



## OPEN LETTER

**REVISED** A cascade of care for people with epilepsy: learning from “HIV/AIDS 90-90-90” [version 2; peer review: 2 approved]

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Epilepsy is now more prevalent in many countries than HIV/AIDS. Building upon the advances of global policymaking for HIV/AIDS and creating a framework for countries and organizations to monitor progress in epilepsy care will help direct and justify much-needed novel programming. Given the clarity of the HIV/AIDS care continuum model and the UNAIDS 90-90-90 targets, I propose this same approach to the cascade of care could be used as a viable framework for people with epilepsy. In this model, the targets of success include (1) ensuring 90% of all people with epilepsy are aware of their diagnosis as a brain disorder, (2) starting 90% of people with epilepsy on quality controlled, appropriately chosen and well stocked antiepileptic drugs, and (3) achieving seizure freedom in 70% of those treated. At least 90% of all people with epilepsy must also be linked to and retained in appropriate care. Although the precise numbers may be debated, this cascade of care approach will assist in deconstructing the barriers to epilepsy care in populations better than the more familiar concept of the epilepsy treatment gap. These reflect concrete goals for health systems for epilepsy care that, if achieved, could lead to seizure freedom for the many people in lower income countries living with poorly controlled epilepsy.

**Keywords**

epilepsy, public health, child health, HIV/AIDS, health policy, health planning

**Open Peer Review**

Reviewer Status

	Invited Reviewers	
	1	2
<b>REVISED</b>		
<b>version 2</b> published 06 Aug 2019	report	report
<b>version 1</b> published 26 Jun 2019	report	report

1 **Wolfgang Grisold**, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

2 **W. Allen Hauser**, Columbia University, New York, USA

Any reports and responses or comments on the article can be found at the end of the article.

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**Author roles:** Mateen FJ: Conceptualization, Resources, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

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**First published:** 26 Jun 2019, 3:1502 (<https://doi.org/10.12688/gatesopenres.13043.1>)

**REVISED Amendments from Version 1**

The final version of this manuscript includes modifications based on the two reviewers' insightful comments. The reviewers found the concept of a cascade of care, with relevance to the 90-90-90 approach as found in HIV/AIDS to be useful and intriguing. The changes to this manuscript include the following: mention of the sociocultural issues of traditional healers and non-allopathic practitioners who are often the first point of contact for epilepsy care in several countries; a reference to the World Health Organization Global Epilepsy Campaign 2015 publication and Information Kit on Epilepsy which includes reporting of demonstration projects; acknowledgement of the difficulty of measuring some of these proposed metrics, including the patient counts in the field given that epilepsy does not have a single point-of-care biomarker like HIV/AIDS; and finally mention of some additional recognized facts such as that newer antiepileptic drugs are not necessarily better from an efficacy standpoint. Although the reviewers and I generally are in agreement, some details are not easy to cite as they may still have limited reporting, and therefore a limited evidence base in lower income countries. I have also attempted to avoid emphasizing any one country, region, or even supranational organization's approach. This is on purpose, since future success for people with epilepsy may take a different pathway than what has been done in any prior situation. Future change also requires a substantial amount of innovation to achieve these perhaps lofty goals. I hope this manuscript opens up a larger conversation on global epilepsy, an under-discussed topic compared to its substantial (and likely growing) burden.

See referee reports

**Background**

Epilepsy is an important cause of chronic disability and a preventable cause of early mortality in low- and middle-income countries (LMICs). More than 1% of the population in LMICs, >60 million people, suffers from epilepsy<sup>1</sup>. Phenobarbital, the oldest antiepileptic medication still in use today, was discovered in 1912. Phenobarbital costs 1 to 2 US cents per day or <5 USD per year and remains the drug of choice for several presentations of epilepsy. Four additional older antiepileptic drugs are commonly found on the World Health Organization's Essential Medicines List and typically cost <50 cents per day.

