Case Report

Seizures in HIV: The case for special consideration

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A B S T R A C T

Purpose: This study aimed to determine the rate, cause and management of seizures in the context of potential ART–ASD interactions in a cohort of HIV+ individuals.
Methods: Records of 604 HIV+ patients were reviewed and those reporting epilepsy/seizure diagnosis were further evaluated.
Results: This cohort exhibited a seizure rate of 2.4%. HIV+ patients treated for epilepsy displayed low serum ASD levels and failed to achieve seizure control. They were more likely to disengage from Neurology follow-up.
Conclusion: For HIV+ patients presenting with seizures/epilepsy the ASD prescription and the provision of supplementary support services needs to be carefully considered.

1. Introduction

In Ireland newly diagnosed cases of HIV have been reported at an annual rate that ranges from 7.0 to 7.5 per 100,000 [1]. Despite the introduction of highly active anti-retroviral therapy (HAART), 40–60% of HIV-infected individuals develop neurological complications [2–4]. The frequency of new seizures in the HIV positive (+) population is estimated to be between 4 and 11% in the populations studied [5]. To date the literature on the epidemiology of seizures and epilepsy in HIV has not generated reliable per patient year incidence estimates. Also no prevalence rates have been determined that can easily separate recurrent provoked seizures from recurrent unprovoked attacks (epilepsy). The data we have so far suggest a prevalence of all seizures of about 6% in a reasonably large HIV+ cohort with approximately half of these identified as being unprovoked attacks [3].

These data compare with a point prevalence of 0.8% for epilepsy in Ireland in the general population [6], although there is an expected 10% life time risk of a seizure of any type in the general population [7]. Taking into account the wide variations in prevalence estimates for epilepsy due to differences in definitions and methodological approaches, a reasonable estimate of the prevalence of seizure disorders in people with HIV in Ireland is at least 3 times that of the general population.

Acute symptomatic seizures can be the presenting feature of HIV infection [8]. The main causes of seizures in HIV-infected individuals include the expected background genetic and environmental risk of epilepsy in that population, HIV infection itself or its CNS complications such as cerebral toxoplasmosis, tuberculoma, cryptococcal meningitis, PML, CNS lymphoma, syphilitic meningitis and HIV associated dementia [5,8–11]. HIV-related seizures may also be provoked by concurrently administered drugs [12]. Both HIV and seizures (including epilepsy and provoked seizures) may necessitate long term treatment with both antiretroviral therapy (ART) and anti-seizure drugs (ASD), which can lead to potentially serious ART–ASD interactions [11,13].The aim of this study was to determine the rate, type, cause and practiced treatment of new onset seizures (NOS) and epilepsy in a cohort of HIV-infected individuals attending St James's Hospital (SJH) in Dublin and to inform best practice seizure management in the context of potential ASD–ART interactions.

2. Methods

A dedicated HIV clinic in SJH is attended by a population of approximately 2200 HIV+ patients. A subset of 604 HIV+ individuals accessing this service previously participated in the Cognitive Impairment Prevalence Study, conducted between January 2011 and November 2013. Participants were screened for HIV-related cognitive impairment (CI) using the Brief Neurocognitive Assessment Screening (BNCS) tool [14]. In the current study, we further evaluated in detail the occurrence of seizure/epilepsy as another frequent neurological comorbidity in this population. For this purpose the Electronic Patient

Records (EPR) of the 604 participants in the Cognitive Impairment Prevalence Study were reviewed for the diagnosis of "seizure", "seizure disorder" and "epilepsy"; as well as for neurology/epilepsy clinic attendances, EEG evaluations and ASD prescriptions. In those patients who met our search criteria, medical notes and EPR notes were further reviewed to obtain more detailed information about their history of seizures and epilepsy. This included recording the frequency of acute seizures and epilepsy in this cohort of patients, cause of seizures and their management.

Our assessment of patient adherence to prescribed treatment relied on the review of clinical notes. Adherence to ART was easier to ascertain as the ART therapy is observed in the HIV clinic. ASD therapy compliance on the other hand is usually interrogated with the patient (and with a family member or a caregiver where available) during the clinic appointment and is reconciled with the dispensing pharmacy. Checking serum ASD drug levels was also a helpful tool; however, the results were interpreted with caution in the context of possible drug–drug interactions.

