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Seizures in Children with HIV infection in South Africa: A retrospective case control study

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ABSTRACT

Purpose: Data relating to the role that Human immunodeficiency virus (HIV) contributes towards seizures in HIV-infected children is limited. The management of seizures in this group is complex due to potential interactions between antiseizure medication and antiretroviral therapies. This study explores the seizure semiology and course of a population of affected children based on questions raised from a previous epidemiological study.
Methods: A retrospective case-control study of all patients presenting to an HIV neurology clinic between 2008–2015 was conducted. A multinomial logistic regression model was used to identify risk factors for seizure occurrence in HIV-infected children, as well as factors associated with seizure control.
Results: Of 227 HIV-infected children (*median* 82 months, interquartile range 41–109), 52 (23%) reported a past or present history of seizures. Prior bacterial meningitis ($p = 0.03$, *OR* 12.5, *95% CI* 1.2–136.1), cerebrovascular accident (CVA, $p = 0.005$, *OR* 8.1, *95% CI* 1.9–34.9) and or tuberculous meningitis (TBM, $p = 0.0004$) was associated with an increased risk of seizures in HIV-infected children. Generalised tonic-clonic seizures were the predominant seizure type (64%) with the majority caused by an infectious aetiology (62%). Thirty-two (62%) of these patients had epilepsy in-line with the latest diagnostic criteria. HIV-infected children with epilepsy who were treated with efavirenz were more likely to have poor seizure control (*OR* 23.1 *95% CI* 3.4–159.6, $p = 0.0001$).
Conclusions: This study provides new data highlighting the complex clinical presentation and management challenges of HIV-infected children with seizures.

1. Introduction

Human immunodeficiency virus (HIV) remains a major cause of neurological disease among South African children despite increasingly efficient perinatal mother to child transmission prevention programmes [1,2]. The neurological disease may be primarily caused via direct infection by the virus as observed in HIV encephalopathy (HIVE) [3]. In addition, HIV infection leads to increased risk of secondary insults to the nervous system in the form of cerebrovascular disease [4], peripheral neuropathy [5] and, most commonly, opportunistic infections such the acute bacterial meningitis [6] or tuberculous meningitis (TBM) [7,8].

Seizures are a common reason for children to present to emergency units and may be indicative of neurological or systemic disease. Samia et al. [9] investigated whether or not HIV infection predisposes children to develop seizures and or epilepsy and reported a prevalence of seizures in 7.5% of a clinic population of HIV-infected children which appeared to be associated with higher levels of developmental delay and neurological deficits. However, the seizure characteristics were not reported nor the number of these children who could be classified as epileptic. Furthermore, epilepsy in HIV-infected patients is complex to manage without upsetting the balance between seizure control and viral load suppression [10]. Many of the commonly used antiseizure medications (ASMs) and antiretroviral therapies (ART) are known to interact via a shared metabolism by the cytochrome p450 3A4 enzyme (CYP3A4) [11,12].

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In this study we have extended the work previously published by Samia et al. [9] by providing a more specific and detailed focus on HIV-infected children who present with seizures. Specifically, we explored the demographics, HIV profile and past medical history of HIV-infected children to identify risk factors which may be associated developing seizures and epilepsy in this group. Lastly, we describe the ASM and ART regimens of these children and identify drug interactions that may have impacted on seizure control.

2. Methodology

This was a retrospective case-control study of all HIV-infected children referred to the Red Cross War Memorial Children's Hospital (RCWMCH) HIV neurology clinic. Children referred to this clinic were under 13 years of age and had acquired HIV through vertical transmission with their diagnosis confirmed by either PCR and or ELISA testing. Only paediatric patients under the age of 13 were included in keeping with the age limit of RCWMCH. When patients were seen at the HIV Clinic, the attending clinician obtained written consent from the child's caregiver to give permission for their child's clinical data to be uploaded into a registry for research purposes (under the University of Cape Town Human Research Ethics Committee – protocol HREC 126/2011).

A total of 252 new children were seen at the HIV neurology clinic between 2008–2015. This is a specialised referral clinic aimed at managing HIV infected children with complex neurological problems. Of these, 25 were excluded as their patient records were no longer available. Clinical data was acquired from the patient records using a standard data capture template which included the following data fields: demographics; anthropometry; neonatal history, past medical history and details of HIV profile including World Health Organisation (WHO) clinical staging. In addition, data was obtained on the neuroimaging of these patients along with data on associated primary HIV neurological conditions.

