Correspondence

AIDS 2017, **31**:1775–1780

Neuropsychiatric events and dolutegravir in HIV patients: a worldwide issue involving a class effect

We read with interest the work of Menard *et al.* [1] that brings additional knowledge on the neuropsychiatric tolerance of dolutegravir. They also provide pharmacokinetic data which is very welcomed as published works concerning the potential association between neuropsychiatric adverse drug reactions (ADRs) and dolutegravir concentrations are scarce. Their data are in line with other studies that recently reported neuropsychiatric adverse effects in patients receiving dolutegravir-containing regimen in other countries in Europe [2–4].

However, neuropsychiatric adverse effects in patients treated with integrase strand transfer inhibitors (INSTIs) is not an emergent story [5–7]. One year after raltegravir (Isentress; MSD, Hoddesdon, UK) was marketed, Harris *et al.* [7] described an exacerbation of depression symptoms in four patients with psychiatric medical history after starting raltegravir. A few months after dolutegravir was available in France, we reported psychiatric disorders in four patients receiving dolutegravir-containing regimen without any other psychoactive comedication [5]. Respectively, these case series contributed to label psychiatric symptoms such as depression or suicidal ideation in the summary of product characteristics of drugs containing raltegravir (Isentress) or dolutegravir (Tivicay, Triumeq; Viiv Healthcare, Brentford, UK). In a case/noncase study of drug-induced depression performed in the French Pharmacovigilance Database, the French pharmacovigilance network found a significant association between raltegravir and depression [8]. Although Harris

Table 1. Overview of psychiatric disorders involving integrase strand transfer inhibitors reported in the WHO international pharmacovigilance database.

	All INSTIs *n*, (%)	Raltegravir *n* (%)	Elvitegravir *n* (%)	Dolutegravir *n* (%)
Initial US approval		2007	2012	2013
Initial EU approval		2007	2013	2014
Number of reports in the Psychiatric disorders SOC	1159	410 (35.4%)	203 (17.5%)	550 (48.4%)
Gender (M/F/U)	839/249/71 (72.4/21.5/6.1)	283/91/36 (69/22.2/8.8)	154/46/3 (75.9/22.7/1.5)	404/114/32 (20.7/73.5/5.8)
Age (years)				
2–17	6 (0.5)	4 (1)	1 (0.5)	1 (0.2)
18–44	371 (32.0)	114 (27.8)	81 (39.9)	176 (32.0)
45–64	446 (38.5)	158 (38.5)	73 (36.0)	216 (39.3)
65–74	40 (3.5)	14 (3.4)	5 (2.5)	21 (3.8)
≥75	6 (0.5)	3 (0.7)	0	3 (0.5)
Unknown	290 (25.0)	117 (28.5)	43 (21.2)	133 (24.2)
Geographical area				
Americas	575 (49.6)	244 (59.5)	123 (60.6)	210 (38.2)
Europe	516 (44.5)	137 (33.4)	73 (36.0)	308 (56.0)
Asia	48 (4.1)	25 (6.1)	5 (2.5)	18 (3.3)
Oceania	20 (1.7)	4 (1.0)	2 (1.0)	14 (2.5)
Top five most reported HLGT				
Sleep disorders and disturbance	577 (42.6)	161 (31.9)	106 (42.4)	314 (51.9)
Depressed mood disorders and disturbances	277 (20.5)	123 (24.4)	46 (18.4)	108 (17.9)
Anxiety disorders and symptoms	212 (15.7)	85 (16.9)	27 (10.8)	100 (16.5)
Suicidal and self-injurious behaviours	162 (12.0)	55 (10.9)	19 (7.6)	88 (14.5)
Mood disorders and disturbances	123 (9.1)	47 (9.3)	19 (7.6)	57 (9.4)
Number of reports within the 'Depression suicide self-injury' SMQ	521	211 (40.5)	81 (15.5)	235 (45.1)
Coreported substances	FTC/TDF 245 (21.1)	FTC/TDF 245 (21.1)	FTC/TDF/COBI 197 (97)	ABC/3TC 337 (61.3)
	ABC/3TC 100 (8.6)	Ritonavir 79 (19.3)	FTC/TDF 10 (4.9)	FTC/TDF 96 (17.5)
	Ritonavir 100 (8.6)	Darunavir 62 (15.1)	EFZ/3TC/TDF 8 (3.9)	Darunavir 16 (2.9)
	Darunavir 82 (7.1)	Etravirine 51 (12.4)	Gabapentin 5 (2.5)	Ritonavir 16 (2.9)
	3TC 53 (4.6)	ABC/3TC 100 (8.6)	Omeprazole 5 (2.5)	Colecalciferol 14 (2.5)

