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Women with epilepsy in sub–Saharan Africa: A review of the reproductive health challenges and perspectives for management

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ABSTRACT

Background: Epilepsy is one of the commonest neurological conditions affecting women of reproductive age. Epilepsy management during pregnancy is a clinical conundrum, requiring a balance between seizure control and risk minimization for the women with epilepsy (WWE) as well as for their fetuses. The objective of this comprehensive review is to explore the reproductive health challenges of WWE in sub-Saharan Africa (SSA) and ways to address them.

Method: Relevant documentation published until June 2019 were retrieved via literature searches performed in PubMed and Google Scholar, as well as a manual search to identify grey literature.

Results: WWE in SSA are generally more stigmatized and sexually exploited than women without epilepsy. Contraception use among WWE was reported only in Senegal (51%) and Kenya (14.7%). Only two prospective studies (one in Senegal and one in Nigeria) investigated pregnancy outcomes for a total of 97 WWE. The prevalence of convulsive epilepsy in pregnancy was estimated at 3.33 per 1000. Among pregnant WWE treated with first line anti-epileptic drugs, 16.2% had miscarriages, 41.9% premature births, and 4.1% had babies with malformations. Carbamazepine, which is frequently prescribed to pregnant WWE in SSA, still entails a 2.1-fold increased risk of congenital malformation. No reports were found concerning pre-conceptual counseling and post-natal outcomes in WWE in SSA.

Conclusion: Our review underscores the need for contextualized evidence-based clinical guidelines and a collaborative approach to treat WWE in SSA. High risks of congenital malformations and drug interactions with first line AED warrant the provision of safer second line alternatives.

1. Introduction

Epilepsy is a leading neurological condition characterized by recurrent seizures and affecting more than 50 million people worldwide [1]. There is a disproportionate geographical burden of epilepsy, with 80% of cases living in low- and middle-income countries [1]. In sub–-Saharan Africa (SSA), the estimated median prevalence of epilepsy is 14.2 per 1000 [2]; there is a peak prevalence in the 20–29 years age group, with both sexes being equally affected particularly for individuals under 40 years [3]. Persons with epilepsy (PWE) in SSA are faced with a plethora of challenges, including stigma and associated cultural barriers, a dearth of diagnostic capacity, and inadequate anti-epileptic drug (AED) supplies resulting in a > 70% treatment gap [4,5]. As of 2007, the median number of neurologists in SSA was estimated at 0.3 per 1 million population, and 11 SSA countries had none [6].

In addition to seizures and related complications experienced by all PWE, women with epilepsy (WWE) require a more comprehensive management strategy that takes into account reproductive health needs

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Table 1
First and second-line AED available in SSA.

	Indication	Impact on pregnancy outcomes and child development [8,9]
First line AED		
Phenobarbital	First option because of its low cost, recommended for most seizure types [5,10].	- Prevalence of foetal malformations: 6.5%* - Lower IQ in exposed children
Carbamazepine	Focal onset epilepsies. Can be used with caution in pregnancy if no second line AED available [10,11].	- Prevalence of foetal malformations: 5.5%* - Reduced verbal abilities in exposed children
Phenytoin	Most seizure types, except absence seizures [10].	- Prevalence of foetal malformations: 6.4%* - Lower locomotor scores in exposed children - Lower IQ in exposed children
Valproic acid	Most seizure types [10].	- Prevalence of foetal malformations: 10.3%* - Worse IQ in exposed children
Second line AED		
Lamotrigine	Most seizure types [12]	- Prevalence of foetal malformations: 2.9%* - Reduced verbal abilities in exposed children
Levetiracetam	Focal and generalised seizures [12]	- Prevalence of foetal malformations: 2.8%* - No difference in developmental scores when compared to unexposed children

*The prevalence of congenital malformations in the absence of foetal AED exposure is 2.6%, which is not significantly different from the prevalence of congenital malformations with the second line AED [13].

[7]. Given the high epilepsy prevalence observed among women of reproductive age in SSA [3], it is crucial to achieve optimal seizure control in WWE to ensure optimal reproductive health outcomes. However, the first-line anti-epileptic drugs (AED) recommended by the World Health Organization (WHO) for use in SSA settings [5] have been associated with adverse outcomes for the child in contrast with the less available second-line AED (Table 1).