Epilepsy is an exemplary disease for health systems planning for brain disorders. Epilepsy presents across the lifespan, with the predominance of first presentations in childhood and in the elderly. The stigma of epilepsy, including its formal and informal prohibitions on school attendance, employment, and marriage in some societies, emphasizes it as an important challenge for the global public health community. Medically, it represents a final common manifestation of a myriad of possible causes: genetic conditions, developmental conditions, central nervous system infections, head trauma, stroke, and sometimes defies clear explanation of its etiology. This is typical of several neurological disorders in which etiologies may reflect the so-called "triple burden" of communicable, noncommunicable, and traumatic disorders. Access to diagnostic services for epilepsy, such as electroencephalogram and neuroimaging, enhances the diagnostic clarity of epilepsy, but the absence of

infrastructure in LMICs does not preclude antiepileptic medication treatment. Women of childbearing potential represent a special treatment group since some antiepileptic medications should be avoided during pregnancy, especially valproic acid, given the risk of this medication causing congenital malformations including neural tube defects.

**Updating the approach to epilepsy treatment: a cascade of care**

Prior framing of the global epilepsy challenge was through the epilepsy treatment gap<sup>2</sup>, or the number of people with epilepsy (PWE) who are eligible for but not taking an antiepileptic medication. This gap reaches up to 90% in LMICs<sup>3,4</sup>. Meanwhile, a "zero" treatment gap remains unattainable, even in high-income settings. In this way, "getting to zero" is not a realistic goal for epilepsy care as it would be for infectious diseases, which could be eliminated or even eradicated. Although demonstration projects have shown important progress in the number of PWE who are able to become seizure free or reduce their seizure burden in lower income settings<sup>5</sup>, even more can be done to detail the ways in which seizure freedom has occurred. Targeted epilepsy initiatives, such as the WHO Global Campaign on Epilepsy<sup>6</sup> *What you can do* can be evaluated with more precision.

Using the treatment gap approach, essential steps in the care pathway of PWE have been overlooked. Since epilepsy is both a clinical problem and a matter of global policy, it requires metrics to optimize care and achieve population-based outcomes. Although countries may be meeting treatment gap goals, many PWE are not adequately diagnosed by seizure type. Some are treated with an inappropriate choice of antiepileptic medication. And in spite of adequate medication adherence, seizure freedom for many PWE may be difficult to attain due to inadequate dosing as well as limited quality and inconsistent supplies of antiepileptic medications<sup>4,7-9</sup>.

As HIV prevalence rates drop in many countries, epilepsy may be more prevalent in many countries than HIV/AIDS. People living with HIV/AIDS have benefitted from global advocacy, political will, and dedicated and sustained financial investments. Private-public partnerships and supranational agencies have brought light to the extreme tragedy of the HIV epidemic. This was achieved in spite of the stigma of HIV/AIDS and the disproportionate burden of HIV/AIDS in resource-limited settings and vulnerable populations.

The same efforts have not been made in epilepsy, an ancient disease, that can learn from the progress of HIV/AIDS. Building upon the progress of global policymaking for HIV/AIDS and creating a framework for countries and organizations to monitor progress in epilepsy care will help organize and justify novel programming. It may not achieve the stature of HIV/AIDS programming, but a framework for identifying the steps in epilepsy care pathways can be realized. Given the clarity of the HIV/AIDS care continuum model and the UNAIDS 90-90-90 targets, I propose this same approach to the cascade of care<sup>10</sup> could be used as a viable framework for PWE. In the HIV

model, the measured targets include (1) ensuring 90% of all people with HIV infection know they are infected, (2) starting 90% of infected people on antiretroviral therapy, and (3) achieving viral suppression in 90% of those treated. At least 90% of all people with HIV are also linked to and retained in care. By comparison, similar stepwise targets could be applied to epilepsy care:

- (1) *Diagnosis* of epilepsy allows patients to be successfully given their medical diagnosis, distinct from supernatural causes but also distinct from primary psychiatric behavioral events, cardiac dysrhythmias, symptomatic hypoglycemia, and related conditions.
- (2) *Linkage to epilepsy care* allows the establishment and organization of services for PWE - and the minimum standards for epilepsy care - including medication management, as well as access to neuroimaging, EEG services, and/or supportive laboratory studies such as antiepileptic drug levels<sup>11</sup>.
- (3) *Antiepileptic medication treatment* enables the management of seizures through efficacious, appropriately chosen and prescribed, available, accessible, and affordable medicines.
- (4) *Seizure control and freedom* requires the antiepileptic medication or, in some cases, multiple medications to effectively reduce the number of seizures, ideally to zero in at least 2/3 of PWE<sup>12</sup>, and increase the number of seizure-free days. Although not

explicitly required, minimization of side effects such as sedation, would be optimal.

