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NeuroAIDS: Mechanisms, Causes, Prevalence, Diagnostics and Social Issues

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1. Introduction

Human immunodeficiency virus-1 (HIV-1) engulfs 33 millions of life as per the latest UN AIDS report [Saxena, Tiwari., *et al.*, 2012] and the effect worsens up when it causes dementia with alarming occurrence worldwide but the mechanism through which it happens is still not well understood, and is in the embryonic stages. The estimated overall prevalence of nervous system disorders among patients receiving highly active antiretroviral therapy but also requiring neurological care is over 25% (Singh *et al.*, 2011). According to WHO there are ~ 34 million people in the world infected with HIV. Out of that 95 percent of these cases as well as deaths from AIDS occur in the developing world. Dementia (HIV-associated dementia) is becoming common in HIV infected adults having prevalence up to 40% in western countries where clade B prevails (Sacktor *et al.*, 2007). Dementia cannot be considered as a disease by itself but it is the term used to describe a set of symptoms resulting from damages and disorders affecting the brain. These symptoms can be caused by a multitude of diseases and depend upon the specific brain regions affected. These symptoms appear as a variety of cognitive, behavioural, affective, motor, and psychiatric disorders. Dementia can be caused by a variety of diseases, known as neurodegenerative diseases resulting from protein aggregation in the brain. Many studies related to this area are been carried out in respect to this, to provide new insights (Saxena *et al.*, 2012). HIV-1 infects macrophages and microglia, and there is an indirect pathway to neuronal injury which happens due to release of macrophage, microglial and astrocytes toxins and viral proteins. The toxins which are released over stimulate neurons, form free radicals, finally leading to neurodegenerative diseases. The cognitive and motor dysfunction which is observed in HIV patients is termed as HIV associated dementia (HAD). The

prevalence of the dementia is eventually increasing as AIDS patients are now surviving more. HIV-1 replicates in monocyte and macrophage but not as severe as in infected T cells and blood mononuclear cells (Sundaravaradan *et al.*, 2006). These cells differentiate and travel to several organs, henceforth acting as a source of infectious virus and secreted viral proteins to cause pathological issues and alternating several signalling pathways and distorting many cellular transcription factors, ultimately resulting in HIV-1 pathogenesis. Increased transcription leads to the upregulation of virus production, and hence increased production of viral proteins (gp120, Tat, Nef, and Vpr) (Gandhi *et al.*, 2020; Samikkannu *et al.*, 2010; Saiyed *et al.*, 2011; Saxena *et al.*, 2012; Saxena *et al.*, 2012). The high concentration of these toxic proteins lead to distorted cellular functions, and increased production of toxic metabolites, finally leading to organ-specific like neuroAIDS, in case of viral entry inside the brain (Kilareski *et al.*, 2009). Antiretroviral therapy has increased the lifespan of HIV patients, but CNS function often remains diminished sometimes developing into HIV-associated dementia and the severity and progression of dementia is studied to be increased with the effect of drug abuse [Reddy *et al.*, 2012; Ferris *et al.*, 2008].

2. Prevalence

The prevalence of HAD is estimated to be more than 30% of HIV infected patients, and it is still reported to be increasing (Dean *et al.*, 2012). Improvements in control of peripheral viral replication and the treatment of opportunistic infections, helps in extending life expectancy, resulting in an increase in neuropathogenesis. We are seeing a linear increase in prevalence in rich countries, but an exponential increase in low-income countries. Just under half of people with dementia live in high-income countries, 39% live in middle-income countries, and only 14% live in low-income countries. Increasing living standards, in low income countries such as India (Shankar *et al.*, 2005), may lead to increased life expectancy, which may increase the frequency of dementia cases. As biggest risk factor for dementia is age, a longer-living global population means there will be more people with dementia. The report predicts that the numbers of people with dementia will double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Most of this increase will be in developing countries (Prince *et al.*, 2012). A more complete understanding of the pathogenesis of HAD will help in identifying therapeutic targets for its prevention and treatment. The global age standardized death rate for dementia is ~ 6.7 per 100,000 for males and 7.7 per 100,000 for females. According to the World Health Organization, dementia mortality rate for India is 13.5 per 100,000 males and 11.1 for 100,000 females, which is quite alarming (Prince *et al.*, 2012).