To date, much has been documented concerning the reproductive health of WWE in USA, Europe and some developing countries, all suggesting worse outcomes among WWE compared to women without epilepsy [14–16]. However, little is known regarding the pre-conceptual, pregnancy and post-partum outcomes for WWE in the African continent. In this comprehensive review, we examine the reproductive health challenges of WWE in SSA and suggest ways to address them.

2. Methods

Literature searches were performed on the electronic databases PubMed and Google Scholar on June 1st, 2019. Key search terms included “epilepsy”, “women”, “reproductive health”, “pregnancy”, and “sub-Saharan Africa” (see Appendix 1). We retrieved both original articles and review articles written in English and French. An additional manual search was undertaken to include the bibliographies of the retrieved references and also to identify grey literature. Articles in which the main study outcome was preeclampsia/eclampsia were not included in our review, as these refer to acute seizures during pregnancy and do not conform to the International League Against Epilepsy (ILAE) definition of epilepsy [17]. Results are presented following different life contexts of the WWE including seizure treatment, pre/post-gestational periods, and quality of life.

3. Results

Seventeen articles were retained after screening the search results; these included 16 research articles [18–33] and one review paper [34]. One additional study was found via manual search [35].

There are currently many challenges and lacunae in the care of WWE in SSA, which reflects the poor understanding and neglect of the reproductive health needs of this population. There is a paucity of data on the subject of epilepsy and pregnancy in the African setting, with only two studies which investigated various reproductive health outcomes of WWE using a prospective approach [18,19]. One of these studies estimated the prevalence of convulsive epilepsy among pregnant women to be 3.33 per thousand [19].

3.1. Quality of life, sexuality and marriage among WWE

With epilepsy being heavily stigmatized in SSA, WWE are often rejected by their families and communities, and also face serious marital limitations [20–22]. In a Nigerian study, lower marriage rates and higher stigma scores were more frequent among WWE than matched controls [22]; a similar situation was reported in Cameroon, with only 20.9% of WWE being married versus 65.1% of matched controls after 10 years of follow-up ($p < 0.001$) [35]. WWE in SSA were also reported to be more vulnerable to sexual exploitation and rape [23,24], thereby exposing them to greater risk of contracting sexually transmitted diseases and unwanted pregnancies. In addition to these vulnerabilities, WWE who do get married are more likely to be divorced or abandoned by the partner after the birth of a child [22]. In contrast with these trends, more than half (74/120) of the WWE in a Senegalese study reported that epilepsy rather brought them closer to their partner [18]. However, a similar proportion of WWE in that study admitted being affected psychosocially by their condition.

Upon assessing the prevalence of sexual disorders among Nigerian WWE, it was not different from the prevalence in age-matched controls without epilepsy, albeit a significantly higher Arizona Sexual Experience Scale (ASEX) scores indicative of poorer sexual functioning in WWE [25]. The Senegalese study found that 75% of WWE were sexually active, of which four out of five experienced reduced sexual drive which was attributed to AED (phenobarbital, carbamazepine and valproate) [18]. In Kenya, WWE were found to have reduced rates of reproductive fitness compared to the general population [26]. Notwithstanding, the characteristics of the menstrual cycle of WWE (age at menarche, length of cycle, and duration of flow) were within normal limits [26].

When compared with male PWE, most studies did not find an association between gender and anxiety and depression [27–29], although a small study in Nigeria ($n = 63$) reported a higher frequency of psychopathology among WWE [30]. Furthermore, the female gender was found to be a significant predictor for low quality of life of the PWE [31] and higher odds of withdrawing from AED therapy after 12 months [32].

3.2. Pre-conception period and family planning

Two studies examined contraceptive use among WWE in SSA [18,26]. In a Senegalese cohort, 62/120 (51.2%) WWE reported using contraception, with about one third of them (24/62) resorting to oral contraceptives [18]. Forty-two WWE in this study reported using hormonal contraceptive methods, concomitantly with regular anti-