In patients in whom a previous episode of seizures was reported, the characteristics of the seizures were captured along with the ASMs and ARTs they received. Seizures were classified according to what was reported in the clinical notes based either on what was reported by the caregiver attending the clinic and/or what was witnessed by the attending clinician who saw the patient at the clinic. Furthermore, in patients who received an EEG, the semiology was compared against the findings of the neurophysiology study. In the case where there were conflicting findings (most notably in identifying generalised seizures versus focal onset with secondary generalisation), the final classification of the seizure was based on the EEG findings. The classification of underlying aetiology of the seizures was done by reviewing all the clinical evidence reported in the patient records (doctors notes, serum biochemical, haematological and metabolic investigations, imaging and EEG). Only ASMs used repeatedly were included in the analysis, while those used in the acute setting (namely lorazepam, diazepam, phenobarbital and phenytoin) were excluded from this analysis.

A diagnosis of epilepsy was made if the patient had presented with two or more unprovoked seizures or if they had a single seizure and there was high probability of them having another without intervention [13]. In addition, status epilepticus was defined as any seizure that persisted for more than five minutes and typically required medical intervention to terminate the seizure [14]. HIV encephalopathy (HIVE) was diagnosed in children who presented with at least one of the following signs that had persisted for a minimum of 2 months in the absence of any illness other that HIV [15–17];). The signs include: (i) a failure to attain or loss of developmental milestones or intellectual ability, (ii) impaired brain growth seen by head circumference measurements or imaging and or (iii) acquired symmetric motor deficits that include paresis, pathologic reflexes and or ataxia. The diagnosis of HIV neurocognitive disorder (HAND) remains poorly defined in childhood. In adult populations the diagnosis is made when individuals have formally demonstrated cognitive impairment not meeting criteria for HIV associated dementia [18]. For our purposes we diagnosed children as having HAND when they had evidence of cognitive or academic difficulties as evidenced by significant school difficulties (as indicated by formal report from school) and/or assessment by neuropsychologist indicating impairment which was not severe enough to meet criteria for HIVE.

All statistical analysis was performed using custom scripts written using MATLAB (Statistics Toolbox, Release 2018a The MathWorks, Inc., Natick, Massachusetts, United States). The analysis pipeline started with splitting the data into two groups: the control or 'No seizure' group and the cases or 'Seizure' group. For missing data, we employed a pairwise deletion. For categorical variables, data was reported as frequency and proportion (%). For continuous variables, first a Shaipro-Wilk test was performed to determine the distribution of the data. Parametric data was reported as mean ± standard error of the mean (SEM) and analysed using unpaired t-tests. Non-parametric data was reported as median and interquartile range and was analysed using Mann-Whitney U test. For all comparative statistic tests, a significant difference was defined as a p-value < 0.05.

To identify differences between cases and controls, a multinomial logistic regression was used. The response (dependent) variables was seizure occurrence with cases being compared to controls (set as the reference category). The predictor (independent) variables included categorical and continuous variables of interest. In the model, age and sex were controlled for. In patients who had documented seizures, further analysis was performed using a multinomial logistic regression to identify factors associated with seizure control. For this analysis the model was adjusted to control for age, sex and stage of HIV disease. The reference for response variable was set to the control (i.e. no seizure occurrence). For categorical predictor variables, if they were binomial the reference was set to the last variable (e.g. if female vs male the reference was male). For multinomial categorical predictor variables, the reference was set to the variable that is considered to be the normal state. The model was able to detect and exclude variables that were not reported in patients using pair-wise deletion. The significance of the relationship between a specific variable and seizure occurrence was reported along with the odd ratios (OR) and associated 95% confidence interval. The OR reported reflected the odds of seizure occurrence being affected by a change in a specific predictor variable. The full regression output is provided in the supplementary data.

3. Results

3.1. Demographics of HIV-infected children

We reviewed the records of a total of 227 HIV-infected children (age range: 10–176 months, median: 82, interquartile range: 41–109) who attended the clinic during the study period. In our cohort, 52 patients (23%) reported an episode of at least one seizure while 175 (77%) had no documented seizures. The patients in the control group (termed 'No seizure') included congenitally-infected HIV children referred to the HIV neurology clinic with concerns of an HIV associated neurological disorder. This included 117 patients with HIV encephalopathy (70%), 33 with HIV neurocognitive disorders (18.9%), and for the remaining peripheral neuropathy, cerebrovascular accidents, and cerebral palsy (Table 2).

The demographic and anthropometric profile of the cohort is shown in Table 1 and Supplementary Tables 1 and 2. We found that sex ($p =$ 0.3), age ($p =$ 0.9), weight ($p =$ 0.1), height ($p =$ 0.3) nor occipito-frontal circumference (OFC, $p =$ 0.4) significantly influenced seizure occurrence in our HIV-infected children. In addition, we found no differences in the antenatal and neonatal profile between the control and seizure group (see Supplementary Tables 3 and 4). A large proportion of the antenatal and neonatal data was lacking from the patients' medical records.

Table 1
Demographic and anthropometric profile.