ABC, abacavir; 3TC, lamivudine; COBI, cobicistat; EFZ, efavirenz; FTC, emtricitabine; HLGT, high level group term; SMQ, standardized MedDRA query; SOC, system organ class; TDF, tenofovir.

et al. [7] hypothesized a drug–drug interaction with psychotropic drugs; we suggested a class effect of INSTIs.

In the continuum of our case reports and other published works about neuropsychiatric tolerance of INSTI, we recently reviewed ADRs belonging to the psychiatric disorders system organ class (SOC) of the Medical dictionary for regulatory activities (MedDRA) classification involving an INSTI and registered in the World Health Organization (WHO) worldwide pharmacovigilance database Vigibase between 2007 and April 2017 [9,10]. VigiBase is the international pharmacovigilance database developed and maintained by Upsalla monitoring centre on behalf of WHO in which information is recorded in a structured form to allow analysis of the data. It holds over 15 million anonymized reports of suspected adverse effects of medicines suffered by patients (as of April 2017). This database is at the heart of a global pharmacovigilance system and its purpose is to provide the evidence from which potential medicine safety hazards (signals) may be detected and communicated. Focusing on high level group terms, sleep disorders, depressed mood disorders, anxiety disorders, suicidal and self-injurious behaviours and mood disorders were among the top five reported terms within the psychiatric disorders system organ class independently of the INSTI (Table 1). When using the standardized MedDRA query (SMQ) 'Depression suicide self-injury', we retrieved a higher amount of ADR with raltegravir and dolutegravir compared with elvitegravir.

We believe that this issue is not only focused on Europe and on dolutegravir. Indeed, the presented data are in line with other recent published data suggesting that dolutegravir might be more prone to induce neuropsychiatric ADR compared to raltegravir or elvitegravir. However, it is likely to be an INSTI class effect rather than a phenomenon specific of dolutegravir.

Dolutegravir consistently penetrate central nervous system but to date and to the best of our knowledge, the physiopathological mechanism involved in the onset of neuropsychiatric ADR has not been described [11]. In-vitro studies and the study of potential concentration-related effects would be welcomed to better understand the mechanisms underlying neuropsychiatric tolerance of INSTI, especially dolutegravir.

We acknowledge that our data is not exhaustive because of underreporting of ADRs in addition to the fact that it does not include all ADRs reported to marketing authorization holder. It does not reflect the exact magnitude of neuropsychiatric ADRs involving INSTI which is probably underestimated. Reporting of ADRs is not only compulsory but also a way to contribute to bring knowledge in terms of drug safety. We strongly encourage physicians to report any of these ADR to their local or national health authorities. This knowledge gathered until now should be taken into account during the clinical development of new INSTI (i.e. cabotegravir and bictegravir) that will be marketed in the future years. Indeed, an association with cabotegravir doses and reported rates of insomnia was described in a randomized phase 2b trial [12].

As mentioned by Menard *et al.* [1], INSTIs are part of first line treatment in HIV therapy. Both patients and physicians should be aware of this issue because ADRs such as insomnia can impair patients' quality of life and adherence to treatment leading to virological failure. More serious ADRs such as suicidal behaviour or depression can also happen while treated with INSTI and should not be neglected or remain in the only scope of dolutegravir.

Acknowledgements

The authors are indebted to the national centres who make up the WHO Programme for International Drug Monitoring (WHO PIDM) and contribute reports to VigiBase. The opinions and conclusions are not necessarily those of the various centres nor of the WHO. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The information does not represent the opinion of the World Health Organization.