epileptic treatment, including-enzyme inducing AEDs; two of them (4.8%) still conceived despite proper contraception [18]. In Kenya, only 14.7% of WWE of reproductive age (15–49 years) were using any form of contraception and for a median duration of 5.5 years (range 1–10 years) [26]. Findings from AED-treated WWE in Uganda showed that the menstruation periods were significantly associated with breakthrough seizures [33], while 7/23 (30.4%) WWE in Nigeria identified menstruation as a seizure trigger [19]. None of the retrieved studies reported on pre-conceptual counseling for WWE in SSA. Nonetheless, a review paper on women and epilepsy by authors from Mali recommended pre-conceptual discussions with WWE about the risks of seizures during pregnancy, as well as multidisciplinary collaborations (between physicians, obstetricians and pediatricians) to ensure optimal maternal and child outcomes when caring for pregnant WWE [34]. The review also highlighted the risks of contraceptive failure due to interactions with AED, and suggested to use either mechanical methods or hormonal methods with ≥50 μg of oestrogen in WWE of childbearing age [34].

3.3. Pregnancy and related outcomes in WWE

Two studies (in Senegal [18] and Nigeria [19]) provided prospective data for pregnancy outcomes, for a total of 97 WWE. The Senegalese cohort [18] reported that 40% of WWE experienced an increased seizure frequency during pregnancy, despite AED treatment (phenobarbital 64.16%, carbamazepine 20.83% and valproate 15%). While all WWE took folic acid during the pregnancy, only 25% had received it prior to conception. In the 74 pregnant WWE, twelve (16.2%) miscarriages occurred, mostly in WWE taking phenobarbital (7/12) [18]. Thirty-one (41.9%) WWE in the Senegalese study had premature deliveries, with the neonate weighing under 2500 g; a higher prevalence of prematurity was observed among WWE who used phenobarbital (32.5%), compared to those treated with carbamazepine (16.0%) and valproate (11.1%), but the difference was not significant (p = 0.206). Malformations were observed in the babies of three WWE, of which one was treated with valproate and the two others with carbamazepine/phenobarbital. Eight still births were registered (four among WWE treated with phenobarbital, two treated with carbamazepine, and two with valproate) [18]. The Nigerian cohort was much smaller (n = 23) and reported five negative pregnancy outcomes: one spontaneous abortion, one still birth, one intra-uterine fetal death, one neonatal sepsis and one congenital malformation (hypoplastic nail) [19]. These negative outcomes were unrelated to the type of AED used; however, WWE who had experienced seizures within the six months preceding their enrollment into the study reported worse pregnancy outcomes [19]. The mode of delivery in WWE was retrospectively investigated in Kenya; findings showed that of 173 live babies, 151 (87.3%) were born via spontaneous vaginal delivery, 4 (2.3%) by breech delivery and 18 (10.4%) via Caesarian section [26].

Regarding pregnancy follow-up, fewer WWE attended antenatal clinics compared to controls without epilepsy in Zambia (91% vs 97%, p = 0.07) [23]; that same study also reported more frequent home deliveries among WWE than other women (40% vs 15%, p = 0.0007) [23]. Regular AED use was reported in 15/23 (65.2%) pregnant WWE in the Nigerian cohort [19]. Carbamazepine was the most frequently used AED by pregnant WWE in both Nigeria [19] and Kenya [26]; meanwhile in Senegal, phenobarbital was prescribed in up to 64.2% of pregnant WWE [18]. Of note, negative pregnancy outcomes were observed in all WWE who used diazepam as antiepileptic medication (n = 2) [19].

3.4. Post-natal management of WWE in SSA

Although post-partum issues including depression, safety, breastfeeding and AED treatment have been investigated among WWE in developed countries [36], our literature search did not identify any such study from SSA. However, a survey in Sudan showed unsatisfactory knowledge about the post-natal management of WWE, as only 38.3% of healthcare professionals were aware that AED-treated WWE can safely breastfeed.

4. Discussion

Managing WWE in SSA is a complex process not only because of the physiological changes associated with their hormonal cycles and pregnancy, but also due to a unique psychosocial landscape for female PWE compared to male PWE in the African context. The scarcity of reproductive health data from WWE in SSA shows that this is a neglected population, and also explains the absence of evidence-based clinical guidelines to manage them. Overall, we identified a lack of continuum of care encompassing seizure control, sexuality, contraception, pre-natal, intrapartum, and post-natal management of WWE. Also, very little is known regarding the well-being of WWE in SSA during the puerperal period. A major constraint in addressing the reproductive health problems of WWE is the scarcity of adequate health facilities and well trained personnel [6].

