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Review

Prevalence and incidence of new-onset seizures and epilepsy in patients with human immunodeficiency virus (HIV): Systematic review and meta-analysis

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ABSTRACT

Background: The prevalence and incidence of seizures are substantially higher in patients with human immunodeficiency virus (HIV) compared with the general population and is associated with higher mortality rates. Despite this, the condition remains poorly understood, and there is variation in reported epidemiological studies. The aim of this systematic review and meta-analysis was to investigate the risk factors associated with seizures in the population with HIV, explore the source of variations, and describe management plans that can aid clinicians in the acute and long-term treatment of these patients.
Methods: A structured electronic database search of MEDLINE, EMBASE, and Cochrane Library was conducted. Studies were included if they described clinical details of patients with HIV with seizures or epilepsy. We extracted select variables from each included study, and we estimated pooled estimates of the incidence and prevalence of seizures using random-effects meta-analysis of proportions.
Results: Information on 6639 cases of patients with HIV was extracted from 9 included studies. These comprised of 2 studies from the United States of America (USA), 3 from Europe, 3 from Asia, and 1 from Africa. The pooled prevalence and incidence rate of seizures in HIV were 62 per 1000 population and 60 per 1000 population respectively. Among those who presented with new-onset seizures, 63% had seizure recurrence. At the time of first seizure, 82.3% had acquired immunodeficiency syndrome (AIDS). Factors that appeared to be linked to seizures in HIV included advanced HIV disease, opportunistic infections particularly toxoplasmosis, and metabolic derangement. Most seizures were effectively controlled by common antiepileptic drugs (AEDs).
Conclusions: The prevalence and incidence of seizures and epilepsy in the population with HIV are substantially higher than the general population. Our results suggest that advanced HIV and opportunistic infections are associated with the majority of the seizures. Early initiation of highly active antiretroviral therapy (HAART), prophylactic use of cotrimoxazole (trimethoprim–sulfamethoxazole) and routine electroencephalogram (EEG) in patients with HIV may reduce seizure incidence and frequency and help in early diagnosis of nonconvulsive seizures in this population. We recommend long-term seizure management with AED, and for patients on HAART, enzyme-inducing AED should be avoided when possible.

1. Introduction

The prevalence of seizures and epilepsy in patients with human immunodeficiency virus (HIV) is substantially higher than the general population [1]. Human immunodeficiency virus carries a risk for seizures through metabolic disturbances [2], opportunistic infections of the central nervous system (CNS) such as toxoplasmosis, CNS lymphoma, cryptococcal meningitis, tuberculous (TB) meningitis or progressive multifocal leukoencephalopathy (PML) [3–8], and HIV encephalopathy [6,7,9]. However, the majority of seizures are not associated with any identifiable focal brain lesion, and it has been suggested that HIV infection alone could be the sole cause of these seizures [10]. Seizures associated with HIV infection lead to a substantially high mortality rate [11]. Furthermore, in approximately 18% of patients with HIV, seizures are the initial presenting sign [6]. However, there exists heterogeneity in the prevalence and incidence of seizures or epilepsy in people living with HIV/acquired immunodeficiency syndrome (AIDS). Anecdotal data suggest rates to be higher in children, in Africa [12], and the setting of advanced disease [10], and lower in high-income countries [13]. In a prospective study of 550 patients with HIV recruited in Spain

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over 1 year, 3% had a new-onset seizure during the study period [14]. However, in a hospital-based study in the USA where 71% of the study population had AIDS, the incidence of new-onset seizures was 12% [10]. Across all countries, age groups, and disease stages, the seizure semiology remains constant. Over 80% of seizures in patients with HIV are primary generalized [4], followed by partial with secondary generalization (10%) and only partial. Furthermore, antiretroviral therapy (ART)–antiepileptic drug (AED) interactions pose a challenge in the management of seizures in patients with HIV [15]. The objective of this systematic review was to estimate the pooled incidence and prevalence of seizures in the population with HIV, to explore seizure etiologies, investigate variations in the incidence rates, and to discuss acute and long-term management.

2. Methods

2.1. Search strategy and selection criteria

For this systematic review and meta-analysis, we developed a study protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Text 1 and Table 1). We searched three databases (MEDLINE, EMBASE, and Cochrane Library) to identify all studies published before December 7, 2018, which reported on prevalence or incidence of seizures or epilepsy in the population with HIV. As elaborated in Supplemental Table 2, we did an initial keyword search and subsequent searches based on Medical Subject Headings (MeSH) with various combinations of search terms "HIV*", "human immunodeficiency virus*", "AIDS*", "acquired immunodeficiency syndrome*"AND "epilepsy", OR "seizures". No restrictions were imposed on the gender, ethnicity, whether diagnoses were done in public or private settings, age at diagnosis, or language of the publication.