This cascade of epilepsy care should have globally agreed targets, likely 90% of PWE being diagnosed; 90% of PWE linked and retained in care for epilepsy; and 90% of PWE who need an AED receiving it (Figure 1). In addition, a reasonable goal of 70% of all PWE achieving seizure control should be targeted. This provides a fair comparison for services across higher and lower income settings and may indeed reflect, like in HIV/AIDS, that lower income countries are better able to implement cascades of care for more of their population. Although these precise numbers may be debated by the global community, they are goals that reflect actual processes of epilepsy care.

There are several barriers to measuring and realizing these metrics.

- (1) *Diagnosis* of epilepsy can best be measured through community-based surveys in the population asking key survey questions. The lack of a distinct biomarker for epilepsy, such as a laboratory test, makes measurement often depend on semi-skilled providers.
- (2) *Linkage to epilepsy care* is perhaps the most difficult step in the care pathway since it requires functionality of the health care system that will not be overwhelmed by new referrals or under-prepared to deal with a potential influx of patients if diagnoses are made. Long traditions of seeking non-physician healers in the care of PWE may be difficult to overcome<sup>13,14</sup> and require

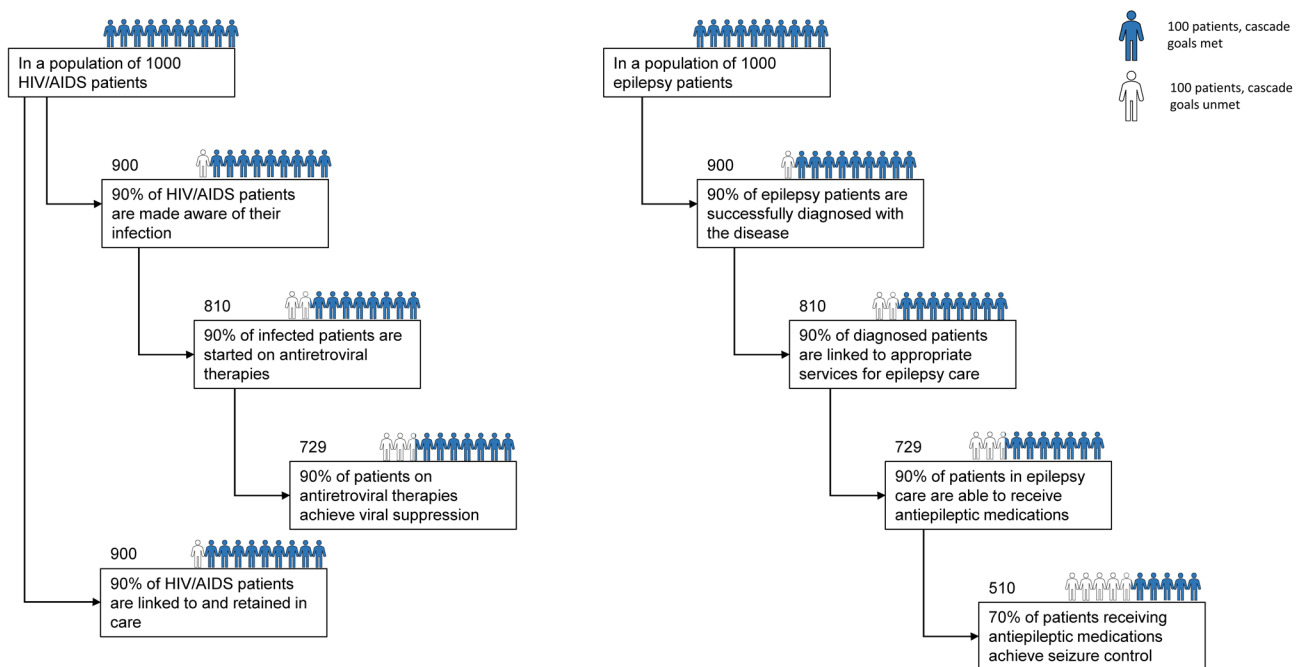


Figure 1. A comparison of the Cascade for Care of HIV/AIDS and Epilepsy in 1000 people with each condition.

dedicated efforts and educational initiatives to encourage patients to accept more scientific approaches. Counting of PWE who are not linked to care can be difficult.

