

[4] Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet (London, England) 2017;390: 2073–82.

[5] Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013;369:1807–18.

[6] Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet (London, England) 2009;374:796–806.

[7] Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet (London, England) 2014;383:2222–31.

[8] DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet (London, England) 2012;379:2429–38.

[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] Zolopa AR, Berger DS, Lampiris H, et al. Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. J Infect Dis 2010;201:814–22.

[11] 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.

[12] 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.

[13] Powderly WG. Integrase inhibitors in the treatment of HIV-1 infection. J Antimicrob Chemother 2010;65:2485–8.

[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] Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. AIDS (London, England) 2017;31:1853–8.

[16] 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.

[17] de Boer M, van den Berk G, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS (London, England) 2016;30:2831–4.

[18] Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS (London, England) 2017;31:1201–3.

[19] Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. J Antimicrob Chemother 2019;74:754–60.

[20] Llibre JM, Montoliu A, Miro JM, et al. Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. HIV Med 2019;20:237–47.

[21] Jaeckle M, Khaykin P, Haberl A, et al. Efficacy of raltegravir-containing regimens in antiretroviral-naive and -experienced individuals in routine clinical practice. Int J STD AIDS 2016;27:1170–9.

[22] Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother 2017;72: 1752–9.

[23] Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr 2010;55:39–48.

[24] Jacobson K, Ogbuagu O. Integrase inhibitor-based regimens result in more rapid virologic suppression rates among treatment-naive human immunodeficiency virus-infected patients compared to non-nucleoside and protease inhibitor-based regimens in a real-world clinical setting: a retrospective cohort study. Medicine 2018;97:e13016.

[25] Naumann U, Moll A, Schleehauf D, et al. Similar efficacy and tolerability of raltegravir-based antiretroviral therapy in HIV-infected patients, irrespective of age group, burden of comorbidities and concomitant medication: real-life analysis of the German 'WIP' cohort. Int J STD AIDS 2017;28:893–901.

[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] Lee FJ, Amin J, Carr A. Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: a systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. PloS One 2014;9:e97482.

[28] Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015;373:795–807.

[29] 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.

[30] Stellbrink HJ, Reynes J, Lazzarin A, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS (London, England) 2013;27:1771–8.

[31] Letendre SL, Mills AM, Tashima KT, et al. ING116070: a study of the pharmacokinetics and antiviral activity of dolutegravir in cerebrospinal fluid in HIV-1-infected, antiretroviral therapy-naive subjects. Clin Infect Dis 2014;59:1032–7.

[32] de Boer MG, Brinkman K. Recent observations on intolerance of dolutegravir: differential causes and consequences. AIDS (London, England) 2017;31:868–70.

[33] Palich R, Tubiana R, Abdi B, et al. Plasma cystatin C as a marker for estimated glomerular filtration rate assessment in HIV-1-infected patients treated with dolutegravir-based ART. J Antimicrob Chem 2018;73:1935–9.

Darstellung der Publikation

Einleitung

Die Empfehlung aktueller Leitlinien zur Behandlung nicht vorbehandelter (therapienaiver) HIV- infizierter Patienten basiert derzeit in der Regel auf einer kombinierten antiretroviralen Therapie (cART), bestehend aus zwei Nukleosidanaloga (NRTIs) in Kombination mit einem dritten antiretroviralem Medikament[1–3]. Dieses kann entweder ein nicht-nukleosidischer Reverse-Transkriptase-Inhibitor (NNRTI), ein „geboosteter" Proteaseinhibitor (PI) oder ein Integrase-Strangtransfer-Inhibitor (INSTI) sein. Die HIV-Integrase ist eines der zentralen Enzyme im HIV-1-Replikationszyklus, indem sie den Einbau der bereits von der Reversen Transkriptase umgeschriebenen viralen DNA in das Wirtsgenom katalysiert. Die INSTIs hemmen den Strangtransfer, einen der wesentlichen Schritte des Enzyms, und verhindern so die Integration der viralen DNA in das Wirtsgenom[4].