3. HIV- Mechanism of neuronal injury

Presently, neuropathogenesis is winning, because there is an incomplete knowledge about the mechanism of HIV infection causing neuronal injury and apoptosis in the host (Fig. 1). HIV

enters the central nervous system through infected monocytes and leads to pathogenesis involving activation of macrophages and microglia and further toxin release, that activates several pathways leading to neuronal dysfunction. There are several extracellular and intracellular signalling pathways, which when activated lead to macrophage or microglial activation, and induction in neurons and astrocytes. These pathways are of potential therapeutic importance as targets for the prevention or treatment of neuropathogenesis.



Figure 1. HIV virus can enter the CNS by altering the integrity of blood brain barrier.

4. Neuropathology of AIDS

HIV-1 is capable of causing a multi-system disorder including the CNS. HIV-1 enters the CNS at the early phase of infection, it persists and induces several motor and cognitive disorders leading to behavioural changes. Major clinical symptoms include impaired short term-memory, reduced mental concentration, weakness, slowness of hand and leg movement and depression accompanied by behavioural issues like personality disorders, lethargy and social withdrawal. These neurological and psychiatric symptoms caused by HIV-1 infection, constitute together as neuropathogenesis. A more subtle form of CNS dysfunction, known as minor cognitive motor disorder (MCMD), is also seen common in HIV patients. HAD cannot be controlled by HAART, HIV-1 infection becomes chronic and even rise in disease has been reported. The HIV-1 associated neuropathology is characterized by the infiltration of macro-

phages into the CNS, the formation of microglial nodules and multinucleated giant cells, astrocyte activation and damage; neuronal loss in ganglions and hippocampus, myelin damage, axonal damage and presence of HIV-1 in the CSF. MRI reports say that HIV infection is associated with progressive cortical atrophy which might be caused by neuronal loss and demyelination worsening in certain cognitive functions (Ghafouri *et al.*, 2006).

5. HIV entry into the brain and initiation of HAD

HIV-1 infects cells having major HIV-1 receptors, CD4 and CD8, and several chemokine receptors which are known to be as HIV-1 co-receptors which help in the attachment of the virus to the cell and membrane fusion leading to viral entry. Infected CD4+ T cells and monocytes circulating in the blood are the potential source of CNS infection. HIV-1 infected cells can be either highly active producers or low/non producers of viruses. Both types of infections occur in the CNS. Studies of different astrocytes cell lines, demonstrated the presence of large quantities of Rev in the cytoplasm. Changes in cell environment, like the elevation in the level of cytokines such as TNF- α and IL-1 β , might reactivate virus production (Ghafouri *et al.*, 2006). During early infection, HIV enters the CNS (Bertin *et al.*, 2012) and attacks cells macrophages and microglial cells (Foley *et al.*, 2008). But along with this infection, periphery factors (non-CNS) are also important for initiating neurodegeneration and triggering dementia, which are like for example; increased number of circulating monocytes that express CD16 and CD69. The cells which get activated by viral entry, progressively adhere to the endothelium membrane of the brain microvasculature, and further transmigrate, triggering a spontaneous array of harmful processes which might finally lead to the loss of Blood Brain Barrier (BBB) integrity making it easy for virus to enter and replicate inside the brain. The BBB is crucial in HIV infection of the CNS. BBB is composed of specialized Human brain microvascular endothelial cells (HBMECs), which do not have any opening and are connected by intercellular junctions in an impermeable single layer. BBB plays a central role in neuropathogenesis as it serves as the channel through which free virus and infected immune cells enter the brain. The BBB loses its integrity and permeability due to progressive HIV infection and immune compromise, which leads to easy entry of toxins, free virus, infected and activated monocytes into the brain. It has been reported that HIV-1 gp120 protein and also Tat protein are behind BBB disregulation. PKC signaling pathways and receptor-mediated Ca²⁺ release are the involved pathways resulting into cytotoxicity of the brain endothelial cells (Kanmogne *et al.*, 2005) leading to downregulation and rupture of tight junction proteins (TJPs) of HBMECs, by the induction of proteasome by HIV-1. It has been studied that circulating virus or envelope proteins may also cause BBB dysfunction during primary infection. CNS infection of HIV is detected by viral RNA load in CSF (Woods *et al.*, 2009; Morgan *et al.*, 2011). Chemokines like monocyte chemoattractant protein (MCP)-1 control PBMCs relocation through BBB. Cellular migration engages adhesion molecules and differential regulation of inflammatory cytokines, leading to BBB disintegration and finally immune

dysregulation by letting sufficient entry of infected or activated immune cells into the brain causing neuronal injury.