3. Results

3.1. Demographic and clinical characteristics of HIV + patients with NOS

Out of 604 HIV+ patients, a total of 15 (2.4%) had a history of epilepsy or a single provoked or unprovoked seizure at some stage in their life. The rate of epilepsy or seizures in those who screened positive for CI (311/604) was higher at 3.2% (10/311) than the 1.7% (5/293) for those who screened negative for CI. The male to female ratio amongst those who had seizures/epilepsy was 11:4. This ratio was consistent with the gender distribution in the Cognitive Impairment Prevalence Study cohort with the majority of participants being male (78.8%) [14]. In four of 15 patients, the history of epilepsy or seizures predated the diagnosis of HIV, of which two had established childhood onset epilepsy. Seizures re-occurred after the HIV diagnosis in one of the patients with childhood onset epilepsy and the other one experienced increased seizure frequency after the HIV diagnosis was established.

NOS, epilepsy diagnosis, or adulthood reoccurrence of seizures after or around the diagnosis of HIV was documented in a total of 13 patients with a mean latency of 69 months (5.8 years). A total of 14 out of 15 cases underwent further detailed analysis with one case excluded from the detailed analysis due to the lack of further information. (This participant had a single provoked event in childhood in the setting of a medication adverse event.) The mean age at NOS was 36 years, ranging from 13 to 57 years. Further clinical characteristics of HIV + patients with seizures are presented in Table 1.

3.2. Seizure semiology, etiology and evaluation

Repeated seizures led to the diagnosis of epilepsy in 6/14 (43%) patients necessitating ongoing ASD therapy. One of these had previously been diagnosed with Idiopathic Generalized Epilepsy (IGE) (or *Genetic Generalize Epilepsy (GGE)* according to the new ILAE classification of the epilepsies) [15]. Seizures were the presenting symptom of HIV in three cases (21%). This includes one case where the seizure occurrence was reported one year prior to the HIV diagnosis. In five patients (36%), seizures were the presenting feature of and were caused by a CNS opportunistic infection (one of them at the time of HIV diagnosis). Other causes included benzodiazepine withdrawal (4 patients). Alcohol withdrawal was documented during the first two presentations with seizure re-occurrence in adulthood in one of the patients with a previous history of childhood epilepsy. However, this patient developed further events while abstinent and was eventually diagnosed with epilepsy. No cause other than HIV was found in three patients, two of whom had focal gliosis shown by MRI (Table 2).

With regards to seizure type, one patient had *generalized tonic–clonic seizures*. *Focal seizures (aware* or *with impaired awareness)* were documented in four patients. In six patients seizure type was classified as probable *focal onset to bilateral tonic–clonic seizure*. Two patients had

Table 1
Demographic and clinical characteristics of HIV-positive patients with seizures.

Seizure onset relative to HIV Diagnosis (n = 15)	
Before HIV Diagnosis	Total 4
Acute Symptomatic Seizure in childhood	1
Childhood Epilepsy[a]	2[a]
One year before HIV Diagnosis	1
At/After HIV Diagnosis	Total 12
New Onset Seizure	11
Childhood epilepsy with seizure re-occurrence[a]	1[a]
Gender (n = 15)	M:F
	11:4
Way of infection (n = 15)	
Heterosexual	5
MSM	3
IVDU	7
Age at NOS/seizure re-occurrence (n = 14)[b]	
Mean	36
Range	13–57
Seizure onset latency after HIV Diagnosis (range; mean) (n = 14)[b]	0–168 months (14 years); 69 months (5.8 years)
0 (childhood with subsequent poor seizure control)	1
0 (12 months prior to HIV diagnosis)	1
At HIV diagnosis	2
1–6 months after HIV diagnosis	2
6–12 months after HIV diagnosis	1
36–168 months (3–15 years) after HIV diagnosis	7
CD4 + lymphocyte count at the time of NOS (n = 14)[b]	
<200 cell/mm^3	5
>200 cell/mm^3	5
NK	3
N/A	1
HAART treatment at NOS (n = 14)[b]	
No	8
Yes	3
NK	2
N/A	1

NOS – New Onset Seizure; NK - Not known due to presentation at an overseas healthcare center; N/A not applicable; IVDU – intravenous drug user; MSM – men having sex with men.

[a] In one case of known childhood epilepsy, seizures restarted in adulthood 5 years after the HIV diagnosis. The age at seizure re-occurrence was used for the purpose of this analysis.