- (3) *Antiepileptic medication treatment* is realizable but there are insufficient efforts to make medications universally available, accessible, and affordable. Treatment of at least 70% of PWE will require non-governmental organizations, governments, supranational organizations, and patients. Barriers to realization of medication provision in 2019 remain common including out-of-date essential medicines lists, the variable quality of medication supplies in LMICs, lack of appropriate supply chains, excessive regulations on some medications, and high out-of-pocket costs to patients.
- (3) *Seizure control and freedom* are both scientific and educational challenges. Barriers to achieving this metric include expertise on dosing medications, choosing medications appropriately, and having the time and resources to adequately educate patients. It requires addressing causes of medication-resistant epilepsy including preventable causes such as neurocysticercosis, vaccine-preventable perinatal infections, and many cases of preterm birth. It includes changing the behavioral pattern of taking a drug temporarily, as is common for an infectious disease, to taking a medication constantly and potentially lifelong. Additional barriers include the lack of epilepsy surgery opportunities for many LMICs and lack of access to an expanded list of newer scientifically proven antiepileptic medications. Although newer medications may be similarly efficacious to older medications, minimization of side effects and improving the range of options in locations without laboratory capacity can be particularly important.

## Conclusions

Epilepsy is a medically complex and historically poorly understood condition across cultures worldwide. In lower-income countries, neurologists are present in staggeringly low proportions. However, the metrics of achievement for epilepsy care can be made clearer and therefore can become achievable. Efforts to improve epilepsy care require more than appropriate metrics. Investment, both intellectually and financially; political interest and determination; establishment of a trained and capable health care workforce for epilepsy care; and consistently supplied antiepileptic drugs that are not prone to stock outs, poor quality, and market interests are all within our global capability. Downstream measurements of care at the level of the individual person with epilepsy can one day include the amount of out of pocket health expenditures, catastrophic health expenditures due to epilepsy, and missed opportunities such as schooling, work, and social functioning. Disaggregating these barriers to epilepsy treatment can inform the implementation of solutions and ultimately come full circle and “close” the more familiar “epilepsy treatment gap.”

## Data availability

No data are associated with this study.

## Grant information

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

## Acknowledgements

I thank Mr. Andre Vogel, BA, of the Massachusetts General Hospital, Boston, MA, for his help with [Figure 1](#).

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## Open Peer Review

Current Peer Review Status:  

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### Version 2

Reviewer Report 23 August 2019

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#### W. Allen Hauser

Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

The author proposes a "cascade" of epilepsy care similar to that developed for the diagnosis and treatment of the HIV/AIDS epidemic in LMIC countries. They now allude to the considerable efforts that have been undertaken over the past 20 years to address some of these problems and which seem to incorporate many of the basic strategies suggested. The goals set in the suggested cascade may be difficult to attain, but either as an independent effort or in concert with ongoing intervention strategies the proposal should be further explored.

One additional comment: under section 3 (4?), the points mentioned to be addressed (neurocysticercosis, vaccines, preterm birth) are causes of all epilepsy, not just medication-resistant epilepsy. Addressing these problems will have far reaching consequences - well beyond a goal of epilepsy prevention.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neuroepidemiology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 08 August 2019

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**Wolfgang Grisold**

Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

The points were addressed, and I can accept from my side.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neurology, neuromuscular, neurooncology. education , global neurology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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**Version 1**

Reviewer Report 25 July 2019

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**W. Allen Hauser**

Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

The author proposes a novel approach to the problem of getting appropriate treatment worldwide for people with epilepsy. There are parallels of epilepsy and AIDS and suggests an approach similar to that used to address the AIDS's epidemic. This involved global advocacy, public-private partnerships, political will, and most importantly, sustained financial support for the programs which were implemented with specific metrics to allow ongoing evaluation of success.

It seems that many of these strategies have been implemented through the Global Campaign Against Epilepsy - a collaborative project between WHO and two international epilepsy organizations. It seems that some discussion of the successes and failures as well as mention of the long term activities related to these initiatives in the People's Republic of China would be worth including in this comment along with a review of the 2015 WHO recommendations.

The treatment gap is at this point an ill-defined concept and I agree that it is a poor metric (without definition) to measure success of a program. I do not agree that it has been the sole metric used to assess interventions to improve care with epilepsy in the past. I don't see the term mentioned in the guidelines. The development of a 90, 90, 90 metric to measure success is intriguing however and could be further developed although the actual measurement will be complicated.

