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Tolerability of integrase inhibitors in a real-life setting

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Background: Integrase inhibitors have shown better tolerability than other drugs in clinical trials, but some post-marketing data have suggested potential differences among them.

Aims: We compared rates and reasons for discontinuation of raltegravir-, elvitegravir- and dolutegravir-based regimens in a large cohort of HIV-infected patients.

Methods: Retrospective analysis of a prospectively followed cohort including all antiretroviral-naive and all virologically suppressed antiretroviral-experienced patients prescribed a first regimen containing raltegravir, elvitegravir or dolutegravir with at least one follow-up visit. Major outcomes were early discontinuation ($\leq$1 year) due to any reason and more specifically due to toxicity. Incidence was calculated as number of episodes per 1000 person-years. Risk factors for discontinuation were assessed by multivariate Cox models.

Results: Early discontinuations due to any reason were 271 (raltegravir), 168 (elvitegravir) and 264 (dolutegravir) per 1000 patient-years ($P = 0.0821$). Early discontinuations due to toxicity were 76 (raltegravir), 103 (elvitegravir) and 81 (dolutegravir) per 1000 patient-years ($P = 0.6792$). Overall, the most common toxicities leading to discontinuation were neuropsychiatric, osteomuscular or digestive. Most frequent neuropsychiatric manifestations reported at discontinuation were insomnia, dizziness, headache and anxiety irrespective of the integrase inhibitor. Among discontinuations due to toxicity, neuropsychiatric effects were more common with dolutegravir than with raltegravir or elvitegravir ($P = 0.0046$). Age (HR 1.04, 95% CI 1.02–1.07, $P = 0.0007$) was the only independent risk factor for early discontinuation due to toxicity.

Conclusions: Discontinuations due to any reason tended to be less common with elvitegravir, but discontinuations due to toxicity did not differ among integrase inhibitors. Neuropsychiatric toxicity leading to drug discontinuation was more frequent with dolutegravir.

Introduction

Currently available integrase inhibitors have become preferred anchor drugs for antiretroviral-naive patients in different guidelines worldwide[1–3] because they have compared favourably with efavirenz[4–6] and boosted protease inhibitors[7–9] in randomized clinical trials. Discontinuation of raltegravir, elvitegravir or dolutegravir due to adverse effects in clinical trials has been usually lower than that of the comparator drug, ranging between 1% and 4% of patients at 48 or 96 weeks.[4–9] No specific organ toxicity associated with integrase inhibitors was identified in clinical trials. Raltegravir was the first integrase inhibitor approved (US FDA, October 2007; EMA, January 2008) but its initial use was preferentially addressed to salvage antiretroviral therapy. Elvitegravir [as a single-tablet regimen (STR) combination with tenofovir disoproxil fumarate, emtricitabine and cobicistat] was subsequently approved (FDA, August 2012; EMA, May 2013) and dolutegravir has been the one most recently approved first as a single drug (FDA, August 2013; EMA, November 2013) and later as an STR in combination with abacavir plus lamivudine (FDA, August 2014; EMA, September 2014). In contrast with raltegravir, elvitegravir and dolutegravir use was preferentially aimed at antiretroviral-naive patients or to treated patients requiring antiretroviral switch for reasons other than virological failure.

Initial publications on the tolerability of integrase inhibitors focused on raltegravir-associated muscular toxicity that usually consisted of mild or asymptomatic transient increases in muscular enzymes and was reported as a severe event in just a handful of patients.[10,11] However, last year an observational Dutch cohort study

reported an unexpectedly high rate of dolutegravir discontinuation due to toxicity, mainly neuropsychiatric effects.[12] It was followed by other cohort reports at major HIV conferences informing on variable rates of dolutegravir discontinuation due to adverse effects.[13–21] Preliminary 24 week data from the STRIIVING open-label randomized clinical trial assessing the efficacy and safety of switching from boosted protease inhibitors to dolutegravir in virologically suppressed HIV-infected patients also showed several patients discontinuing dolutegravir due to neuropsychiatric effects in the first days of therapy.[22] In contrast, switching from efavirenz to dolutegravir in virologically suppressed patients with ongoing efavirenz-associated CNS side effects was associated with significant improvement in CNS toxicity, with a reduction in overall CNS score and improvement in depression, dizziness and quality of sleep, without affecting antiretroviral efficacy.[23,24] Interestingly, the potential for neuropsychiatric effects is acknowledged in the current EMA Summary of Product Characteristics of all three available integrase inhibitors.[25–27] Whether there may be differences in the rate of discontinuation due to toxicity among currently available integrase inhibitors and whether neuropsychiatric adverse effects leading to discontinuation may be more common with dolutegravir than with other integrase inhibitors is currently unclear.

