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COMMENTARY: NEUROSCIENCE

NEUROAIDS: A REAL CONCERN

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ABSTRACT

Improved antiretroviral treatments are still unable to cure HIV infections, therefore chronically low levels of HIV replication continues in patients. Long-term low replication of HIV leads to accumulation of virotoxins, which could be a reason for neurotoxicity in long-term HIV survivors. Nowadays, more than 50% of HIV patients are presented with neuropsychiatric complications, known as NeuroAIDS. Increase in life-span of HIV seropositives, along with addition of new infections every year is a real concern for NeuroAIDS as a new and emerging health problem.

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Keywords: **NeuroAIDS; neuropsychiatric disorder; HIV; ART; BBB**

COMMENTARY

Some of the common neuropsychiatric diseases are mood disorders, schizophrenia, addiction, dementia, epilepsy, *etc.* Usually, a combination of neurological and psychiatric disorders is categorized under neuropsychiatric disorders, which contribute ~15% of world's disease burden [1]. In the recent past, various neuropsychiatric complications have been reported among human immunodeficiency virus (HIV) seropositive individuals with much higher frequencies than their normal occurrence in uninfected population. Neuropsychiatric complications among AIDS patients are collectively called as NeuroAIDS. Some of the most common neuropsychiatric complications among HIV seropositives are HIV-associated dementia (HAD), HIV-associated encephalopathy (HIVE), HIV-associated minor cognitive/motor disorder (MCMD), *etc.* It has been estimated that >50% HIV seropositives show signs and symptoms of neuroAIDS at later stages of HIV infection [2].

In 1981, the first report of HIV infection came from Los Angeles, USA, where five gay men were infected with *Pneumocystis carinii* pneumonia (PCP) [3]. At that time, neither the HIV nor the AIDS terms were in use in medical dictionary. The AIDS name was adopted for this disease by Center for Disease Control and Prevention (CDC), Atlanta, USA, in 1982. The causative organism for death of these gay men was discovered by Luc Montagnier (France) in 1983 and confirmed by Robert Gallo (USA) in 1984. Both of them proposed different names for the same virus and those names were Lymphoadenopathy-Associated Virus (LAV) and Human T-cell Lymphotropic Virus (HTLV), respectively. But the final name was coined as HIV in 1986 by the International Committee on Taxonomy of Viruses. Soon, reports of HIV infections started pouring in from all over the world. Explosion in the number of HIV-infected patients gave a sense of an epidemic, and HIV was widely spreading without any limitations of physical boundaries. No one was immune to HIV infections; HIV was known to infect men, women, children and even newly born babies alike. People from all age groups, ethinicity and nationality are known to be victims of HIV infections. Spread of HIV infections has been brought under control to a great extent by now; still, it is spreading and affecting various communities. The impact of HIV infection to certain communities *e.g.*, African countries has been devastating [4].

Statistics about HIV infections, prevalence and progression towards AIDS are still shocking. As per new estimates by UNAIDS (2009), >34 million HIV-infected people are living in the world, out of which >2 million HIV infection cases are diagnosed in children below the age of 15 years. Although various effective measures are taken to control the spread of HIV, it is still an astonishing fact that according to UNAIDS

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report >2 million people get new HIV infection every year **[Table–1]**. Additions of such high numbers of new infections are still making this situation worse day-by-day. These numbers do not give any jitter, if calculated as percentage of total world population, which turns out to be <0.5% of total human population. But the absolute numbers of 34 million infected people along with addition of 2.4 million new infections every year is a serious and real concern for a chronic and fatal disease like AIDS [5].

