The neurobiology of HIV dementia: implications for practice in South Africa

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Abstract
In this review, the neuropathogenesis of HIV dementia (HIV-D) is discussed in the context of the local epidemic. HIV-D continues to be prevalent in the era of highly active anti-retroviral therapy. HIV neuro-invasion into the central nervous system may result in the development of separate HIV genotypes in an individual through compartmentalisation. The blood brain barrier continues to limit penetration of anti-retroviral drugs into the cerebrospinal fluid. Individuals with active neuro-inflammation appear to respond well to HAART. In some cases low grade neuro-degeneration persists with consequent clinical deterioration. In South Africa, the emergence of a sub-epidemic of HIV-D is being driven by various factors, including the incomplete coverage of HAART to all who need it, the late stage presentation of people living with HIV/AIDS (PLWHA) and a co-occurring methamphetamine epidemic. Differences in viral subtype do not appear to confer protection against HIV-D. Implications for PLWHA who are at risk for HIV-D in South Africa are explored, with a view to providing suggestions for improving practice and research into this area.

Key words: Dementia; HIV; HAART; South Africa

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Introduction

Infection with human immuno-deficiency virus type 1 (HIV) is an important health concern globally but especially in South Africa, which has the highest number of people living with HIV/AIDS (PLWHA).[1] HIV is known to cause adverse neurological sequelae (also known as ''neuroAIDS'') in a substantial proportion of individuals. Despite improved survival and quality of life following the use of highly active anti-retroviral therapy (HAART), neuroAIDS remains prevalent. In this review, we describe the neurobiology of dementia associated with HIV. In particular, we describe the process of neuroinvasion, subsequent neurodegeneration and treatments. We further aim to address how the sub-epidemic of neuroAIDS may impact individuals and services in South Africa and suggest strategies for approaching this problem.

NeuroAIDS remains prevalent, with as many as 60% of PLWHA going on to develop some form of HIV associated neurocognitive disorder (HAND) in their lifetime.[2] Furthermore nearly 90% of individuals have autopsy evidence of neuropathology. Neuro-invasion is likely to occur early in the course of HIV infection following dissemination of HIV into lymphoid tissues and cells.[3] The blood brain barrier not only limits ongoing passage of HIV into the central nervous system (CNS) following this early peak in viral load, but also acts as a barrier to drug penetration.[4] The active infection of CNS microglial cells results in the development of a neurotoxic inflammatory cascade, which involves primarily the sub-cortical white matter and striatum.[5] Neurocognitive dysfunction follows the disruption of these circuits, while neuronal apoptosis produces cortical atrophy.[6] Early response to HAART is probably associated with a rapid suppression of acute neuro-inflammation (an ''encephalopathy'' syndrome), while delayed improvement may occur following immune reconstitution and restoration of white matter.[7]

Numerous clinical variables are now known to be associated with the development of HIV-D, including low CD4 cell count and late stage disease.[7] These are especially relevant in South Africa where the epidemic is greatest and HAART coverage is yet incomplete. The abuse of methamphetamine not only increases HIV risk behaviour, but is independently associated with neurotoxicity.[8,9] While the use of HAART has resulted in a dramatic reduction in the incidence of HIV-D, PLWHA with milder HAND do not qualify for treatment. Mild neurocognitive disorder may be a predictor of HIV-D, or at least is associated with neuropathological changes of HIV encephalitis.[10] Non-HAART treatments including the use of lithium and memantine have been studied but results are not robust enough to warrant widespread use.[8,11] In a resource-limited setting such as South Africa, broad screening for HIV-D should be routine, and the use of HAART in PLWHA who have demonstrable neurocognitive disorder should be strongly considered. The implications at an individual, community and societal level of untreated or persistent neurocognitive disorders in large numbers of individuals are substantial.