	No seizures (n = 175, 77%)	Seizures (n = 52, 23%)	p	OR (95% CI)
Sex – female/male (%)	70 (40%) / 105 (60%)	26 (50%) / 26 (50%)	0.3	1.5 (0.78– 2.7)
Age (months) – median (*IQR)*	82.0 (67)	82.5 (68.1)	0.9	1.0 (1.0 – 1.1)
Weight - *Z*-score (%)			0.1	1.3 (1.0 – 1.7)
< −3: severely underweight	54 (30.9%)	8 (15.4%)		
−3 to −2: underweight	39 (22.3%)	11 (21.2%)		
−1 to −1: normal	37 (21.1%)	13 (25%)		
+2 to +3: overweight	42 (24%)	17 (32.7%)		
> +3: severely overweight	0 (0%)	2 (3.8%)		
Not reported	3 (1.7%)	1 (1.9%)		
Height - *Z*-score (%)			0.3	0.9 (0.6 – 1.2)
< -3: severely stunted	56 (32%)	19 (37.5%)		
−3 to −2: stunted	44 (25.1%)	11 (21.2%)		
−1 to −1: normal	32 (18.3%)	11 (21.2%)		
+2 to +3: tall	36 (20.6%)	9 (17.3%)		
Not reported	7 (4%)	2 (3.8%)		
OFC - *Z*-score (%)			0.4	0.8 (0.5 – 1.3)
< -3: severe microcephaly	52 (29.7%)	20 (38.5%)		
−3 to −2: microcephaly	32 (18.3%)	4 (7.7%)		
−1 to −1: normal	32 (1.7%)	13 (25%)		
+2 to +3: macrocephaly	53 (30.3%)	13 (25%)		
> +3: severe macrocephaly	4 (2.3%)	2 (3.8%)		

'IQR', interquartile range; 'OFC', occipitofrontal circumference.

3.2. HIV profile and past medical history

In our cohort, 69% of children presented with Stage 4 disease (see Table 2). However, the stage of HIV disease did not affect seizure occurrence (p = 0.27, Supplementary Table 5). The vast majority of patients (98%) were on ART at the time they were seen at the clinic. However, we noted that median age at which ART was started was 15 months (*IQR* 40.1). Both being on ART (p = 0.2) and the age at which ART was started (p = 0.7) did not significant affect seizure occurrence (Table 2 and Supplementary Table 5).

We also explored if differences in absolute CD_4 count and viral load influence seizure occurrence (Supplementary Table 7). We were specifically interested in the CD4 and viral load measurements at the time of HIV diagnosis and then the most recent time after ART had been initiated. We saw no difference in the CD4 count (p = 0.2) at diagnosis or after ART (p = 0.5) between the HIV-infected children who had seizures and those who did not. Furthermore, there was also no difference in the viral load at diagnosis (p = 0.9) and after ART (p = 0.6) between both groups. The median viral load reported after ART was 4.8 (log_{10}, *IQR* 3.1) indicating that these patients are not virally suppressed after starting ART. However, only 43 of the 227 patients (19%) in the cohort had a viral load measurement available after they were started on ART.

In terms of past medical history (Table 2 and Supplementary Table 6), we found that a history of bacterial meningitis (p = 0.03, *OR* 12.5, *95% CI* 1.2–136.1), a cerebrovascular accident (CVA, p = 0. *005, OR* 8.1*, 95% CI* 1.9–34.9) and or tuberculous meningitis (TBM, p = 0.0004, *OR* 7.8, *95% CI* 2.5–24.2) significantly increased a child's probability of having a seizure. In contrast, we found that children who had either cerebral palsy (p = 0.5), ENT disease (p = 0.3), foetal

Table 2
HIV profile and past medical history.

	No seizures (n = 175, 77%)	Seizures (n = 52, 23%)	p	OR (95% CI)
HIV Stage (%)			037	1.4 (0.8 – 1.2)
Stage 2	25 (14.3%)	7 (13.5%)		
Stage 3	26 (14.9%)	13 (25%)		
Stage 4	124 (70.9%)	32 (61.5%)		
ART				
On ART (%)	171 (98%)	51 (98%)	0.2	1.4 (0.8 – 2.5)
Age ART started– *median (IQR)*	14.0 (49.0)	18.0 (31.5)	075	0.9 (0.9 – 1)
HIV neurological disorders				
HIV encephalopathy	117 (66.9%)	28 (53.8%)	0.3	0.6 (0.2 – 1.7)
HIV neurocognitive disorder	33 (18.9%)	12 (23.1%)	0.008	3.2 (1.3 – 7.6)
Peripheral neuropathy	2 (1.1%)	0 (0%)	0.1	10.2 (0.5 – 195.3)
Spastic diplegia	0 (0%)	1 (1.9%)	1	5.02e-13 - ∞
Past medical history (%)				
Bacterial meningitis	1 (0.6%)	4 (7.7%)	0.03	12.5 (1.2 – 136.12)
Cerebrovascular accident	4 (2.3%)	6 (11.5%)	0.005	8.1 (1.9 – 34.9)
Cerebral palsy	8 (4.6%)	2 (3.8%)	0.5	1.6 (0.4 – 6.6)
ENT disease	67 (38.3%)	23 (44.2%)	0.3	1.5 (0.7 – 2.9)
Foetal alcohol syndrome	19 (10.9%)	2 (3.8%)	0.3	1.9 (0.6 – 6.4)
Gastrointestinal disease	30 (17.1 %)	6 (11.5%)	0.1	0.5 (0.2 – 1.3)
Metabolic disease	27 (15.4%)	5 (9.6%)	0.3	0.6 (0.2 – 1.7)
Respiratory disease	107 (61.1%)	32 (61.5%)	0.3	0.7 (0.3 – 1.4)
Tuberculosis meningitis	8 (4.6%)	10 (19.2%)	0.0004	7.7 (2.5 – 24.2)