Table: 1. HIV/AIDS epidemic till 2008: At Glance*

	Living with HIV	New Infection†	Death†
	←	(in millions)	→
Men	15.70	1.15	0.85
Women	15.70	1.15	0.85
Children	02.00	0.43	0.28
Total	**33.40**	**2.73**	**1.98**

*; Adapted from UNAIDS Report, 2009. †; Annual estimate

AIDS is the final stage preceded with HIV infections, which finally leads to the death of patients. Initially, a high incidence of mortality was reported among HIV seropositives, as there was no medicine available for HIV control. Later, azidothymidine (AZT), an antiretroviral drug became the 1st available treatment for HIV infections. Since then, HIV medications have achieved marked improvements in their efficacy, which helped to reduce morbidity and to increase survival among HIV seropositives. Undoubtedly, antiretroviral drugs have added millions of life years among HIV seropositives, when the data is compounded. Nonetheless, HIV infections can only be controlled and cannot be cured, which simply translates into the fact that if someone is infected with HIV, that person has to live with it life-long and wait for its progression towards full blown AIDS, that will bring an end to his/her painful existence. Certainly, improved medications have significantly delayed the onset of AIDS. The new treatment regimens like highly active antiretroviral treatments (HAART) have significantly contributed towards delay in the onset of AIDS. At present, all the available HIV treatments are far from perfect, because each and every medication and treatment regimen have their own limitations and side effects.

In fact, the benefits and drawbacks of HIV medication represent the two sides of the same coin. On the one side, anti-HIV drugs have enhanced the survivability among HIV seropositives, while on the flip side these drugs have indirectly contributed towards the appearance of various neuropsychiatric complications among these patients. Specifically, longer survival with chronic infections like HIV causes decrease in immune-competency of the host, which in turn increases the probability to be infected with different opportunistic infections like PCP, pneumonia, Kaposi's sarcoma, *etc.* Still, if we take a closer look at initial findings of HIV cases, signs and symptoms of neuropsychiatric disorders are not new. Unfortunately, even initial cases of AIDS had been reported with neuropsychiatric signs and symptoms, but failed to attract a significant level of attention, because at that point of time, priority was given to control HIV infections, and efforts were directed to develop strategies to prevent its spread. At present, better access of antiretroviral drugs to HIV patients have extended their life; as a result HIV seropositives live longer, but they now face NeuroAIDS a new complication associated with HIV infections, as a consequence of their longer survival.

According to some estimates, >50% long-term HIV seropositives show signs and symptoms of NeuroAIDS. With this high prevalence of NeuroAIDS, in the near future, we expect that a huge number of HIV patients will be living with NeuroAIDS worldwide. Therefore, the burden of NeuroAIDS to society is expected to rise as days pass by **[Table–2]**. This fact can be simply understood from the UNAIDS (2009) report, which informs that everyday ~7400 people get infected with HIV, while ~5500 die with AIDS. In other words, every day we are adding ~1900 patients, which translates into ~0.7 million HIV infected individuals annually.

NeuroAIDS should be considered as a significant health issue due to variety of reasons: 1) the number of patients is ever increasing on daily basis, 2) symptoms of NeuroAIDS hit almost at the prime of age of a human being, *i.e.* between the age of ~35-45 years, 3) high costs for continuous supply of antiretroviral medications, 4) NeuroAIDS patients need additional medication, 5) usually, NeuroAIDS symptoms render these patients least productive in their life resulting in substantial loss of their individual or family income, and 6) need for a care-taker or care-giver, which again financially translates into extra loss of income due to active involvement of another family member, who will assume the role of a care-giver, or a possibility of extra expenditure to be incurred to the family for the health care of a NeuroAIDS patient, if they hire a professional care-giver. These are some compelling reasons

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to realize the importance and adverse impact of NeuroAIDS on society [6].