In addition, AED treatment is not always available or affordable resulting in poor seizure control. While the first line AED (phenobarbital, carbamazepine, phenytoin and valproate) are cheaper, their teratogenic potentials [8,13] and possible interactions with hormonal contraception [37] make them unsuitable for women of reproductive age. The second-line drugs (levetiracetam and lamotrigine) are more indicated for women of reproductive age, but are too expensive for most WWE [5,38]. Several other challenges are yet to be addressed in order to ensure and sustain the best reproductive health outcomes for WWE, be it before, during or after pregnancy (Fig. 1).

4.1. Reducing the epilepsy treatment gap for WWE

The fact that seizures prior to conception predispose to worse pregnancy outcomes in WWE [19] highlight the need for long term seizure control, both before and during gestation. However, the treatment gap is still wide in SSA, and WWE have been found to stop their AED treatment due to fears of its potential impact on their unborn child (personal communication Dr Marieke Dekker). Low AED adherence by WWE contributes to poor pregnancy outcomes. Therefore, it is crucial to ensure regular availability of AEDs which have a minimal impact on reproductive health outcomes of WWE. Data on post-natal neurocognitive and behavioral development following fetal AED exposure is however still limited, and some results are divergent.

Carbamazepine, considered to be the safest first-line AED and which is frequently prescribed to pregnant WWE in SSA [19,26], is nevertheless still associated with a higher prevalence of congenital malformations, estimated at 5.5% in recent studies [9]. In contrast, second-line broad-spectrum AED are more appropriate for this population as the risk of teratogenicity is negligible [9,13]. Currently, the only second

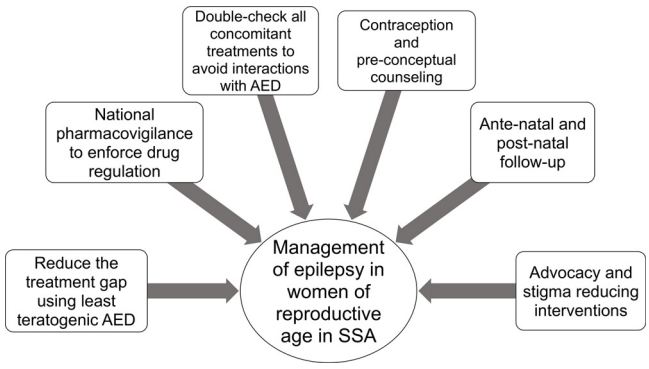

Fig. 1. Suggested perspectives to improve WWE management in SSA.

line AED which has been included in the WHO essential medicines list is lamotrigine, but still as an adjuvant anti-epileptic treatment [39]. A meta-analysis recently suggested that lamotrigine use during pregnancy was associated with an increased risk of autism in the exposed children [40]. Furthermore, there is evidence suggesting an association between lamotrigine and preeclampsia (adjusted OR: 7.5, IQR: 1.4–39.0), which is the most common cause of status epilepticus in pregnancy and is associated with adverse maternal and fetal outcomes [41,42]. Another caveat to consider with lamotrigine use is that during pregnancy, its clearance increases with a considerable risk of reduced seizure control, often requiring a dose adjustment [43]. A key mechanism for this increased clearance is the metabolism of lamotrigine via glucuronidation, which is enhanced by sex hormones during pregnancy [43]. This would underscore the need for pre-pregnancy counseling to help WWE understand this phenomenon and appreciate the need for compliance.

Unlike lamotrigine, levetiracetam, another second line AED approved as an add-on treatment for epilepsy, has not been found to be associated with autism [40]. Although it is not metabolized through glucuronidation, levetiracetam clearance was also reported to increase during pregnancy especially during the first trimester, with a corresponding worsening of seizures [44]. Levetiracetam has also been associated with early onset preeclampsia in pregnant WWE [45]. Both lamotrigine and levetiracetam have the advantage of not interacting with contraceptives or other concomitant anti-infective treatments including antiretroviral therapy (ARV) [37].

Given the current scarcity of second line AED in most SSA countries, valproate is frequently used in HIV-infected WWE because it does not result in ARV failure [46]; the risk of congenital malformations is however high in the advent of a pregnancy. Despite the lack of clinical trials with these second line AED in SSA, we recommend that they should be made more accessible to WWE in SSA in view of their comparative advantages over the first line AED for this particular population (Table 2).