'ART', antiretroviral treatment; 'ENT', ear nose and throat; 'IQR', interquartile range.

Table 3
Seizure characteristics.

Trigger (%)	
Provoked	36 (69.2%)
Unprovoked	16 (30.8%)
Presumed aetiology (%)	
Infectious	32 (61.5%)
Structural	5 (9.6%)
Unknown	15 (28.8%)
Type (%)	
Generalised	35 (67.3%)
Absence	1 (1.9%)
Myoclonic	1 (1.9%)
Tonic-Clonic	33 (63.5%)
Focal	17 (32.7%)
With awareness	10 (19.2%)
With loss of awareness	7 (13.5%)
Frequency (%)	
1 episode	18 (34.6%)
2/more episodes	34 (65.4%)
EEG (%)	
Not done	19 (36.5%)
Done	33 (63.5%)
Normal	18 (54.5%)
Abnormal	15 (45.5%)
Status epilepticus (%)	11 (21.2%)
Diagnosed with epilepsy (%)	32 (61.5%)

Table 4
: Imaging.

	No seizures (n = 175, 77%)	Seizures (n = 52, 23%)
Brain scan performed	92 (52.6%)	36 (69.2%)
Of those who had scans performed		
CT	31 (33.7%)	25 (69.4%)
MRI	71 (77.3%)	16 (44.6%)
Imaging results		
Normal	42 (45.7%)	7 (19.4%)
Of those who had abnormal scans		
Global atrophy	13 (14.1%)	10 (27.8%)
Basal ganglia calcifications	2 (2.2%)	4 (11.1%)
White matter changes	25 (27.2%)	12 (33.3%)
Grey matter changes	3 (3.3%)	1 (2.8%)
Corpus callosum thinning	10 (10.9%)	1 (2.8%)

alcohol syndrome (FAS, $p = 0.3$), GIT disease ($p = 0.1$), metabolic disease ($p = 0.3$) and or respiratory disease ($p = 0.3$) did not have a significantly higher probability of developing seizures.

3.3. Seizure characteristics

Of the children who reported seizures (Table 3), the majority (69.2%) had an identified trigger ('provoked') with the predominant aetiology being of a presumed infectious origin (62%). Generalised tonic-clonic seizures (64%) were the most frequent seizure type reported with 21.2% of children presenting in status epilepticus. Sixty-Five percent had two or more episodes of seizures documented and 62% of children met the diagnostic criteria for epilepsy. Thirty-tree children received EEGs, of which 45% were reported as abnormal.

3.4. Imaging

Overall, 128 (56%) children in the cohort had received a brain scan (Table 4). The children in the seizure group were more likely to have had a brain scan compared to those in the control (OR 2.1 *95% CI* 1.1–4.1, $p = 0.03$, Supplementary Table 8). Of those that received brain scans, 44% underwent a CT scan while 68% had an MRI (Table 4). Furthermore, the HIV-infected children who had seizures were more likely to have had either a CT scan ($p = 0.04$, *OR* 4.3, *95% CI* 1.1–16.6, Supplementary Table 8). There was no significant difference between the groups with regards to the proportion of children that received an MRI ($p = 0.39$, Supplementary Table 8). In terms imaging findings, we found that the proportion of children with seizures with normal brain imaging was less than controls ($p = 0.01$, Supplementary Table 8). Of the children with abnormal scans, the most common abnormality was white matter changes (47%). There were no significant differences between abnormalities seen on imaging between the control and seizure groups (Supplementary Table 8).

3.5. Treatment

In the HIV-infected children who met the criteria for a diagnosis of epilepsy, we further divided this group according to their seizure control. Seizure control was defined as no seizures for a period of at least one year. Children who were seizure free are referred to as 'controlled' while those still having seizures are referred to as 'not controlled'. We were specifically interested in investigating whether the ART and ASM a child received affected their seizure control. We therefore opted to perform a multinomial logistic regression between seizure control vs ASM and ART agents to identify possible risk factors in these patients.