We aimed to compare the rates and reasons for discontinuation due to any reason and more specifically due to adverse effects of raltegravir-, elvitegravir- and dolutegravir-based regimens in a large cohort of HIV-infected patients.

Patients and methods

This retrospective analysis used prospectively registered data from all antiretroviral-naive patients and all antiretroviral-experienced patients with plasma HIV-RNA below the detection level prospectively followed at the Hospital Clinic of Barcelona (Spain) who were prescribed a first regimen containing raltegravir, elvitegravir or dolutegravir and had at least one follow-up visit. Our plan was to restrict the study population to these two groups of patients to avoid selection bias, as raltegravir was the only integrase inhibitor available for several years and almost exclusively used in salvage therapy. In our centre, patients' data are routinely registered into a clinical history database approved by the Local Institutional Review Board that includes detailed information on antiretroviral prescription and reasons for discontinuation. Potential reasons pre-specified in the database for antiretroviral drug discontinuation include virological failure, adverse effects, therapy simplification, risk of interactions, medical decision due to other reasons, lost to follow-up and death. Whenever the reason for discontinuation includes potential toxicity to any antiretroviral drug, a description of relevant clinical symptoms and/or laboratory parameters associated with the potential adverse effect is usually collected in the clinical course of the corresponding follow-up visit.

For the purpose of this study, changes in integrase inhibitor therapy involving dose (either total daily dose or number of doses per day) or pharmacological presentation (either as an individual drug or as a fixed-dose combination) were not considered as discontinuations as long as the originally prescribed integrase inhibitor remained in the regimen. If more than one reason for discontinuation was present in a given patient, we considered the drug discontinuation as due to toxicity whenever adverse effects were reported irrespective of other concomitant reasons. Patients were censored at the end of February 2016 (when the Dutch report at CROI 2016[12] became available, to avoid any potential influence on dolutegravir discontinuation), or when they switched their first integrase inhibitor, were lost to follow-up or died, whichever came first.

We pre-defined the following two major outcomes: early discontinuation (≤1 year), and early discontinuation due to toxicity. We decided to frame major outcomes within 1 year of follow-up for the following reasons: (i) most relevant toxicities associated with integrase inhibitors in clinical trials and cohort studies have been usually acute; (ii) because the longer the duration of antiretroviral therapy, the less clear the relationship between any potential acute adverse effect and a given drug; and (iii) to avoid bias favouring drugs from earlier time points, since patients doing well who started their first integrase inhibitor earlier would contribute more patient-years than those who started more recently. Specific toxicities were grouped by organs/systems according to the description in the clinical history database. We also performed sensitivity analyses restricted to the period 2014–15, when all three integrase inhibitors were available, and results did not change (see Supplementary data Tables S1–S5, available at *JAC* Online). Quantitative data were compared with ANOVA or Kruskal–Wallis tests, and qualitative data with chi-squared or Fisher's exact tests. Incidence was calculated as number of episodes per 1000 person-years. Incidence rate ratios (IRRs) for each integrase inhibitor were estimated considering the arbitrary reference of 1 for raltegravir. Negative binomial regression models using the likelihood ratio or Wald tests were used for IRR comparisons. Risk factors for discontinuation were assessed by multivariate Cox models.

Ethics

According to current Spanish regulations, the study was classified as a post-authorization study with a non-prospective design by the Spanish Agency for Medicine and Health Products[28]; it was approved by the Local Institutional Review Board and informed consent was not required. The authors declare that they have been completely independent in the design, analysis and writing of this study.