A couple of minor points: I have difficulties identifying other neurological conditions that have the scope of antecedents of epilepsy. Can some be provided by the author?

It seems that the process starts with identification. This is not as easy as with AIDS. As pointed out a modicum of training is needed to identify cases; more if it is necessary to identify seizure type.

While the list of essential antiseizure medications may not include all of the latest drugs, there is little evidence that they provide a control advantage over the currently listed medications. They probably have fewer side effects but even if this is the case, (there are virtually no comparative studies) the cost differential may not be justified.

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[PubMed Abstract](#) | [Publisher Full Text](#)

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

No

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neuroepidemiology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 01 Aug 2019

**Farrah Mateen**, Massachusetts General Hospital & Harvard Medical School, Boston, USA

The author proposes a novel approach to the problem of getting appropriate treatment worldwide for people with epilepsy. There are parallels of epilepsy and AIDS and suggests an approach similar to that used to address the AIDS's epidemic. This involved global advocacy, public-private partnerships, political will, and most importantly, sustained financial support for the programs which were implemented with specific metrics to allow ongoing evaluation of success.

*I agree with the reviewer here. More than enthusiasm and recognition will be needed; dedicated and sustained funding are requisite. I have a sentence to this effect in the revised manuscript. This*



*piece is meant to provide metrics for measuring whether efforts can be monitored, evaluated and even compared.*

It seems that many of these strategies have been implemented through the Global Campaign Against Epilepsy - a collaborative project between WHO and two international epilepsy organizations. It seems that some discussion of the successes and failures as well as mention of the long term activities related to these initiatives in the People's Republic of China would be worth including in this comment along with a review of the 2015 WHO recommendations.

*I am trying not to focus on any one particular country in this position piece although I recognize some regions in some countries have made major progress. I now cite the WHO Information Kit on Epilepsy as a pragmatic resource and example of work and progress to date.*

The treatment gap is at this point an ill-defined concept and I agree that it is a poor metric (without definition) to measure success of a program. I do not agree that it has been the sole metric used to assess interventions to improve care with epilepsy in the past. I don't see the term mentioned in the guidelines.

*Although the WHO and its publications have been thought leaders for epilepsy, the recommendations are arguably insufficient. More can be done. Compared to other neurological diseases, such as poliomyelitis which have global campaigns backed by weekly updates, websites, multilateral partnerships, and governmental and supranational prioritization, I believe epilepsy has fallen behind and so this may be a new score card approach for some settings.*

The development of a 90, 90, 90 metric to measure success is intriguing however and could be further developed although the actual measurement will be complicated.

*Yes, I agree. It is not easy but it is an effort to begin this work.*

A couple of minor points: I have difficulties identifying other neurological conditions that have the scope of antecedents of epilepsy. Can some be provided by the author?

*I would suggest dementia and cognitive decline as one. Another could be neurodevelopmental delay. Another – to less extent – could be cerebrovascular disease. One may argue these have communicable, noncommunicable, and traumatic risk factors. I understand the reviewer's point that epilepsy is particularly broad in its antecedents though.*

It seems that the process starts with identification. This is not as easy as with AIDS. As pointed out a modicum of training is needed to identify cases; more if it is necessary to identify seizure type.

*Yes, there is no one definitive biomarker like in AIDS. The movement from a single virus to a neurological disorder is a challenge. Yet, the public health understanding of a high-prevalence, global, life-threatening condition, subject to stigma and in need of global attention made me wish to compare these two. This line of thinking is more of a public health and stakeholder perspective*

*than from the medical diagnostic one. Although non-parallels can be found, I still hope the broader comparison is worthwhile.*

While the list of essential antiseizure medications may not include all of the latest drugs, there is little evidence that they provide a control advantage over the currently listed medications. They probably have fewer side effects but even if this is the case, (there are virtually no comparative studies) the cost differential may not be justified.