As of today, most pharmaceutical drugs in circulation in SSA are imported from abroad, principally from Asia. This poses a number of issues, including high transportation costs, frequent drug shortages and at times, poor quality control. One possible way to address this could be to use the existing regional drug supply networks in SSA to purchase second line AED in bulk, such that contracting countries in SSA would jointly negotiate prices and buy from selected suppliers in Asia by means of a centralized procurement unit. A long-term response to reducing the epilepsy treatment gap in SSA, would be to draw upon the impetus given to the African Union's Pharmaceutical Manufacturing Plan for Africa [51] and attract international investors who would support the local production of affordable generic second line AEDs. To ensure high quality drugs, strict pharmacovigilance strategies should be implemented with the formation of local pharmacovigilance sub-committees as was done in Rwanda [52].

4.2. Contraception and pre-conceptual counseling

Given that Africa registers the highest rates of unintended pregnancies [53], it is important to ensure proper contraception among WWE, more so because planned pregnancies in WWE are associated with good gestational seizure control and less fetal exposure to potentially harmful AED [54]. The low use of contraception, potential interaction of hormonal contraceptives with first line AED, and the scarce practice of pre-conceptual counseling among WWE is a call for concern. We recommend a systematic integration of contraception and pre-conceptual counseling during the routine follow-up of WWE of childbearing age in SSA [7]. WWE and their families should be clearly informed and educated about the risks of teratogenic outcomes especially with unplanned pregnancies on one hand, and the importance of treatment adherence on the other hand to ensure seizure control throughout pregnancy. Given that enzyme-inducing AED (phenobarbital, carbamazepine, phenytoin) interact with steroid hormones and may even lead to contraception failure [37], the use of mechanical contraceptive methods such as condoms should be promoted, as these will not interact with AED [55] in addition to being relatively inexpensive. Pre-conceptual counseling would also allow for proper, balanced nutrition of the WWE, and the administration of folic acid long before conception to ensure better neurodevelopmental outcomes in the baby [56]. Given that the optimal dose of perinatal folic acid remains a subject of debate, the administration of at least 0.4 mg per day is recommended [57].

4.3. Antenatal and post-natal follow-up

Compared to other women in SSA, fewer WWE go for antenatal visits [23]. This might be related to their relatively lower economic status, to the fact that some of them may be cognitively impaired, or as a result of the prevailing stigma by the community and to a lesser extent among healthcare personnel [58]. WWE and their families should be educated on the benefits of following up their pregnancy at the local

Table 2
Comparison of the benefits and disadvantages of AEDs used in women with epilepsy.

Aspect	First line AEDs	Levetiracitam	Lamotrigine
Sexuality	Except for valproate, first-line AEDs are enzyme-inducing and alter the metabolism of sex hormones, thereby increasing the risk for sexual dysfunction [47].	Non-enzyme inducing AED [37], and could be used to avoid altering the metabolism of sex hormones in WWE.	Has been associated with improved desire/frequency of sexual activity in WWE [48].
Contraception	Except for valproate, first-line AEDs are enzyme-inducing and reduce the efficacy of hormonal contraception [37].	Does not affect the efficacy of hormonal contraception [37].	Does not affect the efficacy of hormonal contraception [37].
Teratogenic risk	Increased risk for foetal malformations [9].	No increased risk for foetal malformations [9].	No increased risk for foetal malformations [9].
Breastfeeding	Except for phenobarbital, the first-line AEDs have moderate to high degrees of protein binding in plasma, hence limited passage into breastmilk [49]. They are therefore considered safe for the baby during breastfeeding [49,50].	Low degree of protein binding in plasma, hence extensively transferred into breastmilk [49]. However, it is efficiently eliminated by the neonate and is considered safe during breastfeeding [49].	Moderately bound to plasma protein and passes into the breastmilk. May attain high concentrations in the breastfed neonate [49]. Although no adverse effects of lamotrigine were observed on the cognitive development of breastfed children, monitoring is recommended [49,50].
Drug interactions	Except for valproate, first-line AEDs are enzyme-inducing and therefore interact with several drugs [37].	Not enzyme inducing, hence little or no drug interactions [37].	Not enzyme inducing, hence little or no drug interactions [37].
Neurodevelopment of the child	Overall, children exposed to first-line AEDs have lower IQ, reduced verbal abilities, and/or lower scores for locomotor development compared to unexposed children [8].	Neurodevelopmental scores in exposed children are similar to those of unexposed children [8].	Reduced verbal abilities in exposed children compared to unexposed children [8].

health centers. In addition, epilepsy training should be given to local health staff; they need to be capacitated to provide the essential prenatal care for WWE, including routine evaluation of the gestation, seizure control with appropriate AED, and daily folic acid supplementation for at least the first trimester [7]. Given that most pregnant WWE will have normal vaginal delivery [26], labor and childbirth procedures should be similar as those used in women without epilepsy.