We identified and reviewed articles in a two-step process. The first step consisted of a title and abstract review to identify records that were deemed potentially eligible for inclusion. We excluded publications that were duplicates. In the second step, full-text articles were retrieved and reviewed to further conform eligibility.

2.2. Quality assessment and data extraction

All full-text articles retrieved were reviewed to confirm eligibility and, if eligible, data were extracted. Data on the prevalence and incidence of seizures were extracted. In addition, data on country of the study, date of publication, and mean or median age at time of diagnosis, frequency of AIDS, frequency of seizure semiology, AED used, and etiologies were included. To assess the quality of the papers included in the review, we used a quality assessment criteria that we developed to assess the potential for selection and information bias as well as the

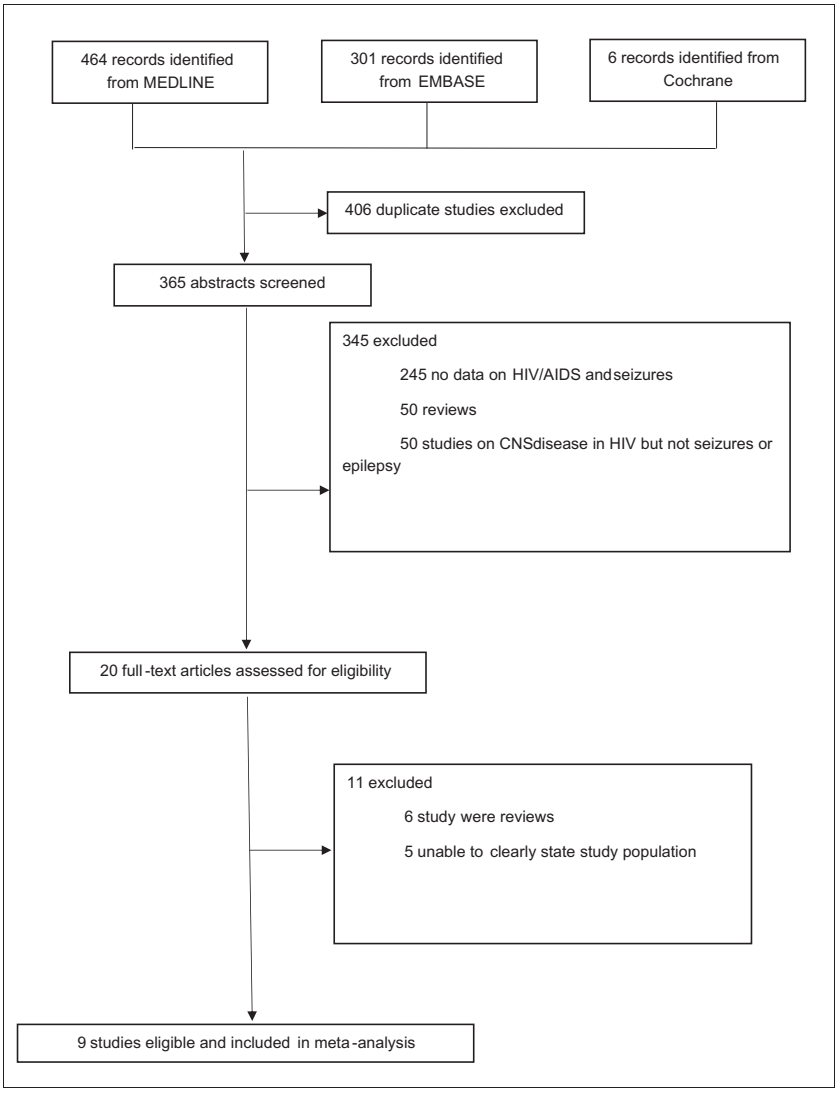

Fig 1. PRISMA flowchart of a systematic review of the global epidemiology of seizures in the population with HIV.

availability of data on major variables (e.g., mean/median age, year of diagnosis, date of publication, mean or median age at time of diagnosis, frequency of AIDS, frequency of seizure semiology, AED used, and etiologies. Details in Supplemental Text 2). A quality score ranging from 0 to 15 (low to high quality) was given to each paper.