Results

Population characteristics

There were 557 patients treated with raltegravir, 322 patients treated with elvitegravir and 212 patients treated with dolutegravir meeting criteria for inclusion in this analysis. Patients treated with raltegravir were also treated with emtricitabine/tenofovir disoproxil fumarate ($n = 390$, 70%), lamivudine/abacavir ($n = 139$, 25%) or with other agents ($n = 28$, 5%). All patients treated with elvitegravir in this cohort had received it as the STR containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Patients treated with dolutegravir were taking it either as the STR containing dolutegravir/lamivudine/abacavir ($n = 93$, 44%) or as the individual dolutegravir tablet together with other antiretroviral agents ($n = 119$, 56%); 36 of those taking the individual dolutegravir tablet were also taking the fixed-dose combination lamivudine/abacavir. Table 1 shows the characteristics of patients in each group. Patients on elvitegravir were younger, more commonly men who had sex with men, and with higher baseline CD4 cell count, and patients on raltegravir were less frequently males.

Incidence of early discontinuation due to any reason

There was a trend to a lower incidence of early discontinuation with elvitegravir (168 episodes per 1000 patient-years) than with raltegravir (271 episodes per 1000 patient-years) or with dolutegravir (264 episodes per 1000 patient-years) ($P = 0.0821$) (Table 2). Relative to raltegravir, unadjusted IRRs (95% CI) for elvitegravir and dolutegravir early discontinuation were 0.62 (0.39–0.97) (Bonferroni corrected P value 0.1091) and

Table 1. Baseline characteristics

Characteristic	Raltegravir ($n = 557$)	Elvitegravir ($n = 322$)	Dolutegravir ($n = 212$)	*P* value
Age (mean, SD)	45 (11)	39 (10)	46 (11)	<0.0001
Gender, *n* (%)				
men	443 (80)	283 (88)	183 (86)	0.0025
women	114 (20)	39 (12)	29 (14)	
Route of infection, *n* (%)				
heterosexual sex	127 (23)	47 (15)	40 (19)	<0.0001
MSM	292 (52)	237 (74)	143 (67)	
IDU	98 (18)	17 (5)	23 (11)	
other or unknown	40 (7)	21 (7)	6 (3)	
CD4 cells/mm^3 at HIV diagnosis, median (IQR)	343 (193–519)	404 (241–556)	370 (201–533)	0.0176
HIV RNA copies/mL at HIV diagnosis (median, IQR)	17170 (1339–138000)	24625 (2364–118800)	30773 (3055–132100)	0.2917

Table 2. Incidence of early discontinuation (≤1 year) with each of the three integrase inhibitors: overall results

Drug	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
Raltegravir	557	71 (12.7)	262.06	270.93	1	0.0821
Elvitegravir	322	26 (8.1)	155.06	167.68	0.62 (0.39–0.97)	
Dolutegravir	212	26 (12.3)	98.66	263.53	0.97 (0.62–1.52)	

0.97 (0.62–1.52) (Bonferroni corrected *P* value 1.0000) respectively; relative to elvitegravir, unadjusted IRR (95% CI) for dolutegravir was 1.57 (0.91–2.71) (Bonferroni corrected *P* value 0.3092). There were no differences in the rate of overall discontinuation between antiretroviral-naive (241 episodes per 1000 patient-years) and antiretroviral-experienced with undetectable plasma HIV-RNA (234 episodes per 1000 patient-years) ($P = 0.8897$) (Table 3). However, the rate of early discontinuation for raltegravir was higher in naive versus non-naive patients (304 versus 193 episodes per 1000 patient-years, $P = 0.1039$), for dolutegravir lower in naive versus non-naive patients (186 versus 450 episodes per 1000 patient-years, $P = 0.0329$), and for elvitegravir roughly similar in naive versus non-naive patients (158 versus 184 episodes per 1000 patient-years, $P = 0.7032$) (Table 3).