Overall, 33% of the HIV-infected children with epilepsy did not have their seizures controlled. The distribution of ASMs used in the HIV-infected children with epilepsy is shown in Fig. 1A (raw data shown in Supplementary Table 9). Overall, sodium valproate was the most common ASM used in both the controlled (40.0%) and not controlled groups (82.4%). Furthermore, using our multinomial logistic regression model and controlled for age, sex and HIV stage, we found significant associations between seizure control and the use of carbamazepine ($p = 0.04$) and sodium valproate ($p = 0.01$, Supplementary Table 10). Specifically, children whose seizures were not controlled were more likely to have received carbamazepine (*OR* 7.7, *95% CI* 1.1–54.7) and or sodium valproate (*OR* 7.6, *95% CI* 1.6–35.0). In

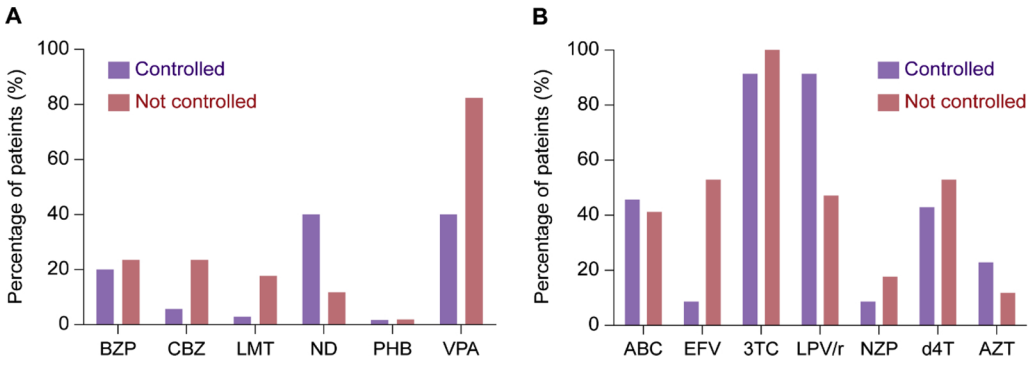

Fig. 1. Differences in antiseizure and antiretroviral therapy between patients with or without controlled seizures. Children were divided into two groups: those whose seizures were controlled (purple) and whose seizures were not controlled (red). The proportion of patients in the two groups who received each of the different anticonvulsant (A) and antiretroviral agents (B) are presented in the two bar graphs. 'BZP', benzodiazepine; 'CBZ', carbamazepine; 'LMT', lamotrigine, 'ND', not on antiseizure medication; 'PHB', phenobarbitone; 'VPA', sodium valproate; 'ABC', abacavir; 'EFV', efavirenz '3TC', lamivudine; 'LPV/r', lopinavir/ritonavir; 'NVP', nevirapine; 'd4T', stavudine; 'AZT', zidovudine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

addition, of the 30% of children who were not receiving ASMs there was no statistical difference in the proportion who were seizure controlled compared to outcomes for those prescribed ASMs ($p = 0.07$).

In terms of ART, overall lamivudine (3TC, 95%) was the most commonly used followed by liponovir/ritonavir (LPV/r, 40%, Fig. 1B). Moreover, our regression model showed a significant association between seizure control and the use of efavirenz (EFV, $p = 0.001$) and LPV ($p = 0.001$, Supplementary Table 11). Notably, patients with poor seizure control were more likely to have received EFV (*OR* 23.1 *95% CI* 3.4–159.6) and less likely to have received LPV (*OR* 0.04, *95% CI* 0.01 – 0.3).

4. Discussion

This retrospective case control study extends the previous work by Samia et al. [9] and adds to the limited current knowledge regarding HIV-infected children with seizures. The findings further characterize the clinical profile of these children, their varied seizure semiology and identifies important drug interactions that warrant consideration in management approaches and policy in this area.

In our patient cohort, there were no differences in the demographic, anthropometrical or HIV profile between children with and without seizures (Table 1). Overall there was a high prevalence of microcephaly (32% combined), which was higher than the 20% reported in a smaller cohort from a previous study in the same population [1]. Within this HIV-infected population, this is especially relevant as microcephaly is a well-documented feature of HIVE, which was diagnosed in 64% of the children reviewed (Table 2).

In the seizure group there was a higher prevalence of documented neurological comorbidities prior to the child presenting with seizures (Table 1). A documented history of acute bacterial meningitis and TBM were prevalent in the seizure group which is consistent with previous reports [7,9]. This finding supports that these infections have long-lasting implications by predisposing these children to developing seizures and even epilepsy. Moreover, in the seizure group there were more children with documented cerebrovascular disease in the absence other concurrent CNS infections. This is most probably as a direct consequence of an HIV-associated vasculopathy [4].