2.3. Data analysis

The primary outcome was the prevalence and incidence of seizures in the population with HIV. R package *metaprop* was used to graphically display population-specific prevalence and incidence of seizures and to estimate pooled prevalence and incidence of seizures using random effect models. Between-population heterogeneity was assessed using I^2 statistic and the p value for heterogeneity (Cochrane's Q statistic). To examine potential sources of heterogeneity, population-specific estimates were calculated by meta-regression. Study-level determinants of seizure incidence were expressed as absolute differences (AD) in the incidence rates of seizures. The potential for small study bias was assessed using funnel plots and Egger's test.

3. Results

Our search retrieved 365 articles, of which 20 were carefully reviewed and considered as potentially relevant (Fig. 1). The full text was retrieved for all of these articles, and each was carefully reviewed. The full-text review identified 9 eligible papers from 7 countries, 3 of which were from Europe (German, Spain, and Ireland), 2 from the USA, 3 from Asia (India and South Korea), and 1 from Africa (South Africa). Two studies reporting seizures in HIV only included patients with HIV that had seizures [16,17]. Because they did not have a comparison group, they were excluded from the meta-analysis. Study-specific details and references are given in Table 1.

These articles reviewed comprised a total of 6639 patients with HIV, with sample sizes ranging from 354 to 1574 (median: 604). Of these, 404 patients had seizures, either before or after being tested positive for HIV, and 393 patients had new-onset seizures. The median age of the patients included in the study was 34 years (range: 6–47 years). Among those with epilepsy or seizures, 77% were men. The average frequency of patients with seizures that had AIDS was 65%. On average, 58% of seizures were primary generalizing (range: 13–94%), followed by 23% partial with secondary generalization, complex partial 16%, and simple partial 10%.

The pooled prevalence and incidence of seizures in the population with HIV were 62 per 1000 (95% CI: 37.3–93.1) and 60 per 1000 (95% Confidence Interval (CI): 34.7–91.9) respectively (Figs. 2 and 3). There was a wide variation in prevalence and incidence of seizures in the studies analyzed. The prevalence of seizures in the population with HIV ranged from 2% (95%CI: 1.4%–4%) in Ireland to 19.8% (95% CI: 16.4–23.6) in India (Fig. 2). The incidence rate ranged from 1.8% (95% CI: 0.9–3.2) in Ireland to 19.8% (95% CI: 16.4–23.6) in India (Fig. 3). Between-population heterogeneity for prevalence and incidence was wide (I^2 = 95%; p < 0.01) and (I^2 = 96%; p < 0.01) respectively. Displayed in Fig. 4 are the continent-specific incidence rates. Asia had the highest incidence of 7.8% (95% CI: 1.1–19.8), and Europe had the lowest incidence rate of 3.4% (95% CI: 1.5–6.1). Global distribution of seizure in the population with HIV is shown in Fig. 5.

Infections were the primary identifiable etiology, with toxoplasmosis diagnosed in 21% of patients with HIV with seizures, followed by

Table 1
Studies reporting seizures in HIV.