[b] The childhood single seizure in acute settings was excluded from further analysis due to no available information.

unknown onset tonic–clonic seizures and in one patient the seizure type was not possible to classify due to the lack of further information — *unclassified seizure* [16]. Status Epilepticus (SE) was documented in a total of three patients (21%) (one – non motor SE and two – motor SE).

EEG reports were available for nine of the patients. Only one of them had evidence of epileptiform discharges. A total of four patients showed focal dysfunction and one patient had generalized slow activity. Three patients showed no abnormality on EEG. Brain MRI or written reports were available for review for eleven patients (Table 2). Seven of them had focal brain lesions, and two had diffuse lesions shown by MRI (Table 2; Fig. 1).

A total of thirteen patients were reviewed by the Neurology service at the time of seizure presentation. Eight of them attended neurology/epilepsy services for follow-up with a subsequent high rate (5/8) of disengagement from these services.

3.3. ASD treatment, side effects and potential ASD–ART interactions

ASD treatment was begun in 10 patients: six of them were diagnosed with epilepsy and four presented with acute symptomatic seizures (Table 3).

The most commonly prescribed ASD was levetiracetam (prescribed 1st in 4 cases and 2nd or 3rd in 3 cases), which also had the highest

Table 2

Seizure semiology and etiology, diagnostic evaluation and Neurology specialist involvement. (n = 14).

Seizure type	
Focal onset seizure +/− to bilateral tonic–clonic	Total 4
- Focal aware	1
- Focal with impaired awareness	3
Focal to bilateral tonic–clonic[a]	6
Generalized Genetic Epilepsy (GGE)	1
Unknown onset tonic–clonic	2
Unclassified[b]	1
Seizure occurrence	
Acute symptomatic seizures	8
Recurrent seizures/epilepsy	6
EEG findings	
Generalized epileptic discharges	1
Focal dysfunction	4
Generalized slow activity	1
No abnormality	3
EEG not available	5
Brain MRI findings	
Focal brain lesions etiology	Total FBL 7
- CNS Toxoplasmosis	3
- Tuberculous meningitis	1
- Progressive multifocal leukoencephalopathy (PML)	1
- Focal gliosis (unspecified)	2
Diffuse brain lesions	2
Normal MRI	2
MRI not available/performed elsewhere[c]	3
Possible etiology of seizure	
CNS complication	Total CNS complications 5
- CNS Toxoplasmosis	3
- TB meningitis	1
- PML	1
Other:	Total other 9
Benzodiazepine withdrawal	4
Previous history of epilepsy	2
No other cause apart from HIV	3
Neurology Specialist Involvement	
Neurology review at NOS	13
Neurology/Epilepsy follow-up	8
Disengaged from Neurology/Epilepsy follow-up	5[d]

GGE – Generalized Genetic Epilepsy.

FBL - Focal brain lesions.

  [a] Patients presented with witnessed episodes of tonic–clonic motor activity with impaired awareness and focal brain lesion on brain imaging or focal EEG changes.

  [b] No further information was available to be able to classify seizure type for one participant.

  [c] Two patients (one with GGE) initially presented elsewhere and information regarding imaging was not available; one patient had normal CT brain at seizure presentation.

  [d] 2 of 5 patients who disengaged with epilepsy service still had documented seizures.

rate of adverse events (4/7), followed by lamotrigine (prescribed 1st in 2 cases, 2nd in one case and 3rd in 2 cases) and valproate (prescribed 1st in 4 cases, never as a second agent). Seizure freedom after introducing the first ASD was achieved in only three cases. In all three cases, patients presented with acute symptomatic seizures in the setting of a CNS opportunistic infection.

4. Discussion

Seizures and epilepsy are important CNS complications of HIV infection. Seizure prevalence in our HIV + cohort is higher than in the general population (2.4% versus approximately 1.5% if we include symptomatic seizures and epilepsy). This difference is lower than in other reported studies [5,11]. Interestingly, we found a higher seizure prevalence rate (3.2%) in the HIV + individuals who screened positive for cognitive impairment. Most of our patients (14/15) had at least one seizure after acquiring HIV infection. However, two of them had been previously diagnosed with epilepsy in childhood. After their diagnosis of HIV, one of these two patients had seizure reoccurrence and the other had increased seizure frequency. Notably, both had seizures

refractory to ASD therapy, which could potentially be due to unfavorable ASD–ART interactions. Furthermore, eight of our patients had no other obvious risk factors for epilepsy apart from HIV and its CNS complications. This was further supported by lesional neuroimaging findings consistent with changes described in HIV encephalitis/encephalopathy or CNS opportunistic infection in seven of them.