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Prevalence of HIV dementia: epidemiology and challenges

HAND remains prevalent despite HAART and clinical characteristics may be different. Prior to the widespread use of HAART, infection with HIV resulted in HIV-D in about 15% of individuals.[12] Less severe forms of HAND were found in about 30-60% of PLWHA.[12,13] The advent of HAART has substantially altered the nature of these disorders, although they do persist.[2,14] Specifically, HAART has reduced the incidence of HIV-D, but with longer life span, the prevalence appears to be increasing.[7,15] Not only does this persistence suggest either ongoing neurotoxocity, but it has implications for PLWHA who may be employed and/or need to adhere to HAART. In addition, the clinical presentation of HIV-D has changed[6], and it has been suggested that the subcortical features previously thought to be characteristic, may be less prominent.[16] As experience in the neuropsychological features of HAND has grown, it has become more apparent that cortical deficits occur frequently.

More recently, efforts to predict the neurocognitive response to HAART have intensified. Currently it is thought that people who initiate HAART prior to severe immunosuppression and achieve plasma viral suppression[17], CSF viral suppression[4] and who use CSF penetrating regimens accrue the most benefit.[4,18] In South Africa, home to the largest number of PLWHA, and despite one of the biggest anti-retroviral rollout programmes internationally, PLWHA still enter treatment late, if at all. Reasons include limited access to HAART, confusing government and media messaging regarding treatment, and socio-cultural issues (such as belief systems regarding the causes of HIV). Accordingly, the profile of this group of individuals resembles a pre-HAART cohort, with a high incidence of HIV-D. The only local study of community prevalence of HIV-D, conducted in the Western Cape reported a rate of 23.5% of HIV-D according to the HIV Dementia Scale.[19] This compares to the rate found in a study in Uganda, where the prevalence was 31%.[20]

In addition to the lateness of presentation of PLWHA, clade-specific differences may contribute to the development of HAND. HIV subtype (or clade) B is predominant in North America and Europe, while clade C is found in about 90% of South Africans.[21,22] The question of whether viral clade is responsible for differences in HAND has not been well-studied in clinical populations. For instance, the neurovirulence of HIV clade C has been associated with less severe forms of neurocognitive impairment in some studies, but with equally deleterious effects in others.[23-25] Variability has been attributed to differences in the dicysteine motif within the neurotoxic region of B-Tat, producing a greater degree of Tat-induced apoptosis.[26,27] However, other viral proteins, such as gp120, may be as neurotoxic. The clade sequence, levels of proviral DNA and tat protein, together with their impact on neuropsychological functions and neuro-imaging findings, is the subject of a study currently being conducted by our group.

Neuro-invasion and compartmentalisation

Neuro-invasion probably occurs early in HIV infection, and is associated with dissemination of HIV into lymphoid tissues, which include the CD4 helper cells and circulating monocytes.[3] All five main types of cell in the CNS are susceptible to the effects of infection, but it is thought that only perivascular macrophages and microglia are actively or productively infected.[28] These cells are derived from bone marrow. Both are immune-competent in the CNS, with microglia arising from the mesoderm- as such they bear receptors related to the mononuclear phagocytic system.[29] In the resting state they are branched, while in the activated state, they are rounded or ''amoeboid''.[28] Active or productive infection implies that HIV is constantly being produced from the cell surface, while non-productive infection implies that HIV DNA is incorporated into host cell, but not actively extruded. This latter type of infection, together with the restricted nature of the blood-brain barrier has led to the idea that the CNS is a ''sanctuary'' site or reservoir of HIV infection. The blood brain barrier is a selectively permeable membrane formed by a continuous cellular barrier with tight junctions. The passage of circulating immuno-competent cells into the CSF is tightly regulated, as is that of drugs.

A number of theories of neuro-invasion have been proposed, but it seems likely that the majority of invasion arises from the passage of HIV inside penetrating circulating macrophages (''Trojan Horse theory'') and from transcytosis- a process of HIV being actively transported through endothelial cells.[30] Perivascular macrophages are probably the cell line most infected and are also readily replenished from the circulating peripheral population.[31] These cells, together with some microglia, fuse to make up the multi-nucleated giant cells (MNGC) which are the hallmark of HIV-encephalitis.[28] HIV encephalitis is the underlying neuropathological correlate of HIV-D. MNGC express CD14 and CD15 receptors, and these are noted on neuropathological examinations.[32]

Following early CNS invasion, HIV probably re-enters the CNS throughout the course of infection during periods of either high viral load or systemic illness.[28] Despite this, phylogenetic reconstruction has suggested that HIV derived from various sites in the CNS in an individual more closely resembles its own sequences, than HIV derived from peripheral tissues.[33] In addition, unproductive infection of cell lines other than microglia and macrophages suggests that genetic drift of HIV may be small. These ideas again have led credence to the notion of the CNS as a sanctuary site.