Durch ihre gute Wirksamkeit und ihr günstiges Sicherheitsprofil im Vergleich zu NNRTIs und PIs haben sich die INSTIs, eine neuere Generation antiretroviraler Therapeutika, in verschiedenen Zulassungsversuchen als bevorzugtes Medikament bei der Behandlung therapienaiver Patienten herausgestellt[5–10].

Raltegravir (RAL, Isentress®) war 2007 der erste zugelassene INSTI [11]. Nicht nur in Bezug auf den Rückgang der Viruslast nach 48 Wochen bei naiven Patienten (RAL: 86%, Efavirenz (EFV): 82%, 95% confidence interval [CI]: -1.9 bis 10.3), sondern auch mit Blick auf behandlungsbezogene Nebenwirkungen (RAL: 44%, EFV: 77%, 95% CI: -40.2 bis -25), stellte sich Raltegravir gegenüber Efavirenz, einem nicht-nukleosidischen Reverse-Transkriptase-Inhibitor, als überlegen heraus[7]. Im Vergleich zu den anderen beiden untersuchten INSTIs, Dolutegravir und Elvitegravir, musste Raltegravir viele Jahre lang zwei mal täglich eingenommen werden, bis eine retardierte Formulierung zugelassen wurde, die nur einmal täglich einzunehmen ist [12].

Elvitegravir (EVG, Stribild® als „single- tablet regimen" (STR) mit Cobicistat (COB), Tenofovir- Disoproxylfumarat (TDF) und Emtricitabin (FTC)) muss in Kombination mit der Nahrungsaufnahme eingenommen werden und benötigt ein pharmakologisches Verstärken (Boosting) durch die Hemmung von Cytochrom P450 3A in der Leber. Dies kann jedoch zu ungewollten Wechselwirkungen mit anderen Medikamenten führen [13]. In randomisierten, kontrollierten Studien deutete sich eine virologische

Überlegenheit Elvitegravirs sowohl gegenüber Efavirenz (EVG: 88% EFV: 84%, 95% CI: -1.6% bis 8.8%) [14] als auch gegenüber Atazanavir/Ritonavir (ATV/r)(EVG: 90% ATV/r: 87%, 95% CI: -1.9% bis 7.8%) [9] an. Nach 96 Wochen zeigten die mit Elvitegravir behandelten Patienten deutlich weniger neuropsychologische Nebenwirkungen als Patienten, die mit Efavirenz (47% vs. 66%, P<.001) therapiert wurden[14] .

Dolutegravir (DTG, Tivicay® oder Triumeq® als STR mit Abacavir(ABC) und Lamivudin (3TC)) weist im Vergleich zu Elvitegravir und Raltegravir eine höhere Widerstandbarriere gegen die Bildung von Resistenzen auf, braucht nur einmal täglich unabhängig von der Nahrung eingenommen werden und hat zudem ein niedriges Interaktionspotential [15,16]. Im Vergleich zu Efavirenz (DTG: 88%, EFV: 81%, 95% CI: 2% bis 12%, P=.003) und Darunavir/Ritonavir (DRV/r) (DTG: 90%, DRV/r: 83%, 95% CI: 0.9% bis 13.2%) zeigt sich unter Dolutegravir ein etwas größerer Rückgang der Viruslast nach 48 Wochen [6,8]. Bei bereits vorbehandelten Patienten zeigten cARTs, die auf einmaliger Einnahme von DTG pro Tag basieren, einen größeren virologischen Effekt als die zweimal tägliche Einnahme mit RAL (DTG: 71%, RAL: 64%, 95% CI 0.7% bis 14.2%)[17].

INSTIs werden gut von den Patienten toleriert und sind generell als sehr sicher einzustufen. Unterbrechungen der INSTI-Therapie auf Grund von Nebenwirkungen in randomisierten, kontrollierten Studien traten nur bei 1% bis 4% der Patienten auf. Auch konnten bisher keine spezifischen Organschädigungen mit INSTIs in Verbindung gebracht werden[18]. In letzter Zeit berichten jedoch vermehrt retrospektive Untersuchungen von Fällen neuropsychiatrischer Nebenwirkungen bei Patienten, die mit DTG therapiert wurden[19–22].