HIV stage and immune status at NOS is important. Five of our patients had an AIDS defining CNS opportunistic infection at the time of seizure presentation. A further two patients had advanced HIV disease with CD4 + counts below 200 cells/mm^3. Slightly less than half (6/14) of those who underwent detailed analysis experienced the first seizure close to the time of HIV diagnosis (+/− 12 months) when infection is more likely to be uncontrolled (Table 1). Eight patients experienced only one seizure, half of these at the time of a concomitant CNS opportunistic infection. This is highly relevant as it highlights the importance of prompt diagnosis and treatment of opportunistic infection in those presenting with seizures in the context of a known or new HIV diagnosis. These patients may only require short term ASD therapy, thus avoiding potential long term ASD side effects and/or ASD–ART interactions.

Patients who were diagnosed with epilepsy (6/14) were less likely to have had CNS opportunistic infections. Only one patient with recurrent seizures was diagnosed with PML. Two patients had a preexisting epilepsy diagnosis. The remaining three had focal brain lesion reported on MRI and for two of these the focal brain lesion description was consistent with the MRI changes reported in HIV encephalitis/encephalopathy. These findings suggest that the direct effect of HIV on the CNS may also be responsible for the recurrent seizures in this category of patients. It was also found that these patients were more likely to present with seizures later in the course of their HIV disease, three years or more after their HIV diagnosis.

ART–ASD interactions can lead to increased serum drug levels in either drug class and increase the risk of toxicity [17]. ART–ASD interactions can also cause reduced drug serum levels with resulting consequences, such as reduced ASD levels and poor seizure control, or reduced ART levels with resulting poor virologic suppression and disease progression [18–20]. The latter is expected with the use of enzyme-inducing, older generation ASDs (phenobarbital, phenytoin and carbamazepine) [21–23]. The direct effects on HIV viral replication that could potentially lead to increased viral load by commonly used ASDs such as valproate have also been described [10,24].

In our study, of the three most prescribed ASDs LEV proved to be effective, provided the patient was compliant with the treatment and did not develop side effects. However, LEV had the highest incidence of side effects reported by patients (4/7) and had to be discontinued in two cases due to mood/personality disturbance. Levetiracetam has the least ASD–ART interactions reported in the literature but its propensity to cause intolerable neuropsychiatric side effects has been documented [10,25]. Therefore, careful consideration needs to be given to LEV prescription in patients as HIV-infected individuals may develop depression as part of their primary diagnosis. In this study, LEV was associated with viral control failure in two cases. However, this was not attributed to a possible ASD–ART interaction but to poor ART compliance.

LTG failed to demonstrate acceptable seizure control in our cohort. This can be explained by either the small dose prescribed or ASD–ART interactions not identified. Prescription of higher doses in these patients would have been appropriate but did not receive consideration. Overall, VPA showed poor seizure control in our cohort. However, VPA–ART interactions maybe possible and persistently low serum levels were recorded despite the high doses being prescribed. It was not possible to evaluate its effect on viral control due to the lack of data prior to 2012. Also, most patients who had been on VPA therapy had it discontinued by 2013.

