Seizures in Human Immunodeficiency Virus (HIV) Patients: What is the Etiology?

Paddy Ssentongo MD, MPH1,2*, Anna Ssentongo, MPH2

1Center for Neural Engineering, Department of Engineering, Science and Mechanics, The Pennsylvania State University, University Park, PA, USA
2Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA

*Corresponding Author: Paddy Ssentongo, MD, MPH, Assistant Professor of Research, Center for Neural Engineering, Dept. Engineering Science and Mechanics, The Pennsylvania State University Millennium Science Complex, University Park, PA 16802, USA, Email: pssentongo@pennstatehealth.psu.edu

The prevalence and incidence of seizures and epilepsy is substantially higher in HIV patients compared to the general population and is associated with higher mortality rates. Although the prevalence of epilepsy in the general population is between 0.4% and 1.0%,1 and the incidence rate is 0.05%,2 the prevalence of seizures or epilepsy in the HIV population ranges between 3% - 12%.3,4 See Figure 1.

Over 2/3 of seizures in HIV patients are caused by metabolic disturbances,5 CNS lymphoma or opportunistic infections of the central nervous system (CNS) such as toxoplasmosis, cryptococcal meningitis, tuberculous meningitis and progressive multifocal leukoencephalopathy.6-13 In the remaining 1/3 of patients, seizures are not associated with any identifiable focal brain lesions but it has been suggested that HIV infection alone could be the sole cause of these seizures.4 In line with this hypothesis, the vast majority of seizures observed in HIV patients are generalized in nature. Therefore, it has been suggested that HIV-infected brain may have diffuse cortical irritability or an impaired mechanism of seizure termination.4

The association between seizures and HIV is more pronounced in those with an advanced stage of HIV also known as acquired immunodeficiency syndrome (AIDS) and in those with low CD4 T-cell counts. AIDS is characterized by opportunistic infections such as disseminated Mycobacterium avium complex, cytomegalovirus, Cryptococcal infections and toxoplasmosis,14 all which are known to induce seizures. Furthermore, HIV viral load is at a higher concentration in patients with advanced stages of the disease, and HIV often leads to neuronal loss from discrete areas of the neocortex and subcortical regions.15 In a study by Gelbard and colleagues, children with HIV-1 displayed neurons with apoptotic cells in the basal ganglia and cerebral cortex.16 The principal pathway for HIV entry into the CNS is through infected monocytes (macrophages and microglia). Therefore, neuronal injury caused by HIV is predominantly indirect through the release of macrophages, microglial and astrocyte toxins, although direct injury by the virus is also possible.17 These toxins over stimulate neurons, resulting in the formation of free radicals and excitotoxicity, which potentially lead to seizure generation and propagation. This information has led to the push for early initiation of highly active antiretroviral therapy (HAART) to reduce the viral load and increase functional CD4 T-cell counts. However, HAART use comes with the cost of the possibility of inducing seizures. The interactions between HAART and antiepileptic drugs are frequent as many members of the 2 classes of medications are metabolized by the cytochrome P450 system.18 Carbamazepine, phenytoin, and phenobarbital, which are routinely used to control seizures in HIV populations, are metabolized by the cytochrome P450 system. There is risk of reduced antiretroviral levels and antiepileptic drug toxicity.

HIV/AIDS is a chronic systemic disease that induces focal and generalized CNS lesions that prime the brain to seizure initiation and propagation. Early initiation of HAART and vigilant use of electroencephalogram to detect non-clinical seizures are potentially effective strategies to prevent the high incidence of seizures in the HIV population. Furthermore, HIV individuals that are diagnosed with seizures should scrupulously be investigated for opportunistic infections. In addition to treatment of causative lesions or organisms, long-term use
of antiepileptic drugs with frequent follow-up by both seizure and infectious disease specialists key in the effective management of these patients. Mimicking other CNS infection animal models such as murine models of cerebral malaria,[19, 20] future efforts should be devoted to the development of animal models of HIV induced seizures to study mechanisms, of neuronal and glial pathology, signaling pathways, and to provide a platform for effective seizure prevention and control.

![Fig1. Incidence (per 1000) of seizures in HIV population shaded by continent](image)

**REFERENCES**


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