The seizure semiology (Table 2) was varied with generalised tonic-clonic seizures being the most common. Almost two-thirds (62%) of the children were diagnosed with epilepsy. The vast majority of seizures were due to a presumed infectious aetiology, a common complication in the setting of HIV infection, as the condition increases the risk for opportunistic infections. In 28.8% of patients an underlying cause for the seizures could not be determined and factors in addition to HIV infection could not be excluded. This is supported by the lack of significant difference in the viral load, microcephaly or HIVE between the group that had seizures and those that did not.

We also noted that in our cohort, children who had started ART still appeared to have an unsuppressed viral load (Supplementary Table 7). The range of viral loads in children who had received ART was quite wide, with many have lower than detectable levels. However, a few children had a very high viral loads which would bias the results and possibly make the situation look worse than it actually is. The reasons for a high viral load after ART could have been due to the non-compliance which may be due to a combination of the children not receiving their medication from their caregivers or refusing to take it (especially in the case of LPV/r which is bitter. Resistance to the ART could also be a responsible, although this is unlikely unless there has been non-compliance. Furthermore, a lack of absorption of the ART could lead to it being ineffective. This was often the case in children who attended this clinic 10 years ago, when the clinic was started.

The imaging practices and findings of the HIV-infected children with seizures differed from those who did not (Table 3). Specifically, the children with seizures were more likely to have received CT brain scans in the acute setting (rather than MRI in an elective context). This observation most likely relates to the clinical guidelines that recommend the use of the most available imaging where an obvious clinical cause for seizures cannot be determined. MRI scans are not available outside normal working hours in this setting. Therefore, whenever there was a relatively urgent indication for imaging, such as seizures, a CT was much more likely to be performed as the modality of imaging. By contrast, in the seizure-free group, a higher proportion (77%) of patients had MRI scans performed although this was not significantly different from the seizure group. Policy in children the HIV neurology clinic is that children are referred for neuroimaging if they had not had at least one neuroimaging study performed previously. If CT imaging was not performed in the acute setting, most were referred for MRI. This approach related to the intent to characterize the neuroimaging findings amongst children with symptoms of primary CNS HIV infection. Furthermore, these findings also highlight an increased demand for imaging in managing these children which is important in resource-limited setting where access to imaging services, especially MRI, is limited.

In terms of the management of these patients, overall sodium valproate was the most commonly used agent in HIV-infected children with seizures. This is likely due to the sodium valproate being the recommended first-line agent for the management of epilepsy in HIV infected children according to local guidelines [19]. Our study has also shown that HIV-infected children with poor seizure control are more likely to have received EFV and were less likely to have LPV/r. EFV is both an inhibitor and inducer of CYP3A4, an enzyme which plays an important role in the metabolism of many ASMs [20]. However, research suggests that interactions between EFV and ASMs are unlikely to be responsible for poor seizure control. A small pharmacokinetic study by DiCenzo et al. [21] found no difference in the levels of VPA in adult patients who received EFV or LPV/r. Furthermore, Yacoob et al. [22] reported improved seizure control and viral suppression in adult patients on VPA and EFV. Therefore, to explain this apparent relationship between EFV and seizure control, one may need to consider the effects EFV has on the central nervous system [23]. Neurotoxic side effects related to EFV are reported but complications of seizures are less frequently noted, especially in children [24]. To date there are 2 published case reports in a 5-year-old South African child and a 45 year old adult with seizures apparently related to use of EFV [25,26]. In the South African setting *CYP2B6 G > T* mutations are more common, putting children with this at increased risk of toxicity due to subsequent impaired metabolism of EFV [24]. However, screening for this mutation is not routinely available. While there still a need for conclusive paediatric evidence on the use which ASM and ART combinations can be used in children, at present it may be practical to follow the evidence that does exist for epilepsy management in HIV-infected adults [27].

While this study has provided new data on this topic, it is limited by its retrospective design, and small sample size. In addition, clinical notes on the seizure history were limited, making it difficult at times to be absolutely sure about correct semiology and or determine whether or not a patient met the epilepsy diagnostic criteria. Specifically, patients with focal motor seizures with secondary generalization may have been incorrectly reported as having generalised tonic-clonic seizures. It is like that many of the children with underlying infectious aetiology (namely meningitis) are left with a structural insult. Moreover, the global brain involvement would put them at risk for faster seizure propagation and generalisation which would explain why they would be reported as being generalised tonic-clonic events.

Another important limitation was the use of HIV-infected children with a neurological disorder other than seizures as the only control group. We chose this group of patients as we were interested in trying to investigate whether or not there were specific risk factors that may separate the HIV-infected patients who developed seizures from those who did not. However, we acknowledge that our choice of control group limited our ability to identify HIV-specific risk factors for seizures in patients who were already thought to have had a neurological

disorder. For this reason, the main focus of our study was to focus on specific characteristics found within the group of HIV infected children presenting with seizures (i.e. semiology, those that met the diagnosis for epilepsy, seizure control, etc) We do acknowledge due to our choice of control group, the data from this study can give no comment on whether seizures were directly associated with HIV infection versus seizures being a manifestation of another neurological disorder. Future studies could make use of control groups with HIV infection and no documented neurological disorders.