Incidence and reasons for early discontinuation not due to toxicity

The incidence of early discontinuation not attributed to toxicity was lower in patients taking elvitegravir (64 episodes per 1000 patient-years) than in patients taking raltegravir (191 episodes per 1000 patient-years) or dolutegravir (182 episodes per 1000 patient-years) ($P = 0.0003$). Incidence of overall early discontinuation not due to toxicity was not significantly different between antiretroviral-naive (137 episodes per 1000 patient-years) and antiretroviral-experienced patients with undetectable plasma HIV-RNA (180 episodes per 1000 patient-years) ($P = 0.2508$). There were no differences between antiretroviral-naive and antiretroviral-experienced patients with undetectable plasma HIV-RNA in the incidence of early discontinuation not due to toxicity in raltegravir-treated patients (206 versus 154 episodes per 1000 patient-years, $P = 0.3713$) and elvitegravir-treated patients (42 versus 100 episodes per 1000 patient-years, $P = 0.1055$), but the incidence of early discontinuation not attributed to toxicity in dolutegravir-treated patients was significantly higher in antiretroviral-experienced patients with undetectable plasma HIV-RNA (415 episodes per 1000 patient-years) than in antiretroviral-naive patients (86 episodes per 1000 patient-years) ($P = 0.0009$). Reasons for discontinuation not due to toxicity included: therapy simplification ($n = 25$), medical decision ($n = 8$), virological failure ($n = 3$) and lost to follow-up/dead ($n = 15$) for raltegravir; risk of interactions ($n = 7$), virological failure ($n = 1$) and lost/dead ($n = 2$) for elvitegravir; and therapy simplification ($n = 15$), risk of interactions ($n = 1$), medical decision ($n = 1$) and lost/dead ($n = 1$) for dolutegravir.

Incidence of early discontinuation due to toxicity

Although the incidence of early discontinuation due to adverse effects was highest for elvitegravir and lowest for raltegravir, there were no significant differences among the three drugs (Table 4). The rate of early dolutegravir discontinuation due to adverse effects was double when dolutegravir was combined with abacavir plus lamivudine than when it was not, although this difference was not significant (Table 5). Overall, the incidence of early discontinuation due to adverse effects was higher in naive (103 episodes per 1000 patient-years) than in experienced (48 episodes per 1000 patient-years) patients ($P = 0.0308$) (Table 6).

Table 3. Incidence of early discontinuation (≤1 year) with each of the three integrase inhibitors: antiretroviral-naive versus antiretroviral-experienced patients with plasma HIV-RNA below the detection level

Group	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
All naive	739	84 (11.4)	349.23	240.53	1	0.8897
All experienced	352	39 (11.1)	166.55	234.16	0.97 (0.67–1.42)	
Raltegravir						
naive	396	56 (14.1)	184.34	303.79	1	0.1039
experienced	161	15 (9.3)	77.72	192.99	0.64 (0.36–1.12)	
Elvitegravir						
naive	196	15 (7.7)	95.13	157.68	1	0.7032
experienced	126	11 (8.7)	59.93	183.55	1.16 (0.53–2.53)	
Dolutegravir						
naive	147	13 (8.8)	69.76	186.35	1	0.0329
experienced	65	13 (20.0)	28.90	449.84	3.11 (1.03–9.39)	

Table 4. Incidence of early discontinuation (≤1 year) due to adverse effects with each of the three integrase inhibitors: overall results

Drug	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
Raltegravir	557	20 (3.6)	262.06	76.32	1	0.6792
Elvitegravir	322	16 (5.0)	155.06	103.19	1.35 (0.70–2.61)	
Dolutegravir	212	8 (3.8)	98.66	81.09	1.06 (0.47–2.41)	

Table 5. Incidence of early discontinuation (≤1 year) due to adverse effects in dolutegravir-treated patients according to the accompanying drugs: abacavir/lamivudine versus other drugs

Dolutegravir	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
+Abacavir/lamivudine	129	6 (4.7)	62.06	96.69	1	0.4795
+Other drugs	83	2 (2.4)	36.60	54.64	0.47 (0.06–3.85)	

Table 6. Incidence of early discontinuation (≤1 year) due to adverse effects: antiretroviral-naive versus antiretroviral-experienced patients with plasma HIV-RNA below the detection level