In der vorliegenden retrospektiven Studie habe ich die Wirksamkeit und das Sicherheitsprofil der drei 2014 erhältlichen INSTIs in einer Real-World-Kohorte HIV-infizierter Patienten untersucht. Dabei wurden die virologischen, immunologischen und klinischen Unterschiede zwischen diesen drei Subgruppen (EVG, DTG, RAL) berücksichtigt und zudem zwischen bereits vorbehandelten (switch-Gruppe) und nicht vorbehandelten Patienten (fist-line-Gruppe) unterschieden. Genvoya (Genvoya® als STR mit EVG, COB, FTC und TDF) und Biktegravir (Biktarvy® als STR mit Biktegravir (BIC) Tenofoviralafenamid (TAF) und FTC)), die neuesten INSTI-Regime, waren zum Zeitpunkt der Studie noch nicht zugelassen und wurden deshalb auch nicht in die Analysen eingeschlossen [5].

Ziele

Das Ziel dieser retrospektiven Kohortenstudie war der Vergleich der drei Integrase-Strangtransfer-Inhibitoren Elvitegravir, Dolutegravir und Raltegravir im Hinblick auf Sicherheit, Wirksamkeit sowie Häufigkeit und Gründe für Therapieunterbrechungen bei HIV-infizierten Patienten. Bemerkenswert ist hierbei, dass die Gesamt-Kohorte in Untergruppen untersucht wurde: Therapie-naive Patienten und bereits mit einer HIV-Medikation vorbehandelte Patienten wurden jeweils für sich betrachtet, sodass die virologische Wirksamkeit, Nebenwirkungen und das Sicherheitsprofil individuell für jede Subgruppe beurteilt werden konnten. Andere Studien haben entweder nicht alle drei zuglassenden INSTIs verglichen [18,20] , haben nicht zwischen vorbehandelten und Therapie- naiven Patienten unterschieden[20] oder fokussierten sich nur auf bestimmte Aspekte wie z.B. die Gründe für eine Therapieunterbrechung[18–20,23].

Methodik

Bei dieser Arbeit handelt es sich um eine retrospektive Kohortenanalyse HIV-infizierter Patienten, die im Ambulanzzentrum für Infektiologie des Universitätsklinikums Hamburg Eppendorf behandelt wurden und bei denen zwischen Mai 2007 und Dezember 2014 eine kombinierte antiretrovirale Therapie (cART) basierend auf einem der drei zu der Zeit zugelassenen INSTIs begonnen wurde. Das Studienvorhaben wurde dem zuständigen Ethikkomitee der Ärztekammer Hamburg (WF-72/18) angezeigt.

Die Patienten wurden aus einer elektronischen Datenbank des Universitätsklinikums basierend auf der Verschreibung eines der drei INSTIs herausgefiltert, wobei sowohl behandlungsnaive als auch schon vorbehandelte Patienten in die Analyse mit aufgenommen wurden. Patienten, die im Zuge einer randomisierten, kontrollierten Studie eine cART basierend auf INSTIs erhalten haben, wurden aus der Analyse ausgeschlossen. Damit das virologische Ansprechen der auf INSTI basierenden cART genau bewertet werden konnte, wurden nur Patienten in die Kohorte eingeschlossen, bei denen die initiale Viruslast im Zeitraum von 3 Monaten vor Start der Therapie bis 1 Woche nach Start erhoben wurde. Wenn die jeweiligen initialen immunologischen und virologischen Daten vorhanden waren, wurden auch die Laborwerte der routinemäßigen Kontrolluntersuchungen in die Analyse eingeschlossen. Eine messbare Viruslast von >50 Kopien/ml nach 12 Monaten wurde als virologisches Versagen bewertet. Demografische und klinische Parameter

wie Viruslast, CD4- Zellzahl, Kreatinin, High-density Lipoprotein (HDL), Low-density Lipoprotein (LDL), Alanin- Transaminase (ALT), Aspartat- Transaminase (AST), Cholesterol, Triglyceride und C-reaktives Protein (CRP) wurden elektronischen Gesundheitskarten entnommen. Die behandelnden Ärzte dokumentieren normalerweise die Gründe für einen Wechsel oder eine Unterbrechung der cART, ebenso die Nebenwirkungen, sodass auch diese Informationen der elektronischen Datenbanken entnommen werden konnten. Die Symptome Depressionen, Schwindel und Schlafstörungen wurden als neuropsychiatrische Nebenwirkungen klassifiziert.
Die erhobenen Daten wurden mit Hilfe des Student t-Tests oder Wilcoxon rank-sum-Tests verglichen. Wo es erforderlich war, wurde der Chi-square- Test oder der Fischer exact-Test zur Analyse der Daten angewendet. Die deskriptive Analyse der Daten wurde mit Hilfe von Stata v. 14.2 (StataCorp, CollegeStation, TX) durchgeführt.