6. Types of CNS cells invaded by HIV-1

BBB is selectively permeable, made up of firmly concurrent brain microvascular endothelial cells, and its major role is to separate the CNS from the periphery. It manages the trafficking of cells and molecules across it into the brain parenchyma. For the purpose of brain entry, HIV-1 has to cross the BBB using several mechanisms which are still poorly understood and are unclear. Numerous *in vitro* experimentations have been done to understand the mechanisms of HIV-1 introduction into the CNS via BBB. It is reported that the severity of HIV-1 associated neuropathogenesis is dependent on amount of HIV DNA circulating in PBMCs (Shiramizu *et al.*, 2009). It is hypothesized that HIV-1 enters the CNS, in disguise as a commuter in cells trafficking till the brain (Verma *et al.*, 2010). CD4+ cells, like T cells and monocytes are infected by HIV-1, which circulate in blood and have the ability to cross the BBB and introduce the infection into CNS. Though presence of CD4 receptors in human brain microvascular endothelial cells is still a matter of debate whereas its presence is studied along with expression of HIV-1 co-receptors have also being reported on primary human brain's microvascular endothelial cells. Other proposed hypothesis for the entry of HIV-1 is the migration between/transcytosis of endothelial cells. All types of the CNS cells like astrocytes (Wang *et al.*, 2009), oligodendrocytes, neurons, macrophage and microglia, are easily infected by HIV-1 as they have receptors and co-receptors for HIV-1 entry, but only macrophage and microglia get infected most commonly which are the resident immunocompetent cells of the brain (Gendleman *et al.*, 1985). Expression of CCL2/MCP-1 in astrocytes is enhanced by nef via calmodulin dependent pathway. Consequently, increased CCL2/MCP-1 functions as a chemoattractant for monocytes, thereby facilitating entry of monocytes into the brain (Lehmann *et al.*, 2006). Peripheral macrophage population is necessary to be refilled, which is compensated by the migration of monocytes into the CNS, resulting in major drawback of facilitating the entry of intracellular virus. Microglia and monocyte-derived macrophages are the main culprits of HIV-1 CNS infection. Immunostaining experiments have shown HIV-1 infection in parenchymal microglia, but it is still unclear that whether the HIV-1 immunopositive microglia receives influx of infected cells from blood or directly results from prolonged infection in the CNS. *In vitro* experiments demonstrate that HIV-1 replication takes place in primary microglia isolated from adults and infants leading to cytopathology. Microglial cells are the major targets as they express CD4/CCR5 major receptors/co-receptors which is a necessity for HIV-1 infection. On the other hand astrocytes express CXCR4 and other HIV-1 coreceptors like CCR5, but do not express CD4 receptors and are still reported to be infected by HIV-1 mechanisms to which are still unclear. Also *in vivo*, oligodendrocytes infection by HIV-1 remains unclear and less understood as they do not have CD4 receptors. Mostly there is absence of *in vivo* infection in neurons, however sometimes presence of HIV-1 DNA and proteins in neurons have been reported too, leading to need of further studies. Various pathways for the entry of virus into the brain have been studied like (i) direct entry, (ii) transcytosis, (iii) Trojan horse hypothesis

for entry, which states that HIV enters the CNS via infected CD4 + AND T-cells which are capable of crossing BBB and they reach CNS and are also capable of transferring infection to other CNS cells too (Fig. 2).