Author	Kellinghaus et al. [1]	Pascual-Sedano et al. [14]	Wong et al. [10]	Chadha et al. [3]	Samia et al. [12]	Kim et al. [8]	Zaporojan et al. [13]	Van Paesschen et al. [2]	Sinha et al. [37]
Publication year	2007	1999	1990	2000	2012	2015	2018	1995	2005
Country	Germany	Spain	USA	India	South Africa	South Korea	Ireland	USA	India
HIV, n	831	550	630	455	354	1141	604	1574	500
Seizure or epilepsy, n (%)	51(6.1)	17(3)	70 (11)	23 (5.1)	27 (7.6)	34 (3)	15 (2.4)	68 (4)	99 (19.8)
New-onset seizures, n (%)	48 (5.8)	17 (3)	70 (11)	23 (5.1)	27 (7.6)	30 (2.6)	11(1.8)	68 (4)	99 (19.8)
Age (year)	37	32.8	37	32	6	47	36	38	32
Female, n (%)	13 (25)	6 (35)	11 (16)	NR	13 (48)	3 (9)	4 (27)	NR	9 (10)
Male, (%)	38 (75)	11 (65)	59 (84)	NR	14 (52)	31 (91)	11 (73)	N R	90 (90)
Latency, year	NR	5	NR	NR	NR	3	5.8	NR	NR
AIDS, n (%)	29(57)	14 (82)	50 (71)	NR	328 (95)	16(53)	7(53)	62 (91)	NR
Cryptococcus, n (%)	NR	NR	7 (10)	4 (17)	NR	NR	NR	3 (4)	41(41)
Toxoplasmosis, n (%)	7 (14)	5 (29)	11 (16)	7 (30)	NR	NR	3 (20)	8 (12)	23 (23)
PML, n (%)	7 (14)	1 (6)	NR	1 (4)	NR	14 (41)	1 (7)	NR	1 (1)
CNS-tuberculosis, n (%)	1 (2)	NR	NR	3 (13)	3 (11)	NR	1 (7)	1 (1)	44 (44)
Unknown, n (%)	25 (49)	1 (6)	38 (54)	7(30)	NR	6(18)	3 (20)	NR	6 (6)
Generalized, n (%)	26 (51)	12 (71)	52 (74)	15 (65)	18(67)	12 (35)	2 (13)	43 (63)	63 (63)
Simple partial, n (%)	8 (16)	2 (12)	5 (7)	NR	6 (22)	1 (3)	1 (7)	3 (4)	37(37)
Complex partial, n (%)	3 (6)	0 (0)	9 (13)	6 (26)	3 (11)	10 (39)	3 (20)	3 (4)	37(37)
PSG, n (%)	14 (27)	3 (18)	14 (20)	2 (9)	NR	11 (32)	6 (40)	7(10)	NR
Comment	Recurrence of seizures observed in 67% of patients. Gabapentin common AED used	Recurrence of seizures not reported. Phenytoin common AED used	Recurrence of seizures observed in 54% of patients. Phenytoin common AED used	Recurrence of seizures observed in 69.56% of patients. Phenytoin common AED used	Recurrence of seizures observed in 78% of patients. Sodium valproate common AED used	Recurrence of seizures was observed in 67% of patients. Levetiracetam common AED used	Recurrence of seizures observed in 43% of patients. Levetiracetam common AED used	Recurrence not reported. Metabolic derangements were the major causes of new-onset seizures.	Recurrence not reported. Phenytoin common AED used (51%)

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; PML,: progressive multifocal leukoencephalopathy; PSG,: partial seizures with secondary generalization; USA: United States of America; NR: Not reported; AEDs: antiepileptic drugs.

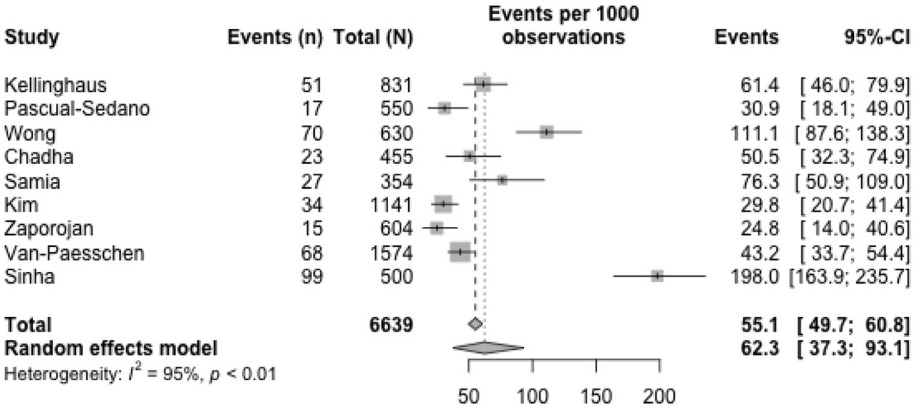

Fig 2. Pooled prevalence/1000 of seizures in the population with HIV.

Cryptococcus infection and PML at 14% each. Other infections included TB, bacterial meningitis, and cysticercosis. However, in approximately 32% of the patients with seizures, the etiology was not identified. Among those who presented with new-onset seizures, 63% had seizure recurrence.

Fig. 6 displays the correlation analysis between the prevalence of seizures in the population with HIV and selected predictors. As shown in Fig. 6A, the frequency of AIDS among studies was positively correlated with the prevalence of seizures, although the correlation did not reach statistical significance ($r = 0.34$, p = 0.45). To understand if the introduction of highly active antiretroviral therapy (HAART) had an effect on seizure frequency, we ran a correlation analysis on the year of publication (Fig. 6C). The year of publication was negatively associated with seizure prevalence ($r = -0.49$, p = 0.21), although the correlation did not reach statistical significance. Finally, age was negatively correlated with seizure prevalence (r = −0.34, p = 0.4), however, this association did not reach statistical significance (p = 0.4). Summarized in Table 2 is the meta-regression results. Incidence rate of seizures in the population with HIV did not differ by age, region (Asia, Europe, Africa, North America), publication score, or study quality score.