Ergebnisse

Es zeigte sich, dass nach drei Monaten von den 189 ausgewerteten Patienten 73% der behandlungsnaiven und 86% der behandlungserfahrenen Patienten eine nicht nachweisbare Viruslast (< 50 Kopien/ml) erlangten. Hierbei konnte unter Dolutegravir nach 3 Monaten eine etwas höhere Rate an Patienten mit vollständiger Virus-suppression im Vergleich zu Raltegravir und Elvitegravir gezeigt werden (First-line: EVG: n=16/22 (80%), DTG: n=17/19 (90%), RAL: n=13/22 (59%), P=.08; Switch: EVG: n=19/24 (79%), DTG: n=50/53 (94%), RAL: n=39/49 (80%) P=.05). Zwölf Monate nach Therapiebeginn hatten 92 % der Patienten der first-line-Gruppe (EVG: n = 22/23 (96%), DTG: n = 34/37 (92%), RAL: n = 28/31 (90%)) und 88% der switch-Gruppe (EVG: n=32/34 (94%); DTG: n=69/77 (90%), RAL: n=67/79 (85%)) eine Viruslast unter der Nachweisgrenze (<50 Kopien/ml). Insgesamt war also nach 12 Monaten bei insgesamt hoher virologischer Wirksamkeit kein signifikanter Unterschied in Bezug auf die virologische Wirksamkeit der drei INTSIs erkennbar.
Die CD4+ T-Zellzahl blieb sowohl in der first-line-Gruppe als auch in der switch-Gruppe nach 12 Monaten Therapie nur bei einigen wenigen Patienten unter 200/ml (First-line: EVG: n=3/18 (13%), DTG: n=6/37 (16%), RAL: n=3/31 (10%), P= .8), (Switch: EVG: n=1/34 (3%), DTG: n=2/77 (3%), RAL: n=11/79 (14%), P=.02).

Die Laborparameter verhielten sich zwischen allen Subgruppen initial sehr ähnlich. Allerdings war nach 12 Monaten der mittlere Kreatininwert etwas höher bei Patienten in der switch-Gruppe, die mit DTG behandelt wurden, im Vergleich zu jenen die EVG oder RAL erhalten haben (EVG:1.0 mg/dl, DTG:1.1mg/dl, RAL: 1.0mg/dl, p=0,12). Die Kreatinin-Erhöhungen kann aber durch eine nichtpathologische Hemmung des organischen Kationentransporters 2 (OCT2) in den proximalen Tubuli, der für die tubuläre Sekretion von Kreatinin verantwortlich ist, erklärt werden[9]. In der first-line-Gruppe zeigten sowohl EVG als auch DTG einen etwas größeren Anstieg der Kreatininwerte verglichen mit RAL (Initial: EVG: 0.9mg/dl, DTG: 0.8mg/dl, RAL: 0.9mg/dl; nach 12 Monaten: EVG: 1.0 mg/dl, DTG: 1.0 mg/dl, RAL: 0.9 mg/dl, p=0,1). Allgemein traten in allen Subgruppen relativ wenig, meist nur recht milde Nebenwirkungen auf (12% first-line- vs. 10% switch- Gruppe). Die am häufigsten beschriebenen Nebenwirkungen waren dabei Schwindel, Depressionen und Grippe-ähnliche Symptome. Allerdings traten unter Dolutegravir in der switch-Gruppe, verglichen mit Elvitegravir und Raltegravir, deutlich mehr neuropsychiatrische Nebenwirkungen wie Depressionen, Schwindel und Schlafstörungen auf (DTG: 11%, n=10; EVG: 2%, n=1; RAL: 1%, n=1) auf. Insgesamt führten die Nebenwirkungen mit 2% (n=2/104) in der first-line- Gruppe und 1% (n=3/219) in der switch- Gruppe aber nur selten zu einer Therapieunterbrechung.