While most PLWHA have evidence of neuroAIDS, few will develop frank clinical features. This might be explained by certain host factors (such as genetic predisposition) and the differing neuropathogenicity of HIV. One possible mechanism is differing ''fusogenic'' potential. In the CNS, cells bearing the chemokine receptor CCR5, as well as CD4, are prone to being fused into MNGC. Highly neuropathogenic forms of HIV might require lower levels of expression of these proteins, possibly leading to more rapid and/or greater MNGC formation.[34] Furthermore, certain HIV strains might evolve into separately neuropathogenic strains through the development of envelope glycoproteins which lower the need for host CCR5 and CD4 receptors.

There has been conflicting data on whether the viral load of HIV in the CSF (as opposed to the periphery) is associated with greater rates of HAND. Some studies have established that improvement in neuropsychological function is correlated with both high CNS penetration of HAART, as well as lower CSF viral loads.[4] A more recent study reported that while penetrating HAART regimens were correlated with lower CSF viral loads, these regimens resulted in poorer neuropsychological performance.[35] The relevance of the penetration of anti-retrovirals is explained below. It must be noted that in the public sector in South Africa, there is access to only a limited number of these agents.

Mechanisms of neuro-degeneration

Neurodegeneration follows a breakdown in the usual interplay between neuroprotection and neurotoxicity. These involve interactions between various protective and toxic host compounds (such as nerve growth factors and glutamate) and the effect of the inflammatory process invoked by HIV. An understanding of the role of CNS chemokines and neurotransmitters has begun to shed light on possible mechanisms of HIV neurotoxicity. Chemokines are cellular cytokines secreted in the CNS and which play various roles including cell migration, differentiation, activation and proliferation. These processes are constantly occurring. Two main families of chemokines are especially relevant to HIV: α- and β-chemokines.[28] α-chemokines (also known as CXC family chemokines) are all expressed in brain, mainly by neurons. The activated CXC receptor increases intra-cellular calcium, and may be key to excitotoxic damage.[36] In contrast, β- chemokines (CCR family chemokines) are only weakly expressed in brain. Despite being weakly expressed, certain β- chemokines play a crucial role in the development of HAND- these include monocyte chemoattractant protein-1 (MCP-1). Higher levels are thought to predict HIV-D over time.[7] Other members of the β- chemokine group may be neuroprotective, such as CCL4, which protects neurons from gp120 induced apoptosis.[36] It can then be seen that when HIV infects and activates CD14/16 bearing cells, pro-inflammatory cytokines are increased, leading to the development of both MNGC and related glial and neuronal cell damage.

Two main theories of HIV-associated neurodegeneration have been proposed. The direct injury hypothesis posits that neuronal injury occurs directly through the effect of toxic HIV proteins - gp120 and tat protein in particular - or through virus-host interactions, whereby gp120 activates glutamate receptors or TNF expression.[37] In the ''bystander'' effect hypothesis, damage occurs due to immune activation out of keeping with levels of HIV in the CNS. This amplification arises out of chemokine activation, the inflammatory activation of uninfected cells and the migration of infected T-cells into the CNS following chemo-attraction.[38]

The result of either direct or bystander effects is the neuropathological entity known as HIV encephalitis. This entity is now established to underlie well defined clinical HIV-D.[10,39] In this process, the activation of inflammatory chemokines and cytokines, including TNF and nitric oxide synthase, leads to the production of free radicals, which in turn leads to astrocyte apoptosis.[40] Astrocytes play a key role in the removal of excitatory amino acids from synapses, leading to a loss of the neuroprotection/neurodegeneration balance. High levels of inflammation and neurotransmitter dysregluation may lead to clinical features of ''encephalopathy'', while neuronal apoptosis and degradation of white matter may lead to less reversible deficits characterised by clinical slowing and subcortical effects.