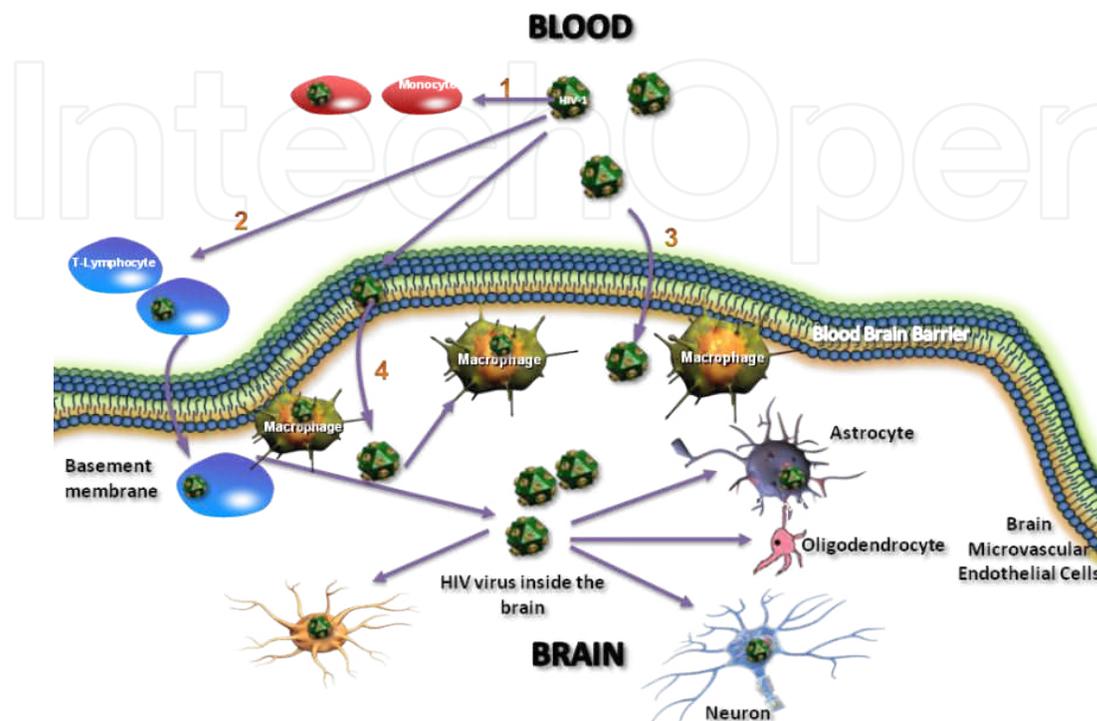


Figure 2. HIV-1 neuroinvasion. 1) "Trojan Horse hypothesis" for entry of HIV-1 into the brain via migration of infected monocytes which differentiate into perivascular macrophage. 2) The passage of infected CD4+ T cells into the brain. Other probable causes of CNS infection might be: 3) the direct entrance of the virus via tight junctions across the membrane and 4) entrance of HIV-1 by transcytosis phenomenon.

7. Crosstalk between the peripheral and CNS immunity

The way by which HIV-1-infected monocytes escape immune surveillance can be explained by "Trojan horse cell" model. The "support" needed for the viral entry is through CNS-produced chemokines like MCP-1 and IFN- γ -inducible peptide, CXCL10, whereas the "opposition" is through peripheral immune activation (Yadav *et al.*, 2009). Upon entry in the brain, HIV-1-infected blood-borne macrophages secrete proinflammatory cytokines like tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), and viral proteins which affect neuronal function (Brabers and Nottet, 2006). Within the brain, astrocytes serve as principal regulators for neural homeostasis. They bring out a neurotoxic secretory response in macrophages, resulting to upregulation of certain acids and metabolites, chemokines, and cytokine secretions. They can also alter macrophage phenotype, which may help in neuroprotection. But on the contrary astrocytes can also influence autocrine and paracrine inflammatory cascades, which may lead to immune activation, increased viral infection, and allowance of