Although the majority of patients were reviewed by neurology/epilepsy services in the acute settings and follow-up appointments were
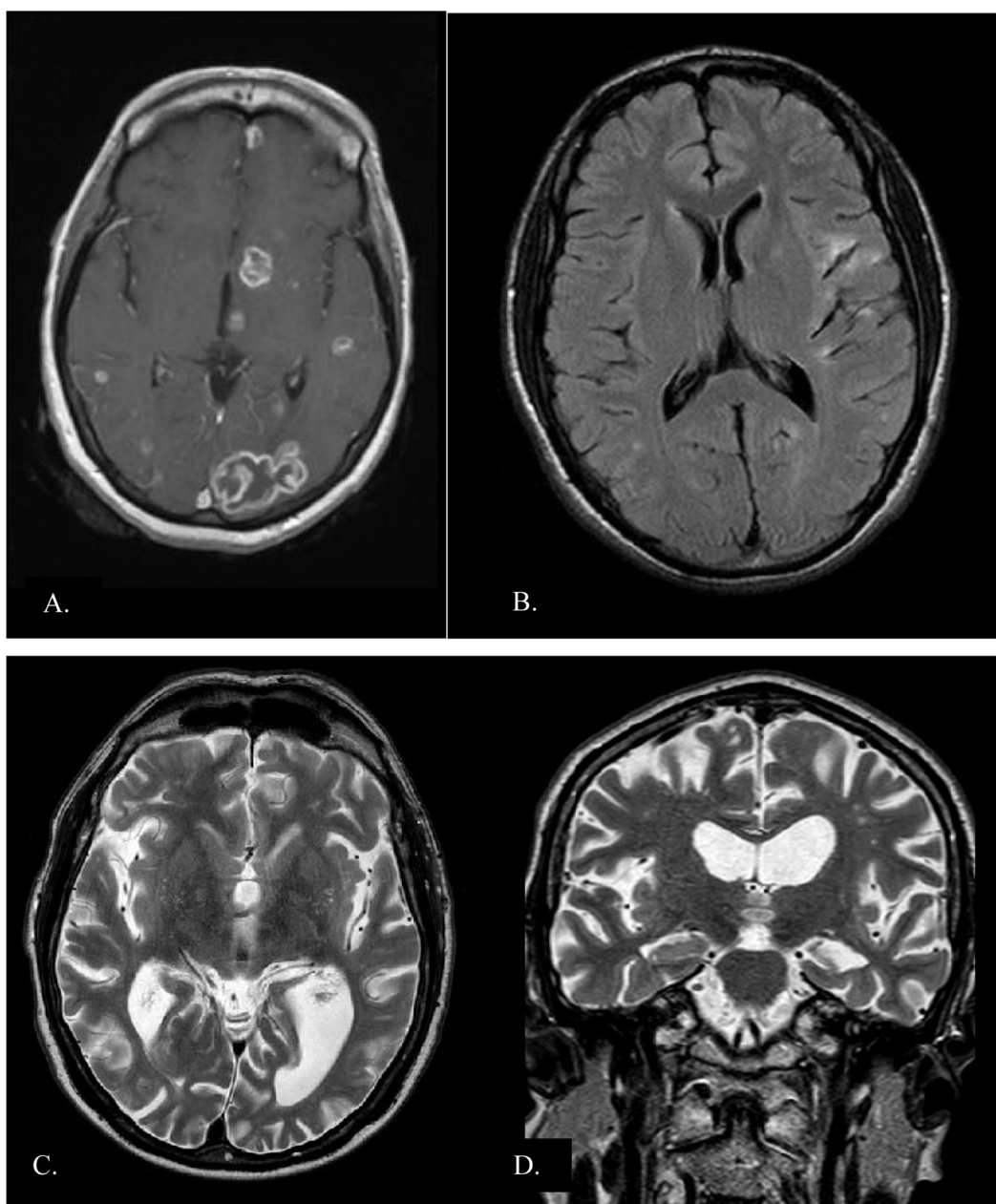
Fig. 1. MRI images: A. Case I - Axial T1 MRI image enhanced with contrast showing multiple ring enhancing lesions in a patient presenting with status epilepticus in the context of HIV and cerebral Toxoplasmosis; B. Case II - Axial T2 FLAIR image showing multiple high signal intensity foci in keeping with gliosis in the site of a previous infection in a patient treated for seizures on background of HIV and ongoing treatment for TB meningitis; C. and D. Case III - Axial and coronal T2 images showing focal atrophy of the left temporal lobe and hippocampus on background global atrophy in a patient with refractory epilepsy in the context of HIV and PML.

arranged, there was a high rate of disengagement with these services observed in our cohort (5/8). This is despite patients being contacted by one of the epilepsy nurse specialists to confirm the follow-up appointments. Additionally, an appointment letter is sent to the patients' home address, and a text message reminder is sent to the patients' mobile phone a week before any SJH follow-up appointment to ensure attendance. This experience suggests that this particular group of patients and especially those with concomitant CI may need supplementary counseling and support services to optimize their clinical care.

This study highlights the importance of both HIV and the neurologist's involvement in the evaluation and treatment of this category of patients and perhaps the need for integrated neurology/epilepsy service in the HIV clinic for relevant patients.