Post-natal counselling of WWE is important but generally not done in SSA. WWE and their families should be informed about a number of safety precautions related specifically to the care of WWE's infants to reduce accidents; these include: changing the baby's napkins on the ground and not on elevated surfaces, not bathing the baby without the presence of anyone else, nor holding the baby while cooking or carrying hot liquids.

Breastfeeding should equally be encouraged among nursing mothers with epilepsy, including those taking AED. Although no studies on breastfeeding WWE and AED were identified in SSA, no negative developmental effects in infants that have been exposed to breastfeeding by AED-treated WWE have been demonstrated in prospective studies conducted in high-income countries [50]. It is however known that the long half-life and low degree of protein-binding of phenobarbital increases the likelihood of accumulation and transfer via breastmilk, possibly leading to higher free drug levels in the infant compared to the mother [59]. In this light, WWE in SSA treated with phenobarbital should be advised to monitor sleepiness in their child, and to take phenobarbital tablets only after baby's last breastfeeding session just before bedtime, given the longer breastfeeding intervals during the night. This is especially important for mothers who embark on phenobarbital after pregnancy, because the infant was never exposed to the drug *in utero*. On the other hand, levetiracetam has been shown to be effectively eliminated by the neonate, and hence is regarded as compatible with breastfeeding [49].

Another issue to address in these women is the likelihood of peripartum depression (PPD). PPD is a frequent mood disorder which can occur during pregnancy or within the first 12 months after delivery, with an estimated prevalence ranging from 16 to 35% among WWE [60]. PPD is frequently overlooked and there are currently no estimates of its magnitude among WWE in SSA. Healthcare workers in SSA should be trained to diagnose and manage PPD early among WWE to prevent poor outcomes both for the mother and child.

Overall, the peri-partum management of WWE requires a multidisciplinary approach. Proper book-keeping via harmonized registers should be encouraged among the different healthcare workers responsible for ante-natal and post-natal follow-up, as this is the only way to obtain large scale, evidence-based information about pregnancy outcomes [34]. Given the scarcity of trained neurologists in SSA, a task shifting model consisting of a network linking neurologists to local non-physicians should be considered to ensure equity of epilepsy care between rural and urban settings [61].

4.4. Epilepsy-related stigma reduction and advocacy

As highlighted by our findings, epilepsy-related stigma still constitutes a major concern in SSA especially among WWE [20–22], with far-reaching negative consequences on pregnancy outcomes via poor pregnancy follow-up and frequent home deliveries among WWE [23]. A lot is still to be done in terms of stigma-reducing interventions for epilepsy in SSA [58]. Educating the community and healthcare personnel will alleviate the rejection faced by WWE and improve their quality of life. In addition, local and global advocacy is required to improve the management of WWE in SSA; it is urgent that their specific reproductive health needs be addressed, and second line AED be made available at little or no cost.

5. Conclusion

Our review has highlighted several lacunae in the continuum of care of WWE in SSA, especially those who are of childbearing age and/or pregnant. Reproductive health services and psychosocial support need to be integrated in the package of care of WWE, and this is only possible via a multidisciplinary approach which also draws upon the combined insights of medical and social sciences. Increased availability of second line AED at little or no cost for WWE will contribute to better reproductive health outcomes. Alongside, community education would be needed to dispel misconceptions, foster tolerance, support and understanding of the vulnerabilities of WWE. Building capacity among local healthcare workers, and initiating collaborations between community leaders, local and international health actors, constitute indispensable components of a sustainable solution. The paucity of available evidence-based policies warrants more research to ensure optimal health outcomes for the several millions of WWE in SSA.

Declaration of Competing Interest

The authors declare to have no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.08.016.

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