cellular entry via BBB (Kraft-Terry *et al.*, 2010). Also CD16+ monocytes are linked to infection of the brain as they can be easily infected by the virus, they carry virus into the brain and help in viral dissemination and serve as viral reservoirs as they are apoptosis resistant. HIV proteins like *nef* require adaptive selection in brain for efficient replication in macrophages or when it is exposed to brain specific immune selection (Olivieri *et al.*, 2010). Neuropsychiatric disorders associated with HIV infection result in substantial morbidity and fatality. HIV injures the CNS and PNS, leading to neuropsychiatric disorders, which together constitute for neuroAIDS (McCombe *et al.*, 2009), which includes neurocognitive disorders like HAD, minor neurocognitive disorder (HAND), mania, anxiety, depression, seizures, myelopathy and neuropathy, and also involves display of several symptoms like neurocognitive impairment, mood disorders, neuropathic pain, epilepsy, addiction, physical disability, loss of memory, mood swings etc (Fig.3).

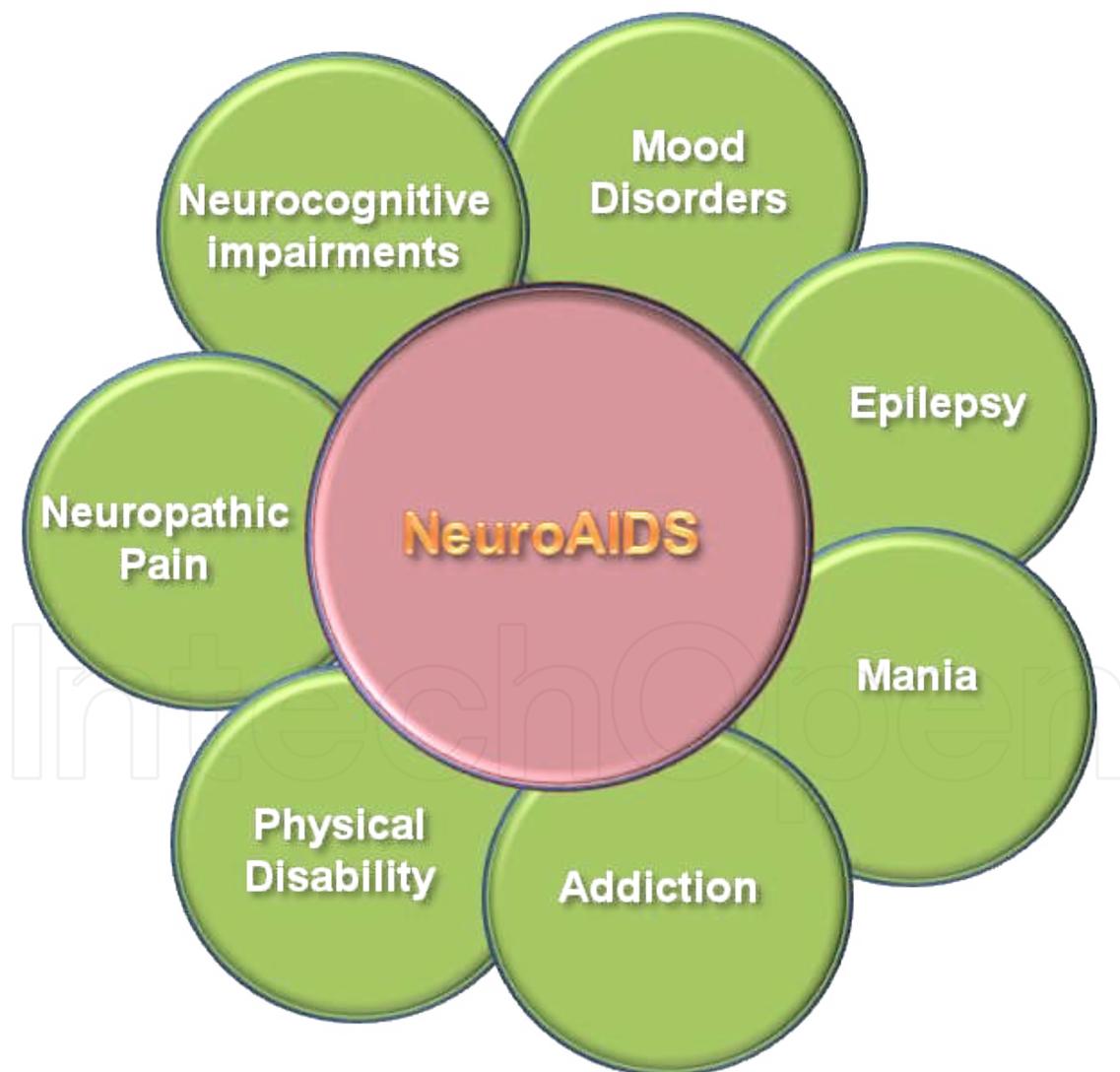


Figure 3. Associated disorders and symptoms which are commonly seen in patients suffering from neuroAIDS.