5. Study limitations

Our study has a number of important limitations. This is a small cohort evaluated by retrospective chart review. Although an initial group of 604 HIV+ patients were looked at, only a small number proved to have suffered from seizures/epilepsy. Selection bias is also possible. However, the 604 patients who consented to participate in the initial Cognitive Impairment Prevalence Study were judged to be fairly representative of the 2200 HIV+ patients attending the HIV services at SJH [14]. It was difficult to draw meaningful conclusions with regard to ASDs' effectiveness, adverse events and possible interactions for a number of reasons including: the small subject numbers, the retrospective nature of the study, the heterogeneity of anti-seizure drugs used in such a small cohort and the limitations of the clinical data available. Finally, many of the

Table 3
ASD treatment, side effects and potential ASD–ART Interactions (n = 10).

no	Engagement with neurology/epilepsy services	ASD/ Serum level	ASD Side effect	SZ free	Possible ART/ASD interactions	CSF penetration	Viral load while on ASD[a]
1	Disengaged	LTG-	–	NO	Abacavir – LTG ↓ Efavirenz – no Lamivudine – no	High High Low	–
2	Disengaged	LTG-	–	NO	Efavirenz – no Tenofovir – no Emtricitabine	High	–
3	n/a	VPA	–	YES	↑ Lopinavir – VPA ↑ Ritonavir – VPA Tenofovir – no Emtricitabine	High High	–
4	Disengaged	PHT↓ LEV	 Mood	YES	Atazanavir – PHT ↓ Ritonavir – PHT Tenofovir – PHT Emtricitabine	 High	2200- < 50 (copies/ml)
5	n/a	LEV		YES	Efavirenz – no Emtricitabine Tenofovir – no	High	–
6	Regular follow-up	VPA↔↓ LEV LTG-		NO	Tenofovir – no Emtricitabine Ritonavir – LTG↓; VPA Darunavir – VPA	 High	ND
7	Regular follow-up	VPA↓↓ LEV LTG- PG ZOS↓↓	 Mood Cog	NO	Darunavir – VPA; ZOS Etravirine Ritonavir – LTG↓; ZOS; VPA	 High	<40/ND
8	Disengaged	LEV-	Mood	NO	Darunavir – no Raltegravir – no Ritonavir – no Tenofovir – no Emtricitabine	 High	<40/ND
9	Regular follow-up	VPA LTG↓↔ LEV↔ LAC↓	 Pers	NO	Efavirenz – VPA; LAC↓ Abacavir – LTG↓ Lamivudine – no Dolutegravir – no	High High Low	ND
10	n/a	LEV	–	–	Zidovudine – no Lamivudine – no Lopinavir – no Ritonavir – no	High Low High High	<40–4000 (copies/ml)

ASD - anti-seizure drug; ART – Antiretroviral Therapy; VL – Viral Load; ND – HIV RNA not detected; n/a - not applicable; no – no reported potential ARV-ASD interactions; n/k – not known. - information not available.
↔ ASD serum level within normal range.
↓ ASD serum level low/lowered by potential interaction.
↑ ASD serum level high/increased by potential interaction.
Cog – cognitive symptoms; Mood – mood disturbances; Pers – personality changes; SZ – seizure; LEV – Levetiracetam; LTG – Lamotrigine; LAC – Lacosamide; PHT – Phenytoin; PG – Pregabalin; VPA – Sodium Valproate; ZOS - Zonisamide.
  [a] Viral Load results were not available prior to 2012.

patients had poor engagement with the neurology/epilepsy services, and adherence to ASD therapy was difficult to ascertain or manage.

6. Conclusion

While comparisons to the general population are difficult, it does appear that the prevalence of both symptomatic seizures and epilepsy (recurrent unprovoked attacks) is greater in HIV + individuals. However, the rates found in our cohort (2.4%) appear lower than other published estimates. An interesting finding is that the rate appears higher in those who screened positive for cognitive impairment (3.2%); a finding that requires further study. With respect to status epilepticus and seizure freedom rates, again, the HIV + population fairs worse than the general population. Finally, an important consideration is that HIV alone may not be the only cause of seizures/epilepsy in this study population. The majority of patients with seizures presented with focal or diffuse lesions shown by MRI and most of these were caused by opportunistic CNS infections.

It is in the area of treatment that more work needs to be done. ART–ASD interactions were not adequately evaluated in this cohort and might be responsible for ineffective treatment and potentially poor outcomes. Recently, evidence based recommendations on ASD treatment in the context of ART therapy have been jointly developed by the American Academy of Neurology and the International League Against Epilepsy [26]. These published guidelines should be carefully considered when it comes to making treatment decisions in patients with HIV.

Conflicts of interest

None.

Acknowledgements

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