Group	Subjects	Episodes (%)	Time at risk (person-years)	Incidence (episodes per 1000 person-years)	Unadjusted IRR (95% CI)	*P* value
All naive	739	36 (4.9)	349.23	103.08	1	0.0308
All experienced	352	8 (2.3)	166.55	48.03	0.42 (0.16–1.05)	
Raltegravir						
naive	396	18 (4.5)	184.34	97.65	1	0.0368
experienced	161	2 (1.2)	77.72	25.73	0.19 (0.03–1.09)	
Elvitegravir						
naive	196	11 (5.6)	95.13	115.63	1	0.5376
experienced	126	5 (4.0)	59.93	83.43	0.72 (0.25–2.08)	
Dolutegravir						
naive	147	7 (4.8)	69.76	100.34	1	0.1587
experienced	65	1 (1.5)	28.90	34.60	0.16 (0.01–2.85)	

Table 7. Profile of early (≤1 year) discontinuation due to adverse effects among the three integrase inhibitors

	Raltegravir ($n = 20$, 3.6%)	Elvitegravir ($n = 16$, 5.0%)	Dolutegravir ($n = 8$, 3.8%)	*P* value
Neuropsychiatric ($n = 17$)[a]	7 (35%)	3 (19%)	7 (88%)	0.0046
Muscular ($n = 12$)	3 (15%)	6 (38%)	3 (38%)	0.2442
Digestive ($n = 11$)	7 (35%)	4 (25%)	0	0.1793
Skin/mucous membranes ($n = 6$)	4 (20%)	2 (13%)	0	0.4557
Systemic ($n = 5$)	2 (10%)	0	3 (38%)	0.0224
Respiratory ($n = 1$)	1 (5%)	0	0	1
Kidney ($n = 1$)	0	1	0	0.5455
Number of organs/systems				
1	17 (85%)	16 (100%)	5 (63%)	0.0656
>1	3 (15%)	0	3 (37%)	

All results are *n* (%).

[a]Neuropsychiatric clinical symptoms among patients discontinuing integrase inhibitors due to adverse effects: Raltegravir ($n = 7$): Patient 1: somnolence, myalgia, malaise; Patient 2: insomnia; Patient 3: dizziness; Patient 4: insomnia; Patient 5: dizziness; Patient 6: insomnia, anxiety, headache; Patient 7: headache, irritability. Elvitegravir ($n = 3$): Patient 1: insomnia, headache, vivid dreams; Patient 2: dizziness, somnolence; Patient 3: insomnia. Dolutegravir ($n = 7$): Patient 1 (+other): dizziness, myalgia, malaise; Patient 2 (+abacavir/lamivudine): insomnia; Patient 3 (+abacavir/lamivudine): insomnia, headache, confusion; Patient 4 (+other): insomnia, nightmares; Patient 5 (+abacavir/lamivudine): insomnia; Patient 6 (+abacavir/lamivudine): anxiety, arthralgia, insomnia, headache; Patient 7 (+abacavir/lamivudine): anxiety, insomnia.

Clinical manifestations of adverse effects leading to integrase inhibitor early discontinuation

Table 7 shows the profile of early discontinuation due to adverse effects among the three integrase inhibitors. The most common adverse effects were neuropsychiatric ($n = 17$), followed by osteomuscular ($n = 12$) and digestive ($n = 12$) (Table 7). Neuropsychiatric and systemic effects were significantly more common with dolutegravir than with raltegravir or elvitegravir. Almost all patients discontinuing dolutegravir due to toxicity had experienced neuropsychiatric effects ($n = 7$, 88%) in contrast to those discontinuing raltegravir ($n = 7$, 35%) or elvitegravir ($n = 3$, 19%) due to toxicity ($P = 0.0046$). Clinical manifestations of neuropsychiatric effects leading to early discontinuation, as reported in the medical database, were heterogeneous but did not substantially differ among integrase inhibitors. The most common clinical neuropsychiatric manifestations leading to early discontinuation were insomnia, dizziness or headache.

Risk factors for early discontinuation of integrase inhibitors

We were unable to find any significant factor influencing early discontinuation of integrase inhibitors in the univariate analysis (Table 8). There were, however, trends to lower discontinuation with lower age and in those taking elvitegravir. Increasing age (4% per year) was the only independent risk factor (adjusted HR 1.04, 95% CI 1.02–1.07, $P = 0.0007$) for early discontinuation of integrase inhibitors due to adverse effects (Table 9). No integrase inhibitor was significantly associated with a higher risk for early discontinuation due to adverse effects in the multivariate analysis [raltegravir, HR 1 (reference); elvitegravir, HR 1.35 (95% CI 0.70–2.61); dolutegravir, HR 1.06 (95% CI 0.47–2.41): $P = 0.06545$] (Table 9).