8. Forms of dementia

One form of dementia is Alzheimer's disease caused by amyloid pathology, during which peptides of amyloid- β generate and clump together into plaques which release toxic fragments of amyloid- β leading to neuropathogenesis. Another form of dementia is caused by vascular pathology in which blood vessels leak and hence deprives small areas of the brain of blood and oxygen, which damage brain tissue resulting in cognitive defects. Both forms exist equally, even though Alzheimer pathology is more common, but it coexists with vascular pathology. (Abott *et al.*, 2011).

TYPES OF DEMENTIA			
Dementia type	Symptoms	Neuropathological findings	Percentage of total dementia cases
Alzheimer's	Weakened memory power, leading to confusion, disinterest depression and bad judgement skills.	Formation of amyloid plaques and also neurofibrillary tangles.	50–80%
Vascular dementia	Memory is weakened, but not as intense as in the case of Alzheimer's patients.	Causing microstrokes due to reduced blood flow to brain	20–30%
Frontotemporal dementia	Personality disorders, mood swings and difficulty in understanding different languages.	Damage limited to frontal and temporal lobes	5–10%
Dementia with Lewy bodies	Weakened memory power, leading to confusion, disinterest depression and bad judgement skills, hallucinations and tremors.	Cortical Lewy bodies (of the protein α -synuclein) inside neurons.	<5%

Table 1. Displaying the types of dementia and their prevalence. (Source: Abbott A. Dementia: a problem for our age. *Nature*. 2011; 475(7355): S2-4)

9. Knowing dementia and its diagnosis

Dementia is considered as loss of memory and other cognitive abilities which reduces the lifespan of patients. Dementia is often associated with physical, mental and financial burden. 37% of the dementic population in developing countries have vulnerable living environment and they require specialised care. Diagnosis of dementia involves investigations for

decline in memory and disturbance in several cognitive abilities like coherent speech, understanding spoken or written language, recognizing objects, executing motor activities, sensory function, thinking abstractly, making sound judgments, planning and carrying out complex tasks. Dementia reduces the lifespan of affected people. In the developed countries life span after dementia diagnosis can be expected to be ~7 years, but in low and middle income countries survival may be shorter. Dementia symptoms and linked issues can be understood in three stages of early stage (1-2 years) which is often overlooked because the onset of dementia is gradual, making it difficult to predict when it begins, leading to problems in talking, memory loss. Secondly, the middle stage (2-5 years) which makes patients life more difficult and restricted, giving them difficulty in day-to-day living and forgetting recent events and people's names, etc. Thirdly, the late stage (>5 years) leading to total dependence and inactivity, serious memory disturbances difficulty in physical works like walking, eating, incapability of communicating, not recognizing familiar objects, displaying inappropriate behavior in public etc.

HIV associated dementia, referred as the syndrome of cognitive and motor dysfunction resulting in progressive neurodegeneration observed after infection with human HIV-1, also known as HIV encephalopathy (HIV-E) and AIDS dementia complex (ADC) (Kaul *et al.*, 2001). In the last stage of HIV, HAD a severe neurological complication affects 15–20% of the patients (Van de Bovenkamp *et al.*, 2002). The relationship between spreading of HIV in brain tissue and pathology has not been thoroughly assessed in HAART era (Lamers *et al.*, 2010). In spite of preventing former end stage complications of AIDS by HAART however, with increased survival times, the prevalence of minor HIV-1 associated cognitive impairment appears to be rising among AIDS patients. Further, HIV-1 associated dementia (HAD) is still prevalent in treated patients as well as attenuated forms of HAD and CNS opportunistic disorders (Ghafouri *et al.*, 2006). Infected macrophages with HIV have an ability to cross BBB infect inhabitant brain macrophages initiating the development of HAD. Cytokines are released from infected resident brain macrophages which further attract more macrophages to sites of infection and a series of self-inflammatory process emerges (Williams *et al.*, 2002). Studies have suggested that the process of entering in the CNS causing HAD mostly depends on the HIV variants as some HIV variants have capability of entering in the CNS and develops HAD but in contrast other variants don't have capability to develop HAD even after entering in the CNS (Fischer-Smith *et al.*, 2008; Fischer-Smith *et al.*, 2005).