Conflicts of interest

There are no conflicts of interest.

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Received: 24 May 2017; accepted: 25 May 2017.

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DOI:10.1097/QAD.0000000000001557

HIV-induced uveitis: would you recognize it if it looked straight at you?

According to the WHO, the number of people of all ages living with HIV infection in South Africa was 7 million in 2015, which translates to a prevalence of 19.2% among individuals aged 15 years and older. The number of new infections reported in South Africa during 2015 was 380 000, with 180 000 deaths attributed to AIDS during the same period [1]. More than 3.3 million (48.0%) people living with HIV received HAART during 2015 and this appears to be slowly turning the tide against the HIV pandemic in the country.

Despite recent gains in the battle against HIV/AIDS, South Africa remains one of the countries with the highest prevalence of this disease in the world and intermittently an unusual clinical presentation is encountered that must be shared with clinicians who work with patients living with HIV. HIV-induced uveitis is such a condition.

A 44-year-old man presented to the Eye Clinic at Tygerberg Academic Hospital in Cape Town with a 3-week history of redness and progressive vision loss in his right eye. He had no previous ocular or medical history of note. On examination, his uncorrected visual acuity was decreased in both eyes. The right eye read 0.6 and the left eye 0.5 on a decimal Snellen chart. Both eyes showed mild circumcorneal injection and large keratic precipitates on the endothelium (Fig. 1a). Inflammatory activity was noted in the anterior chambers and the anterior vitreous humor of both eyes. In both eyes, small fluffy nodules were prominent all along the pupil margin (Fig. 1b). The rest of the eye examination was normal. Topical corticosteroid therapy was commenced to address the inflammation while special investigations were being performed.

Routine first-line investigations were requested to search for the underlying cause of the uveitis. These included a full blood count, erythrocyte sedimentation rate, creatinine, syphilis serology as well as serum angiotensin-converting enzyme level and all had negative results.

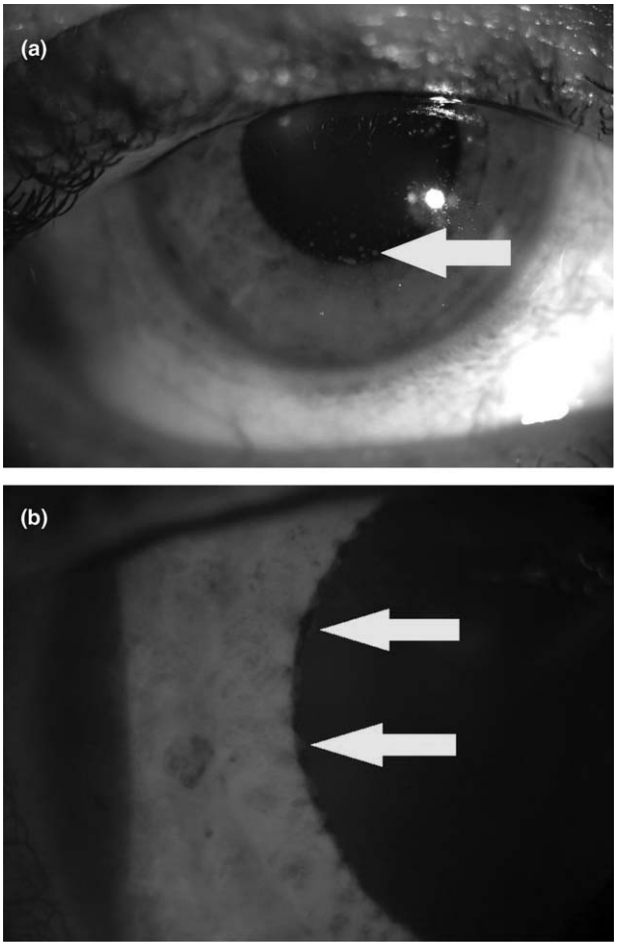

Fig. 1. Eye examination. (a) Large keratic precipitates on the corneal endothelium (arrow). (b) Small fluffy nodules all along the pupil margin (arrows).