Confounding by indication is a further issue which deserves mention. This is most relevant to the apparent associations between poor seizure control and the ASMs sodium valproate and carbamazepine. Specifically, the association may not be due to the drugs leading to poor seizure control, but rather that patients with poor seizure control are more likely to be put on these agents, especially as valproate is first-line recommended therapy in South Africa for children with HIV. Our ability to measure the interaction between ASMs and ART drugs was limited due to the fact that drug levels are not routinely measured in clinical practice. Drug level monitoring is not routine and this prevented a detailed investigation into how complex drug interactions affect the metabolism of these drugs as previously shown by DiCenzo et al. [21]. This is no doubt the gold-standard for measuring the interactions between different drugs and may be a useful way of investigating the cause of poor seizure control in these patients.

Despite the limitations, this study provides needed and important data on the epidemiology and management of seizures in HIV-infected children. Our results which investigated seizures in HIV-infected children within the Southern African area can be compared to Bearden et al. [28]'s previous work with a Botswanan cohort of HIV-infected children. In their study the authors were specifically interested in whether early ART treatment could prevent the onset of epilepsy in these children. Interestingly, the age at which ART was initiated in their cohort was higher (72 months vs 18 months in our study), though similarly the most common causes for epilepsy were infections and direct HIV toxicity. An important difference between our studies is that they actively recruited HIV-infected patients with seizures between the ages 0–19 years and compared to age-matched HIV-infected controls. This differs from our approach which retrospectively reviewed all the patients that presented to our HIV neurology clinic and then investigating possible risk factors that may have contributed towards those who developed developing seizures. Another relevant study is the ongoing Cohort of HIV-associated Seizure and Epilepsy (CHASE) study which continues to provide important new data on the epidemiology underlying epilepsy in HIV-infected Zambian population [29]. While this study is exclusively recruiting adults, it does show similarities to our study in that aetiology of epilepsy in HIV-infected patients appears to be similarly caused by infections, usually in patients with advanced HIV disease. As to how the results of our study can be generalised, although the western cape region is better resourced in terms of health care facilities for children than the rest of Africa and other resource-limited countries globally (and ART programmes well developed), the clinic population from which this cohort is drawn is broadly representative of the South African population which shares many risk factors with other child populations from sub-Saharan Africa.

5. Conclusion

HIV-infected children who present with seizures are complex both in their clinical presentation and management. Their susceptibility to interactions between ASMs and ARTs may have a direct effect on their seizure control. Prospective studies are needed to better characterize the interaction between ASM and ART agents which will help guide the development of more robust treatment protocols.

Author contributions

RJB was responsible for data collection, data analysis and writing the manuscript. SG, LW and KGW assisted in data collection. JMW assisted in data collection and supervised the writing of manuscript. KAD was the principle investigator who was responsible for developing study protocol and writing manuscript with JMW.

Ethical approval

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (UCT HREC 126/2011).

Declaration of conflict of interests

None

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.01.023.

References

[1] Govender R, Eley B, Walker K, Petersen R, Wilmshurst JM. Neurologic and neurobehavioral sequelae in children with human immunodeficiency virus (HIV-1) infection. J Child Neurol 2011;26(11):1355–64. https://doi.org/10.1177/0883073811405203.
[2] Donald KA, Hoare J, Eley B, Wilmshurst JM. Neurologic complications of pediatric human immunodeficiency virus: implications for clinical practice and management challenges in the African setting. Semin iPediatr Neurol; 2014. Elsevier; 2014. p. p. 3–11. https://doi.org/10.1016/j.spen.2014.01.004.
[3] Donald KA, Walker KG, Kilborn T, Carrara H, Langerak NG, Eley B, et al. HIV Encephalopathy: pediatric case series description and insights from the clinic coalface. AIDS Res Ther 2015;12(1):2. https://doi.org/10.1186/s12981-014-0042-7.
[4] Hammond CK, Eley B, Wieselthaler N, Ndondo A, Wilmshurst JM. Cerebrovascular disease in children with HIV-1 infection. Dev Med Child Neurol 2016;58(5):452–60. https://doi.org/10.1111/dmcn.13080.
[5] Chai NC, McArthur JC. HIV peripheral neuropathy. Chronic Pain and HIV: a practical approach. West Sussex, UK: Wiley-Blackwell; 2016.
[6] Madhi SA, Madhi A, Petersen K, Khoosal M, Klugman KP. Impact of human immunodeficiency virus type 1 infection on the epidemiology and outcome of bacterial meningitis in South African children. Int J Infect Dis 2001;5(3):119–25. https://doi.org/10.1136/adc.88.12.1112.
[7] Van Well GT, Paes BF, Terwee CB, Springer P, Roord JJ, Donald PR, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the western cape of South Africa. Pediatrics 2009;123(1). e1-e8.
[8] Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. Lancet Neurol 2013;12(10):999–1010. https://doi.org/10.1016/S1474-4422(13)70168-6.
[9] Samia P, Petersen R, Walker KG, Eley B, Wilmshurst JM. Prevalence of seizures in children infected with human immunodeficiency virus. J Child Neurol 2013;28(3):297–302. https://doi.org/10.1177/0883073812446161.
[10] Romanelli F, Jennings H, Nath A, Ryan M, Berger J. Therapeutic dilemma the use of anticonvulsants in HIV-positive individuals. Neurology 2000;54(7):1404–7.
[11] Liedtke MD, Lockhart SM, Rathbun RC. Anticonvulsant and antiretroviral interactions. Ann Pharmacother 2004;38(3):482–9. https://doi.org/10.1345/aph.1D309.
[12] Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006;61(3):246–55. https://doi.org/10.1111/j.1365-2125.2005.02529.x.
[13] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–82. https://doi.org/10.1111/epi.12550.
[14] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23. https://doi.org/10.1111/epi.13121.
[15] Centre for disease control and prevention (CDC). Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Morb Mortal Wkly Rep Surveill Summ 1994;43(12):1–10.
[16] Van Rie A, Harrington PR, Dow A, Robertson K. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. Eur J Paediatr