The funnel plot (Supplemental Fig. 1) and the value of the Egger's test (p = 0.6) indicated absence of small study bias.

4. Discussion

The prevalence of epilepsy in the general population is between 0.4% and 1.0% [18–20], and the incidence is 0.05% [21]. From the systematic review, our findings estimate the prevalence and incidence of seizures in patients with HIV as 6.2% and 6.0% respectively. To our knowledge, this is the first systematic review of incidence rate and prevalence of seizures in the population with HIV. We compiled data from 9 studies consisting of 6639 patients with HIV and 393 patients with new-onset seizures. The findings highlight two main issues. First, the incidence and prevalence of seizures in the population with HIV are high, 5 times higher than the general population. Second, approximately 32% of the seizures in the population with HIV are hypothesized to be directly caused by HIV infection alone. In addition, the more advanced the HIV disease the higher the likelihood of triggering seizures. Furthermore, a great majority of the seizures are generalized. Furthermore, because most seizures in patients with HIV were generalized, HIV-infected brain may have diffuse cortical irritability or an impaired mechanism of seizure termination.

The association between seizures and the advanced stage of HIV (AIDS) is explained in part by the high prevalence of opportunistic infections in these patients and a high viral load. In our studies, the prevalence of toxoplasmosis and Cryptococcus infections in patients with HIV with seizures was high. However, it should be noted that in almost a third of the population, the cause of seizures was not found and could be linked to the HIV itself. Since new-onset seizures in a patient with HIV infection suggest the possibility of potentially treatable cerebral lesions such as toxoplasmosis or Cryptococcus meningitis, we suggest that in patients with HIV presenting with seizures, scrupulous cerebral spinal fluid (CSF) examination for cryptococcal antigens, fungal cultures should be done.

The lower rates of seizures in the later years, post 2000, could be caused by the introduction and wide use of HAART. Highly active antiretroviral therapy is associated with the reduced rate of stage migration of the disease and therefore, prevention of opportunistic infections. It

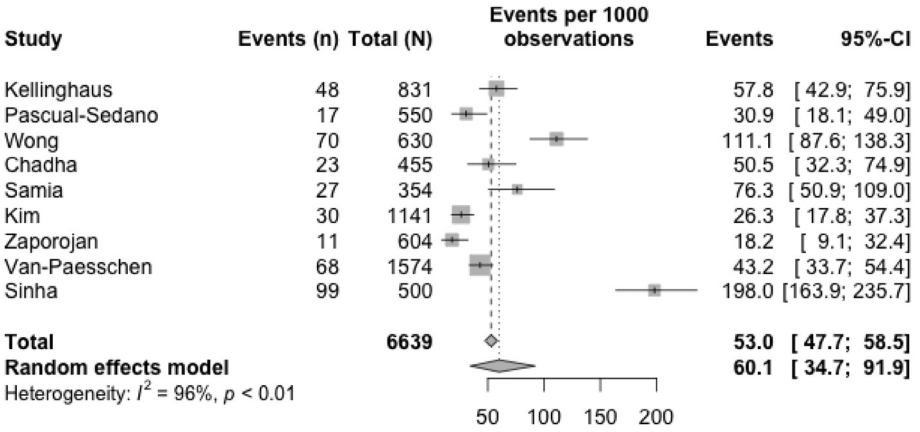

Fig 3. Pooled incidence/1000 of seizures in the population with HIV.