10. Underlying mechanisms and issues

Some studies suggest that neurological involvement of infected patients occurs at different frequencies, depending on the HIV subtype involved in the infection (Liner 2nd *et al.*, 2007). HIV-1 Subtype D has more prominent chance for developing dementia (89%) than subtype A (24%) in the patients localized in a region of Uganda, Africa suggesting genetic determinants exist within HIV that influence the ability of the virus to replicate in the central nervous system. HIV-1 proteins have been shown to be released from HIV infected cell and/ or they have found to be present in the extracellular milieu in the HIV-1-

infected brain. In vitro, neurotoxic and/or neuromodulatory effects have been shown by HIV proteins: *nef*, *env*, *tat*, *rev*, *vpr* and *vpu* that might play a role in the development of HIV-1-associated dementia in vivo (Sactor *et al.*, 2009).

11. Fight against dementia

Dementia is engulfing bigger proportion of HIV patients and is expected to worsen more. It is expected that a significant proportion of dementia is driven by amyloid- β . But so far none of the amyloid-based strategies has been successful, but still drug developers are strategising on the concept which can combat against it. More reliable biomarkers are being developed potentially making it possible to carry out trials on patients before symptoms. Some scientists are also wondering to target vascular pathology as well, which is equally responsible for causing dementia. So cholesterol level lowering drugs and blood pressure reducing drugs are also given long term to patients, who are at higher risk of heart attack which may also help protect from dementias as well (Abott *et al.*, 2011). There are several extracellular and intracellular signalling pathways, which when activated lead to macrophage or microglial activation, and induction in neurons and astrocytes. These pathways may act as a potential therapeutic importance as drug targets against neuropathogenesis. NeuroAIDS is challenge to patients, their families, society and our country, thus development of preclinical models appropriate for new compounds testing with neurotrophic and neuroprotective potential is necessary (Crews *et al.*, 2008; Williams *et al.*, 2008).

12. Therapeutic developments

The biggest issue which comes in front of drug developers is the incapability of the drugs to cross the BBB, which leads to low bioavailability of the drugs into the CNS. HIV-1 protease inhibitors are totally incapable in entering the CNS, while other HIV-1 therapies such as zidovudine (AZT) are reported to have efficient BBB penetration. Recently, a broad range of nanomedicines are being developed to improve drug delivery across BBB, development of nanoparticulate- antiretroviral therapy (nanoART), against CNS disorders as the structure of the BBB, efflux pumps and the expression of metabolic enzymes make it difficult for the regular drug to reach brain. Nanoformulations can evade the BBB and can boost CNS-directed drug delivery (Fig. 4) (Saxena *et al.*, 2012; Nowacek *et al.*, 2010; Nowacek *et al.*, 2009). Efforts are been done in finding long-lasting injectable antiretrovirals to avoid the challenges of therapy adherence (Baert *et al.*, 2009). To specifically target the CNS, NPs are synthesized with various combinations of ART therapies to be taken up by monocytes and carried into the CNS for release at sites of HIV-1 infection, for example Indinavir nanoART and p24 loaded and coated NP, which are providing new avenues for treating or even preventing the spread of HIV-1 in the brain. Adjunctive therapeutics ART is engaged in making combinatory drugs against virus mutation. Efforts are being made to improve penetrability of ART across the BBB, but importance of considering drug toxicity and elicited cellular response for various ART regimens is

always a necessity. Adjunctive therapy like platelet-activating factor (PAF) antagonist, PMS-601, are demonstrated to reduce HAND symptoms and even combination of ART and PAF antagonists, are also studied to have role in reducing neurodegeneration. All of these are also being developed as therapies for neurodegenerative disorders which may prove to be a boon in the combat against NeuroAIDS. Need of the hour is to devise an exact combination of CNS-penetrating nanoART and adjunctive therapies, which might be able to help us against neurocognitive symptoms (Kraft-Terry *et al.*, 2010).