*That is true. However, cost is a matter of negotiation for some of these drugs rather than the scientific challenge; so that could be the next round of measured metrics – i.e. out of pocket payments and catastrophic health expenditures by people with epilepsy. I suspect I am similar to the reviewer here in that I am of the opinion that this is a solvable problem. With enough funding, political will, private-public partnerships, and increased and unrelenting advocacy of our community, surmountable barriers for epilepsy care could be overcome and the evidence base could be expanded to better address these issues.*

**Competing Interests:** None

Reviewer Report 08 July 2019

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### Wolfgang Grisold

Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria

This is interesting and stimulating, to compare the success of the HIV/AIDS campaign, with possible strategies to treat patients with epilepsy worldwide.

Despite the success(es) at many levels, HIV remains a threat in many low income countries, and has not been resolved sufficiently. It may be misleading to celebrate this as a success, as in many countries, in particular in Africa have completely unmet needs.

The treatment of epilepsy also needs to break through many stigmata, misbeliefs and take the fact into consideration, that in Africa, only a small percentage of patients are seen by qualified health care professionals, and most (some estimate 80%) by healers.

Finally, and Dr Mateen points this out, there are 2 more important factors: 1) the work force of HCP, 2) and the drug costs, which seem minimal to us, but may be a large amount for persons in need. Culturally, and this may also be a point to consider, the acceptance of "western" medicine, is often considered with mistrust and afterthoughts of colonialization.

My summary is, that this paper is an important and interesting comparison, between the success of the

HIV campaigns, and its possible use in epilepsy.

I recommend to relativize the HIV success and consider the low income countries, tackle the cultural aspects (which may be prohibitive in accepting treatment), and finally give more consideration on HP workforce, costs and coverage.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Partly

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neurology, neuromuscular, neurooncology. education , global neurology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 01 Aug 2019

**Farrah Mateen**, Massachusetts General Hospital & Harvard Medical School, Boston, USA

This is interesting and stimulating, to compare the success of the HIV/AIDS campaign, with possible strategies to treat patients with epilepsy worldwide.

*I thank the reviewer for his comments.*

Despite the success(es) at many levels, HIV remains a threat in many low income countries, and has not been resolved sufficiently. It may be misleading to celebrate this as a success, as in many countries, in particular in Africa have completely unmet needs.

*I agree with this statement. In order to not over-state the HIV/AIDS field's achievements, I have used words such as "progress" instead of "success." Although scientific and policy efforts have not prevented or cured HIV/AIDS and there remain many million people infected globally, the counterfactual situation to this pandemic being unaddressed is even worse. Although the work is*

*by no means complete, especially for locations like Sub-Saharan Africa, there is much to be learned for people with epilepsy, and arguably, there have still been major successes in this work for HIV/AIDS.*

The treatment of epilepsy also needs to break through many stigmata, misbeliefs and take the fact into consideration, that in Africa, only a small percentage of patients are seen by qualified health care professionals, and most (some estimate 80%) by healers.

*This is almost certainly correct and in fact I have thought about this issue a great deal in recent work published on traditional medicine and epilepsy in Guinea and in Bhutan. This is a cross-cultural and international issue. As such, I have added a new statement on the barriers to epilepsy diagnosis in this paper and thank the reviewer for emphasizing this major challenge. I also include in some additional citations to underscore this point.*

Finally, and Dr Mateen points this out, there are 2 more important factors: 1) the work force of HCP, 2) and the drug costs, which seem minimal to us, but may be a large amount for persons in need. Culturally, and this may also be a point to consider, the acceptance of "western" medicine, is often considered with mistrust and afterthoughts of colonialization.

*This is certainly the case in multiple geographic locations. The workforce and drug supply are additional metrics that need to be measured and could be part of an expanded framework, beyond the 90-90-90 (or 90-90-70 approach). The data on colonization and mistrust is a bit less clear and less available in the literature. Although there are definitely reports on mistrust, the literature is limited and this becomes harder for me to cite. Also, I wanted to avoid focusing on any one geographic region in this paper and take "lower income countries" as a collective.*

My summary is, that this paper is an important and interesting comparison, between the success of the HIV campaigns, and its possible use in epilepsy. I recommend to relativize the HIV success and consider the low income countries, tackle the cultural aspects (which may be prohibitive in accepting treatment), and finally give more consideration on HP workforce, costs and coverage.

*Thank you for your ideas. I emphasize HCP and medications more in the revision. I hope this piece opens up a larger conversation on global epilepsy, an under-discussed topic compared to its substantial (and likely growing) burden.*

**Competing Interests:** None