Schlussfolgerung

Antiretrovirale INSTI-basierte Kombinationstherapien wirken sehr zuverlässig und hocheffizient. Zwischen den INSTIs Raltegravir, Elvitegravir und Dolutegravir sind nur geringe Unterschiede in Bezug auf die Wirksamkeit und das Sicherheitsprofil erkennbar. Allerdings sollte das Bewusstsein geschärft werden, dass bei switch-Patienten unter Dolutegravir ein höheres Potential besteht, neuropsychiatrische Nebenwirkungen wie Schwindel oder Schlafstörungen zu entwickeln.

Literaturverzeichnis

1. 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 HHS Public Access. *JAMA*. 2016;316(2):191-210. doi:10.1001/jama.2016.8900
2. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*. https://aidsinfo.nih.gov/e-news. Accessed July 29, 2019.
3. Ryom L, Boesecke C, Gisler V, et al. Essentials from the 2015 European AIDS Clinical Society (EACS) guidelines for the treatment of adult HIV-positive persons. *HIV Med*. 2016;17(2):83-88. doi:10.1111/hiv.12322
4. Lataillade M, Kozal MJ. The Hunt for HIV-1 Integrase Inhibitors. *AIDS Patient Care STDS*. 2006;20(7):489-501. doi:10.1089/apc.2006.20.489
5. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiori. *Lancet (London, England)*. 2017;390(10107):2073-2082. doi:10.1016/S0140-6736(17)32340-1
6. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection. *N Engl J Med*. 2013;369(19):1807-1818. doi:10.1056/NEJMoa1215541
7. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. doi:10.1016/S0140-6736(09)60918-1
8. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014;383(9936):2222-2231. doi:10.1016/S0140-6736(14)60084-2
9. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-. *Lancet (London, England)*. 2012;379(9835):2429-2438. doi:10.1016/S0140-6736(12)60918-0
10. 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(7):461-471. doi:10.7326/M14-1084
11. Hicks C, Gulick RM. Raltegravir: The First HIV Type 1 Integrase Inhibitor. *Clin Infect Dis*. 2009;48(7):931-939. doi:10.1086/597290
12. Eron JJ, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial.

Lancet Infect Dis. 2011;11(12):907-915. doi:10.1016/S1473-3099(11)70196-7

13. Zolopa AR, Berger DS, Lampiris H, et al. Activity of Elvitegravir, a Once-Daily Integrase Inhibitor, against Resistant HIV Type 1: Results of a Phase 2, Randomized, Controlled, Dose-Ranging Clinical Trial. *J Infect Dis*. 2010;201(6):814-822. doi:10.1086/650698
14. 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. *JAIDS J Acquir Immune Defic Syndr*. 2013;63(1):96-100. doi:10.1097/QAI.0b013e318289545c
15. 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(11):927-935. doi:10.1016/S1473-3099(13)70257-3
16. Powderly WG. Integrase inhibitors in the treatment of HIV-1 infection. *J Antimicrob Chemother*. 2010;65(12):2485-2488. doi:10.1093/jac/dkq350
17. 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. *www.thelancet.com*. 2013;382. doi:10.1016/S0140-6736(13)61221-0
18. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. *AIDS*. 2017;31(13):1853-1858. doi:10.1097/QAD.0000000000001590
19. 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(1):56-63. doi:10.1111/hiv.12468
20. de Boer MGJ, van den Berk GEL, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *AIDS*. 2016;30(18):2831-2834. doi:10.1097/QAD.0000000000001279
21. Llibre J, Montoliu A, Miró J, et al. Discontinuation of dolutegravir, elvitegravir/cobicistat and raltegravir because of toxicity in a prospective cohort. *HIV Med*. 2019;20(3):237-247. doi:10.1111/hiv.12710
22. Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. *J Antimicrob Chemother*. 2019;74(3):754-760. doi:10.1093/jac/dky497
23. Peñafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother*. 2017;72(6):1752-1759. doi:10.1093/jac/dkx053

Zusammenfassung Englisch

The aim of this retrospective cohort study was to compare safety, efficacy and discontinuation rates 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 neuropsychiatric symptoms is warranted during follow-up in those patients.