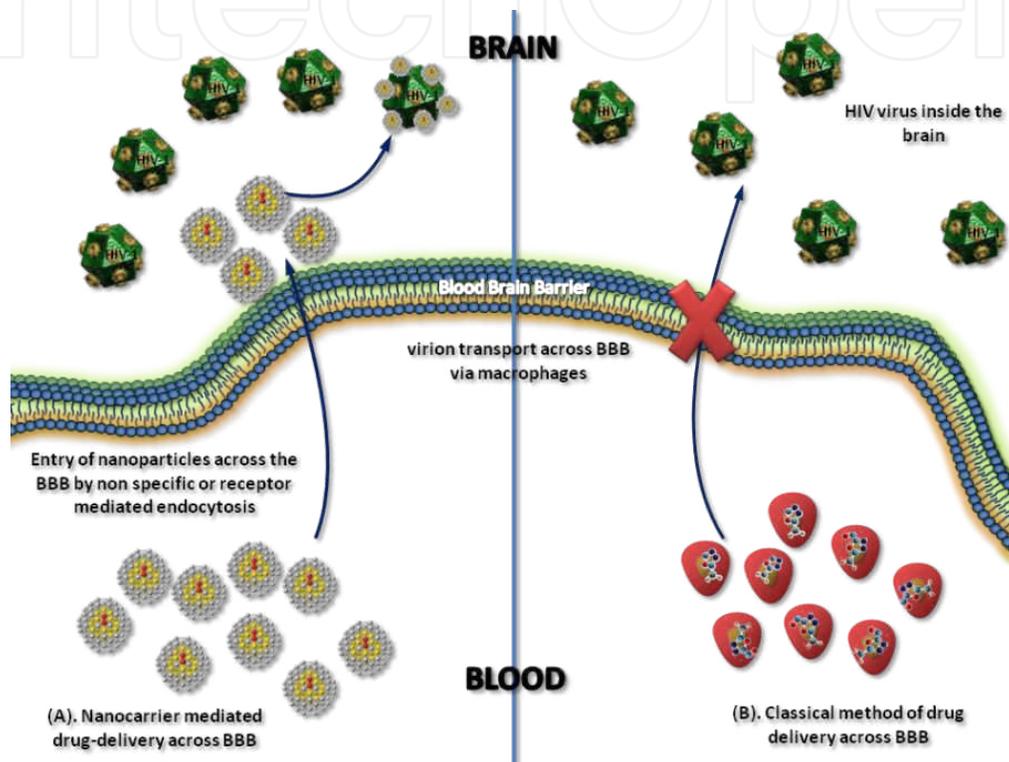


Figure 4. Comparative display of nanocarrier mediated method of drug delivery (A) versus the classical method of drug delivery across the Blood Brain Barrier (BBB), which is less efficient than the former in the process of drug delivery.

13. Future implications and need of the hour

Since dementia is quite prevalent in HIV patients, in developed countries and has also been reported to extend its grip towards developing countries as well due to increase in patient survival rates and life expectancy due to HAART treatment and increased living standards. Low prevalence of HAD in underdeveloped and developing countries have been attributed to under diagnosis, short life expectancy and short survival following HIV infection associated with opportunistic infections and also low prevalence of HIV related neuroinfections and pathology is not available due to inadequate medical facilities, social stigma and ignorance that lead to under diagnosis (Vivithanaporn *et al.*, 2010). So a need of collaboratory studies is there which can be used, for learning the cause, prevalence and diagnosis of neuropathogen-

esis. A synchronised effort is needed by researchers, drug makers, physicians, policy makers, government bodies nationally as well as globally. A proper and deep understanding about the entry of the virus into the CNS and the various mechanisms it employs to undertake the host machinery would be of great help in understanding the issue and combating against the virus.

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