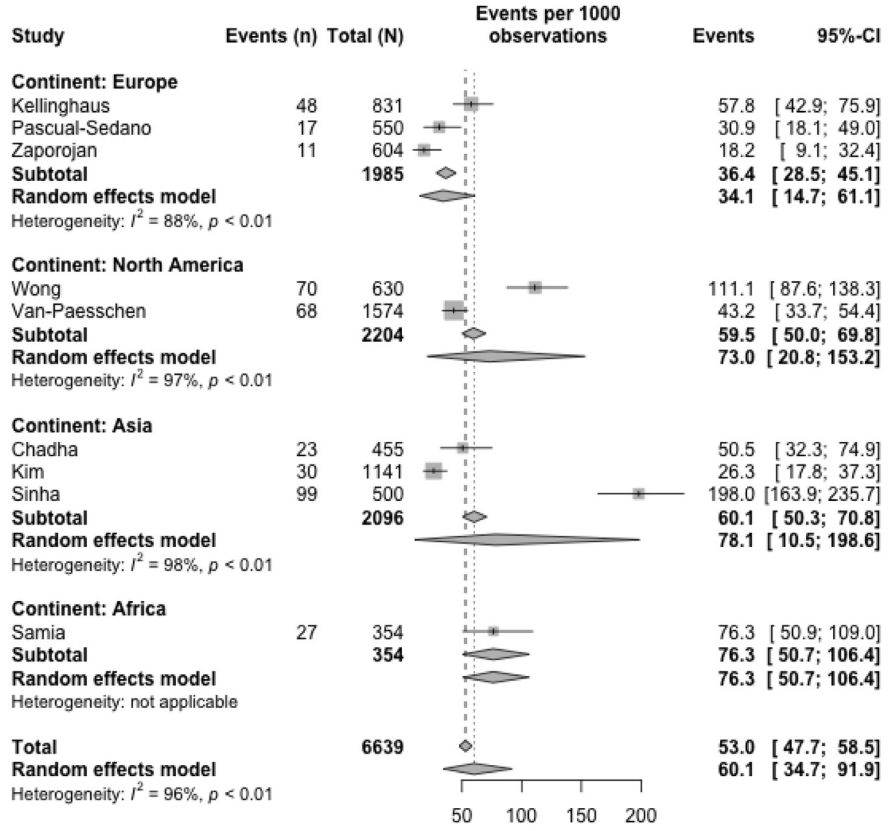

Fig 4. Pooled incidence/1000 of seizures in the population with HIV stratified by continents from which the papers used in the meta-analysis were published.

should be noted, however, that the metabolic disturbance, inflammatory reconstitution syndrome that is sometimes attributed to HAART, could at some level trigger seizures. Therefore, patients on HAART should be monitored for any neurological changes, and appropriate steps should be taken if neurotoxicity is detected in the patients.

Effective treatment of acute seizures in patients with HIV infection is the key in preventing mortality in this population. Phenytoin sodium was the anticonvulsant most frequently used. It was generally well tolerated albeit adverse drug reactions in the form of rash, worsening leukopenia or thrombocytopenia, and worsening liver function reported in one study [10]. The interactions between HAART and AEDs are frequent as many members of the 2 classes of medications are metabolized by the cytochrome P450 (CYP) system [22]. First generation AEDs such as carbamazepine, phenytoin, and phenobarbital, which are routinely used to control seizures in populations with HIV, induce cytochrome P450 and glucuronyl transferase enzymes [23] and can reduce the serum concentration of HAART leading to virologic failure [15,24]. On the other hand, HAART agents can inhibit and induce some of the CYP isoenzymes [25], which can lead to AED toxicity and failure respectively. Therefore, concurrent use of enzyme-inducing AEDs and HAART should be avoided