Pathophysiologiclly, NeuroAIDS is a result of either direct HIV infection to CNS/brain or induction of neurotoxicity, as a consequence of HIV infections. An HIV infection to brain is an intriguing phenomenon for clinicians as well as for biomedical scientists. CNS/brain is the most protected organ system of body, as it is separated from rest of the body by blood brain barrier (BBB). Even with the presence of protective barrier to brain, some evidence for HIV infection to brain was reported from cadaver cases of HIV/AIDS patients. Still, it is difficult to explain HIV infection to brain, as the majority of brain cells are not readily infected by HIV. Some of the most common cells present in CNS are astrocytes, oligodendrocytes, microglia, perivascular macrophages and neurons. So far, neurons have been shown to be non-permissive to HIV infection, which is understandable, because they do not express the primary receptors used by HIV, *i.e.*, CD4 [7]. Microglia and perivascular macrophages express CD4 receptors on their cell surface. However, rather than loss of microglia and perivascular macrophages due to HIV infections, neuronal loss has commonly been observed in cases of NeuroAIDS. Important co-receptors like CXCR4 and CCR5 are under active search for their role in HIV infections to the brain. At present, it seems like NeuroAIDS is more of a result of neurotoxicity rather than HIV infections. This neurotoxicity may play a vital role in neuronal loss, although the triggers of neurotoxicity are currently unknown. Collectively, several issues have been raised that are under active consideration, such as: 1) Is HIV itself responsible for NeuroAIDS? 2) Is NeuroAIDS a secondary complication emerged due to long-term antiretroviral treatment (ART)? 3) Low or negligible penetrance of ART in brain. 4) Are low levels of persistent and chronic HIV infection contributing towards development of NeuroAIDS? or 5) Is it a combined effect of all these possibilities? The present understanding of NeuroAIDS and its causes remain still unclear [8].

Table: 2. Predication for expected numbers for NeuroAIDS*

	Living (in millions)	Expected Rise† (in %)
Men	07.80	15
Women	07.85	15
Children	01.00	7.5

*; Prediction based on the assumption that all HIV seropositives (including new infections) have access to antiretroviral treatment and maintain a reasonable healthy state. †; Annual estimate

A low level of HIV replication continues even when HIV is below detection levels in patients, which can cause chronic accumulation of different virotoxins and cytokines (pro-inflammatory and inflammatory). These biomolecules get accumulated in circulation and may alter physiology of BBB, which may support entry of these molecules as well as HIV along with T-cells and monocytes (infected) present in peripheral circulation. Certainly, it is due to breach in the most protective layer, *i.e.* BBB. It seems like neurons are most vulnerable to any of these physiological/pathological alterations in brain and they respond to these changes by neuronal death. Recovery of neuronal loss is impossible due to the inherent characteristics of neurons, *i.e.* their inability to regenerate. On the other hand, microglia and perivascular macrophages are the only cells that are positive for primary receptors for HIV infection, *i.e.* CD4, and they serve as a reservoir for HIV infection by remaining latently infected for a longer time, or they retain undetectable levels of HIV replication. But at some point in time, HIV replication may get triggered in these cells and they become the major source of HIV replication in brain, although the nature of that trigger, is still a question for scientific discovery and debate. A low level of HIV replication in microglia and perivascular macrophages is considered as one of the major reason for neurotoxicity, which ultimately leads to neuronal loss as a major pathological phenomenon for NeuroAIDS. While at late stages of HIV infection, active replication of HIV in these cells could accelerate progression of NeuroAIDS. Therefore, there are various underlying mechanisms at cellular and molecular levels to induce, maintain and worsen NeuroAIDS. This warrants a need for additional thorough studies on the mechanisms of NeuroAIDS, so that this problem can be brought under control, before it gets out of hand [9].

Unfortunately, we still do not have either *in vivo* or *in vitro* model systems to study or to dissect the exact mechanism for NeuroAIDS, as well as to evaluate efficacy of drugs. Under these circumstances, the world community needs to pay more attention on research efforts by allocating funding to find the means either to control NeuroAIDS or at least to improve the health status of these patients. The menace of NeuroAIDS requires urgent and important attention before its control gets out of hand or drain lot of resources in an already depressed world economy.

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