Discussion

In this large cohort of HIV-infected patients treated with currently available integrase inhibitors, we found rates of discontinuation due to any reason with all three integrase inhibitors in the first year of therapy ranging from 8.1% to 12.7%. There was a trend to fewer overall discontinuations and discontinuations not due to toxicity were significantly less frequent with elvitegravir compared with raltegravir or dolutegravir. In contrast to raltegravir, which is not combined into an STR, or dolutegravir, which first became available as an individual drug, elvitegravir has always been used as an STR. This fact may be responsible at least in part for the lower overall discontinuation rate not due to toxicity with elvitegravir. STRs are considered as the most convenient antiretroviral regimens,[29,30] and convenience has been reported as a major determinant for drug discontinuation in patients starting antiretroviral therapy.[31]

Only a portion of discontinuations were attributed to adverse effects. Proportions ranged from 3.6% for raltegravir, 3.8% for dolutegravir and 5.0% for elvitegravir. These figures were slightly higher than those reported in clinical trials.[4–9] Rates of early discontinuation due to adverse effects did not significantly differ among the three integrase inhibitors. There has been a huge controversy on the potential of dolutegravir for a worse tolerability in real-life settings because an unexpected high rate of discontinuation due to adverse effects has been reported in some cohorts.[12–21] The availability of increasing post-marketing information on adverse effects might have influenced the decision of drug discontinuation in the clinical setting. The data from our cohort reported here were generated before the public release of the Dutch cohort report at the Conference on Retroviruses and Opportunistic Infections (CROI) 2016. Therefore, the potential influence of the Dutch cohort report on the discontinuation of dolutegravir in our cohort should be negligible, if any. Our results do not confirm a higher rate of discontinuation due to adverse effects for

Table 8. Risk factors for early discontinuation (≤1 year) due to any reason

Characteristic	Unadjusted HR (95% CI)	*P* value
Age	1.01 (1.00–1.03)	0.0699
Gender		
men	1	0.8655
women	1.04 (0.65–1.67)	
Integrase inhibitor		
raltegravir	1	
elvitegravir	0.62 (0.39–0.97)	0.0990
dolutegravir	0.97 (0.62–1.52)	
Year of integrase inhibitor initiation		
2007–10	1	
2011–13	1.34 (0.62–2.91)	0.6056
≥2014	1.11 (0.54–2.29)	
Route of infection		
heterosexual sex	1	
MSM	0.69 (0.45–1.05)	
IDU	0.73 (0.39–1.35)	0.3841
other or unknown	0.80 (0.37–1.73)	
HIV RNA(log copies/mL) at HIV diagnosis	0.93 (0.82–1.06)	0.2852
HIV RNA (log copies/mL) immediately prior to integrase inhibitor therapy	1.02 (0.90–1.15)	0.7509
CD4 (cell/mm^3) at HIV diagnosis	1.00 (1.00–1.00)	0.9970
CD4 immediately prior to integrase inhibitor therapy	1.00 (1.00–1.00)	0.9103

dolutegravir as compared with raltegravir or elvitegravir. It is possible that differences in patients' characteristics or other not well-known factors will explain the higher rate of dolutegravir discontinuation due to adverse effects observed in some cohorts.

The most common adverse effects leading to discontinuation for each of the three integrase inhibitors in our cohort were neuropsychiatric and osteomuscular. These effects were already acknowledged in the summaries of product characteristics of raltegravir,[25] elvitegravir/cobicistat/emticitabine/tenofovir disoproxil fumarate[26] and dolutegravir.[27] Nevertheless, the frequency of neuropsychiatric effects among patients with drug discontinuation due to toxicity was significantly higher with dolutegravir compared with raltegravir or elvitegravir, suggesting that this toxicity profile might be more characteristic of dolutegravir. This contention is further supported by recent data from a German cohort study.[18] This is in contrast with data from randomized clinical trials in which the overall incidence of reported neuropsychiatric adverse effects in patients allocated to dolutegravir was similar to that of the competitors (efavirenz in SINGLE, raltegravir in SPRING-2, darunavir/ritonavir in FLAMINGO and atazanavir/ritonavir in ARIA) and very few patients discontinued dolutegravir due to neuropsychiatric adverse effects.[32] Discrepancies in dolutegravir discontinuation due to neuropsychiatric effects between clinical trials and cohort studies might be due at least in part to the promotion of patient retention in clinical trials and the generally mild and apparently transient nature of neuropsychiatric side effects.