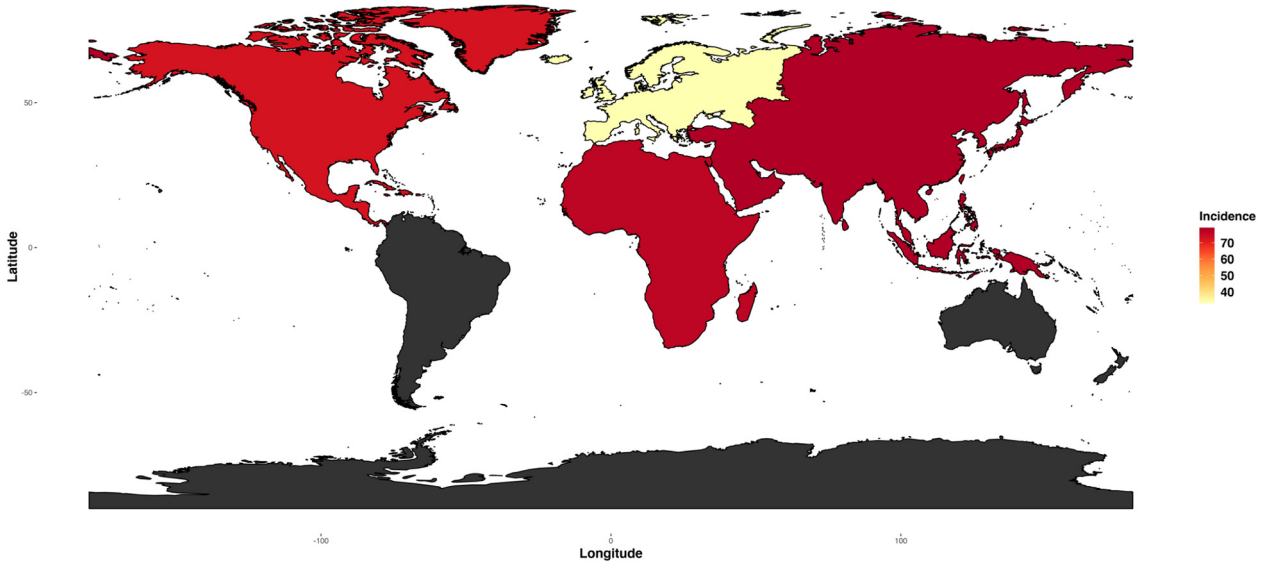

Fig 5. Incidence (per 1000) of seizures in the population with HIV shaded by continents from which the papers used in the meta-analysis were published.

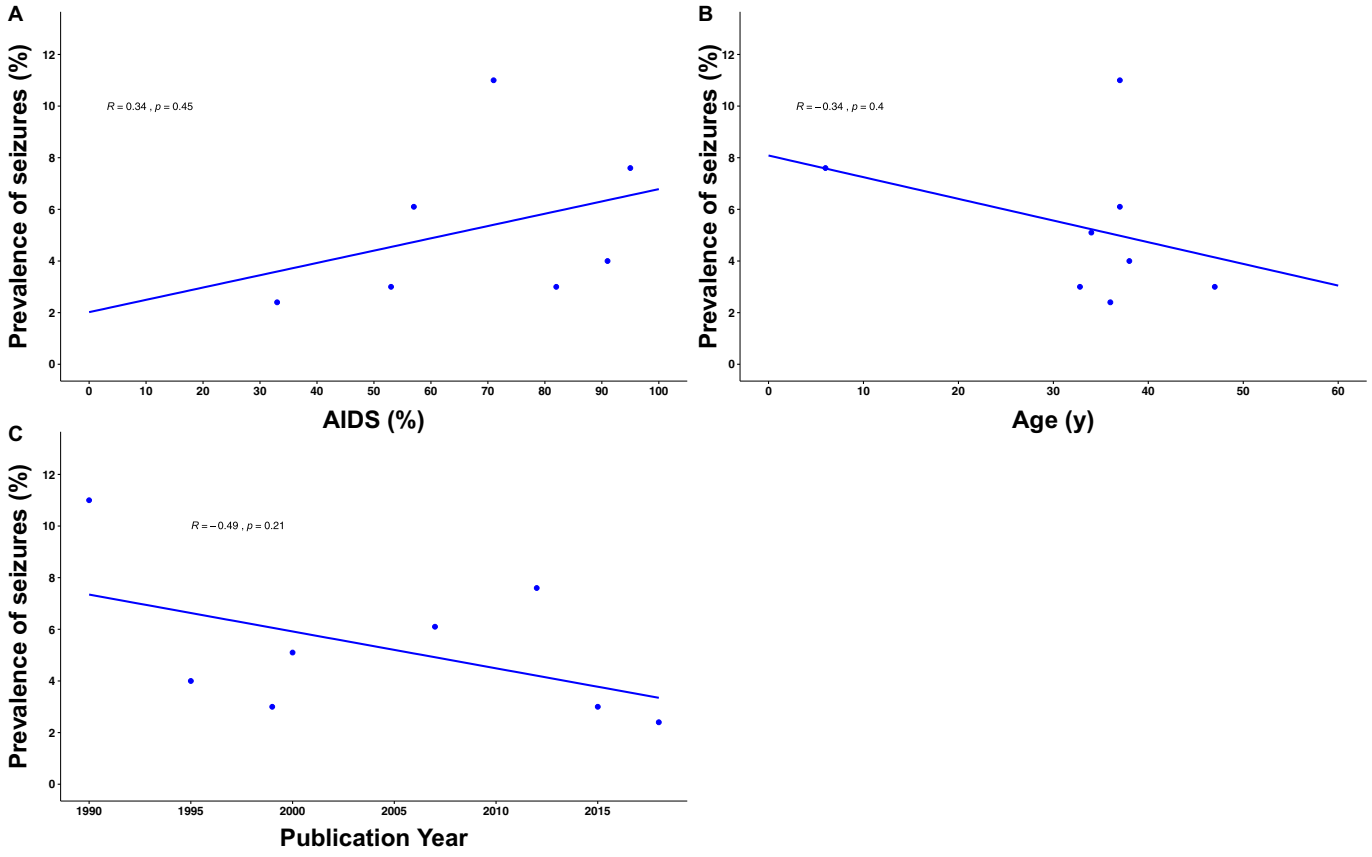

Fig 6. Correlation of prevalence of seizures in HIV and AIDS, age, and year of publication. Image (A) demonstrates the correlation between mean prevalence of seizures in HIV and the frequency of AIDS in the study population. Image (B) demonstrates correlation between mean prevalence of seizures in HIV and age in years. Image (C) demonstrates the correlation between mean prevalence of seizures in HIV and publication year.