Neurol 2007;11(1):1–9. https://doi.org/10.1016/j.ejpn.2006.10.006.
[17] Hilburn N, Potterton J, Stewart A. Paediatric HIV encephalopathy in sub-Saharan Africa. Phys Ther Rev 2010;15(5):410–7. https://doi.org/10.1080/09540121.2011.579942.
[18] Joska JA, Westgarth-Taylor J, Myer L, Hoare J, Thomas KG, et al. Characterization of HIV-associated neurocognitive disorders among individuals starting antiretroviral therapy in South Africa. AIDS Behav 2011;15(6):1197–203. https://doi.org/10.1007/s10461-010-9744-6.
[19] Department of Health. Standard treatment guidelines and essential medicines list for South Africa: hospital level paediatrics. Pretoria, South Africa: National Department of Health; 2017. p. 343.
[20] Johannessen S, Johannessen L. Antiepileptic drug interactions-principles and clinical implications. Curr Neuropharmacol 2010;8(3):254–67. https://doi.org/10.2174/157015910792246254.
[21] DiCenzo R, Peterson D, Cruttenden K, Morse G, Riggs G, Gelbard H, et al. Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2004;48(11):4328–31. https://doi.org/10.1128/AAC.48.11.4328-4331.2004.
[22] Yacoob Y, Bhigjee AI, Moodley P, Parboosing R. Sodium valproate and highly active antiretroviral therapy in HIV positive patients who develop new onset seizures. Seizure 2011;20(1):80–2. https://doi.org/10.1016/j.seizure.2010.09.009.
[23] Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV. Efavirenz and the CNS: what we already know and questions that need to be answered. J Antimicrob Chemother 2015;70(10):2693–708. https://doi.org/10.1093/jac/dkv183.
[24] Hammond CK, Eley B, Wilmshurst JM. Neuropsychiatric complications of efavirenz in children with HIV infection. Future Virol 2016;11(6):469–80. https://doi.org/10.2217/fvl-2016-0030.
[25] Nijhawan AE, Zachary KC, Kwara A, Venna N. Status epilepticus resulting from severe efavirenz toxicity in an HIV-infected patient. AIDS Read 2008;18(7). 386-.
[26] Strehlau R, Martens L, Coovadia A, Dandara C, Norman J, Maisel J, et al. Absence seizures associated with efavirenz initiation. Pediatr Infect Dis J 2011;30(11):1001. https://doi.org/10.1097/INF.0b013e318223b680.
[27] Birbeck GL, French JA, Perucca E, Simpson DM, Fraimow H, George JM, et al. Antiepileptic drug selection for people with HIV/AIDS: evidence-based guidelines from the ILAE and AAN. Epilepsia 2012;53(1):207–14. https://doi.org/10.1111/j.1528-1167.2011.03335.x.
[28] Bearden D, Steenhoff AP, Dlugos DJ, Kolson D, Mehta P, Kessler S, et al. Early antiretroviral therapy is protective against epilepsy in children with human immunodeficiency virus infection in Botswana. J Acquir Immune Defic Syndr 2015;69(2):193. https://doi.org/10.1097/QAI.0000000000000563.
[29] Siddiqi OK, Elafros MA, Bositis CM, Koralnik IJ, Theodore WH, Okulicz JF, et al. New-onset seizure in HIV-infected adult Zambians: a search for causes and consequences. Neurology 2016(88):1–6. https://doi.org/10.1212/WNL.0000000000003538.