We did not see major differences in the clinical profile of neuropsychiatric adverse effects leading to discontinuation among the three integrase inhibitors, although this comparison should be treated with caution due to the inherently subjective nature of both patients' description and physician's registration. The

Table 9. Risk factors for early discontinuation (≤1 year) due to adverse effects

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	1.04 (1.02–1.07)	0.0007	1.04 (1.02–1.07)	0.0007
Gender				
men	1	0.1360		
women	1.68 (0.85–3.33)			
Integrase inhibitor				
raltegravir	1			
elvitegravir	1.35 (0.70–2.61)	0.6545		
dolutegravir	1.06 (0.47–2.41)			
Year of integrase inhibitor initiation				
2007–10	1			
2011–13	1.34 (0.28–6.29)	0.5577		
≥2014	1.82 (0.44–7.56)			
Route of infection				
heterosexual sex	1			
MSM	0.37 (0.19–0.70)			
IDU	0.36 (0.12–1.06)	0.0170		
other or unknown	0.55 (0.16–1.87)			
HIV RNA (log copies/mL) at HIV diagnosis	0.81 (0.66–1.00)	0.0529		
HIV RNA (log copies/mL) immediately prior to integrase inhibitor therapy	0.82 (0.63–1.05)	0.1186		
CD4 (cell/mm^3) at HIV diagnosis	1.00 (1.00–1.00)	0.2815		
CD4 immediately prior to integrase inhibitor therapy	1.00 (1.00–1.00)	0.0686		

predominance of insomnia among neuropsychiatric effects may suggest a potential interference with mechanisms involved in physiological sleep.[33] Several drugs have been reported to cause insomnia as an adverse effect.[34] The coincidence of a common CNS adverse effect profile between efavirenz and integrase inhibitors has led to speculation regarding whether similar pathogenetic pathways may be involved. However, recent data argue against that contention because patients experiencing efavirenz-associated CNS adverse effects showed improvement after switching from efavirenz to dolutegravir.[23,24] Further research is needed to understand the pathogenesis and risk factors for CNS adverse effects associated with integrase inhibitors.

In our cohort, increasing age was the only factor associated with a higher risk of integrase inhibitor discontinuation due to adverse effects. The risk increased 4% per year. Increasing age has been associated with better virological response due to better adherence to antiretroviral therapy, but worse immunological response due to reduced functional reserve.[35] Discontinuation of antiretroviral therapy for reasons other than virological failure has been reported more commonly in older patients but also in younger ones as compared with middle-aged ones, but in the case of older patients the discontinuation was associated with toxicity and in younger ones with lack of adherence.[36] Increasing age is associated with higher incidence of comorbidities[37] and with increased plasma exposure to some antiretroviral drugs,[38] and both factors contribute to a higher propensity for toxicity.[39,40] These results emphasize the need for an increased awareness for potential adverse effects leading to the discontinuation of integrase inhibitors among older patients even though these drugs are preferentially recommended in them because of their better safety profiles compared with non-nucleoside reverse transcriptase inhibitors or protease inhibitors.[1–3]

In conclusion, discontinuation of available integrase inhibitors not due to toxicity was less frequent with elvitegravir than with raltegravir or dolutegravir, although discontinuation due to adverse effects was similar among the three integrase inhibitors and slightly higher than that reported in clinical trials. Neuropsychiatric and osteomuscular effects were the most common ones leading to drug discontinuation with all three available integrase inhibitors, although neuropsychiatric adverse effects were significantly more common with dolutegravir than with raltegravir or elvitegravir. Increasing age was an independent factor associated with a higher risk for discontinuation of integrase inhibitors due to adverse effects.

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Supplementary data

Tables S1–S5 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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