when possible. Summarized are evidence-based recommendations on AED treatment in the context of AED ART [26]. They have been jointly developed by the American Academy of Neurology and the International League Against Epilepsy. First, in patients receiving phenytoin, lopinavir/ritonavir dosage may be increased by about 50% to maintain unchanged serum concentrations. Second, patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations. Third, coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment. Those receiving ritonavir/atazanavir may require a lamotrigine dosage increase by about 50%. However, coadministration of raltegravir or atazanavir and lamotrigine may not require lamotrigine dosage adjustment. Finally, coadministration of raltegravir and midazolam may not require midazolam dosage adjustment. Newer agents such as levetiracetam are well-tolerated [13] and should be used if available.

There has been much debate on long-term AED therapy for patients with HIV who have had only one seizure, with some studies advocating for short-term AED therapy [13] but others recommending long-term treatment with AED, except when reversible metabolic derangements are the cause of the seizure [27]. However, because of high recurrence rates of seizures in patients with HIV, we recommend long-term AED even after the treatable causes have been managed. Clinicians should make sure that patients with HIV taking HAART and who are initiated on long-term AED have serum drug levels monitored frequently so as to avoid toxicity or suboptimal blood levels, which is of greater importance in the prevention of seizures in populations with HIV. A vast majority of seizures were caused by opportunistic infections such as tuberculosis and toxoplasmosis. Recommended by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) is the prophylactic use of cotrimoxazole (trimethoprim–sulfamethoxazole) [28]. In patients with HIV infection, daily cotrimoxazole prophylaxis significantly decreases mortality, hospital admission, and opportunistic infection rates through reducing viral load and increasing cluster of differentiation 4 (CD4) cell count [29–32].

Table 2
Meta-regression results.

Predictors of seizure incidence rate	Sample size	Absolute differences in the incidence rates of seizures (95% CI)	p value
Age (y)	6639	−0.50 (−0.1.23, 0.24)	0.19
Regional			
Asia	2096	−3.8 (−33.8, 26.2)	0.81
Europe	1985	−16.3 (−46.3, 13.7)	0.29
North America	2204	−11.5 (−43.3, 20.3)	0.48
Africa	354	Reference	
Publication year	6639	−0.14 (−1.11, 0.82)	0.77
Study quality score	6639	0.21 (−3.9, 4.3)	0.92

Unlike cerebral malaria, herpes simplex, or *neurocysticercosis* where animal models have been developed [33–35], there is a lack of animal studies exploring seizures in HIV. Such an animal model of HIV-induced seizures is needed to better understand mechanisms of brain damage caused by HIV and to investigate mechanisms of AED–HAART interactions. In addition, more clinical research exploring the seizure and epilepsy rates in patients with HIV is needed especially in sub-Saharan Africa where the prevalence of HIV is the highest in the world [36].

Major strengths of this review include the detailed and inclusive search strategy, which included non-English publications, large sample size of approximately 6000 men and women with HIV, and the use of standard methods for study identification, data extraction, and

synthesis. There were also limitations. The representativeness of the review might have been compromised by several factors. First, we included studies from only 6 countries. Second, most of the patients with HIV with new-onset seizures were not adequately followed up. As a result, the incidence of recurrent seizures in this could have been underestimated.

Nevertheless, this review provides new insight in the frequency of seizures in patients with HIV, explores the etiology, and discusses management goals.

5. Conclusion

This review showed that the prevalence and incidence of seizures in the population with HIV are 5 times higher than the general population. Therefore, early initiation of HAART and prophylactic treatment with cotrimoxazole to prevent opportunistic infections is the key in prevention of seizures and epilepsy in the population with HIV. For those with seizure, long-term AEDs are recommended.

Consent

This is a systematic review and meta-analysis. No consent required.

Conflict of interest

PS has no financial disclosures.

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Appendix A. Supplementary data

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