Zusammenfassung Deutsch

In dieser retrospektiven Studie habe ich die Wirksamkeit und das Sicherheitsprofil der 2014 erhältlichen Integrase- Strangtransfer Inhibitoren (INSTIs) Raltegravir, Dolutegravir und Elvitegravir in einer Real-World-Kohorte HIV-infizierter Patienten untersucht. Dabei wurden die virologischen, immunologischen und klinischen Unterschiede zwischen diesen drei Subgruppen berücksichtigt und zudem zwischen bereits vorbehandelten (switch-)Patienten, die zu einem der drei INSTIs gewechselt sind und nicht vorbehandelten (firstline-) Patienten unterschieden. 104 behandlungsnaive und 219 bereits vortherapierte HIV-infizierte Patienten wurden in die Analysen eingeschlossen, die in einem Zeitraum von Mai 2007 bis Dezember 2014 in unserem Institut vorstellig waren.

Zwölf Monate nach Therapiebeginn hatten 92 % der Patienten der firstline-Gruppe (EVG: 96%, n = 22/23; DTG: 92%, n = 34/37; RAL: 90%, n = 28/31) und 88% der switch- Gruppe (EVG: 94%, n=32/34; DTG: 90%, n=69/77; RAL: 85%, n=67/79) eine Viruslast unter der Nachweisgrenze (<50 Kopien/ml). Nebenwirkungen jeglicher Art traten bei 12% (n = 12/104) der Patienten der first-line-Gruppe und bei 10% (n = 21/219) der Patienten der switch-Gruppe auf. Allgemein traten in allen Subgruppen relativ wenig, meist nur recht milde Nebenwirkungen auf (12% firstline- vs. 10% switch- Gruppe). Die am häufigsten beschriebenen Nebenwirkungen waren dabei Schwindel, Depressionen und Grippe-ähnliche Symptome. Allerdings traten unter Dolutegravir in der switch- Gruppe, verglichen mit EVG und RAL deutlich mehr neuropsychiatrische Nebenwirkungen wie Depressionen, Schwindel und Schlafstörungen auf (DTG: 11%, n=10; EVG: 2%, n=1; RAL: 1%, n=1) auf. Insgesamt führten die Nebenwirkungen mit 2% (n=2/104)in der firstline- Gruppe und 1% (n=3/219) in der Switch- Gruppe aber nur selten zu einer Therapieunterbrechung. In Anbetracht der etwas erhöhten Inzidenz an Schwindel und Schlafstörungen bei switch-Patienten, die zu DTG gewechselt sind, ist allerdings Achtsamkeit bei Kontrolluntersuchen in Bezug auf neuropsychiatrische Symptome geboten.

Erklärung des Eigenanteils

Die gesamte Datenerhebung aus den elektronischen Gesundheitsakten wurde von Marleen Albersmeier (ehem. Franz) durchgeführt. Für die Gesamtanalyse waren Marleen Albersmeier, Dr. Thomas Brehm und PD. Dr. Julian Schulze zur Wiesch gemeinsam verantwortlich. Die statistische Auswertung wurde von Dr. Benno Kreuls durchgeführt. Das Schreiben des gesamten Manuskriptes haben Marleen Albersmeier, Dr. Thomas Brehm und PD. Dr. Julian Schulze zur Wiesch sowie Dr. Benno Kreuls durchgeführt, die Anfertigungen der Figuren und Tabellen wurde von Marleen Albersmeier allein durchgeführt. Beratend und korrekturlesend waren hier PD. Dr. Julian Schulze zur Wiesch und Dr. Thomas Brehm vornehmlich tätig, sowie teilweise Dr. O. Degen. In der Phase des Review Verfahrens des Journals waren Dr. Thomas Brehm und Marleen Albersmeier gemeinsam in der Korrektur des Manuskriptes tätig.

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Lebenslauf

Der Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....