The role of transcriptional transactivator (tat), a toxic viral protein bears mention. Tat has been associated with neuronal nuclear toxicity, alteration of blood brain barrier tight junctions and the upregulation of pro-inflammatory cytokines.[41] It has been found that tat expression differs between HIV clades, and further proposed that a defect in the dicysteine motif in tat in clade C leads to lower levels of neurotoxicity.[42] The implications are that in regions where clade C is predominant, such as South Africa, lower rates of HAND might be expected. Recent work in India, where clade C is also predominant has not supported this idea. Rates of HAND comparable to regions where clade B occurs, was reported in a clinical sample.[25] A large study into potential clade differences is underway by our group.

Clinical mediators of HIV dementia

A number of clinical factors are associated with the development of HIV-D, and are reviewed in this section, with a particular focus on their relevance to SA. These include the presence of neurological impairment, the abuse of methamphetamine, depression, female gender, low CD4 count and advancing age.[7,43-45]

Substance abuse and dependence are linked to both the acquisition of HIV, as well as to compounded neurocognitive effects. The use of intravenous opiates, especially heroin has been associated with the epidemic in North America, and to the co-infection with hepatitis C. In South Africa, heroin use is fairly restricted, although it has the potential to grow.[46] In addition, hepatitis C is thought to be very uncommon in South Africa, as reported by one published study in Kwazulu Natal.[47] The effect of methamphetamine (MA) on both HIV risk behaviour and neuropsychological outcomes is increasingly being studied, and is of especial relevance locally. In a sample of more than 4500 adolescents at Cape Town schools, 12-13% had used MA at least once, and MA was associated with high risk sexual behaviour.[9] There is now good evidence for the deleterious effect of MA on neuropsychological function.[48] It has been proposed that when MA abuse and HIV co-exist, additive neurotoxic effects, such as increased ischaemic events and microglial activity may occur.[8] The implications for South Africa where MA abuse is problematic are enormous.

Also of relevance to South Africa, is that the majority of PLWHA attending clinics are women, and again, that many present with late stage HIV/AIDS. The preponderance of women is a feature that differentiates the Southern African epidemic from the global one. There are some well known gender effects in neuropsychiatry, with depression being more common in women.[49] As depression is commonly co-morbid with HAND, a greater burden of disease in South Africa might be expected. There is also substantial evidence that advancing age is associated with a greater vulnerability to developing HAND, and that this may be aggravated by the use of protease inhibitor containing regimens.[8] As with persons with Alzheimer's dementia, the amyloid protein has been implicated. Specifically, high levels of β-amyloid have been observed in HIV neuropathology, as well as increases in amyloid precursor protein and gamma secretase. Tat may inhibit an amyloid degrading enzyme.[8] With the largest HIV epidemic in the world, and the accordingly large numbers of PLWHA entering treatment, we will face an ageing population with these co-factors.

Pharmacotherapy of HIV-D

Conceptually, the approach to treatment of HIV-D could be considered from either a preventive or curative view. Drug treatments can then be considered to be either directly anti-retroviral, or adjuvant. Current WHO guidelines recommend the use of HAART when either CD4 cell counts fall below 200, or a stage 4 disease-defining illness is present. Among these conditions is HIV encephalopathy. Once HIV-D is established, it may be difficult to reverse neuronal loss. This raises two central issues regarding the treatment of HIV-D: first, whether the brain is a long term reservoir of HIV, and therefore if ongoing low grade neuro-inflammation is occurring; and second, whether less severe

forms of HAND either predict or progress to HIV-D. We will now address each of these issues.

First, regarding whether the brain is a reservoir for HIV, there has been much interest in the issue of the penetration of antiretrovirals through the blood brain barrier. The ability of these agents to pass into the brain, depending on their protein-binding, molecular size and lipophilicity has been categorised into a ''CNS Penetration Effectiveness'' (CPE) rank system.[50] In this system, anti-retroviral drugs are categorised into groups according to the above criteria, with scores of 0.5, 1 and 2 being assigned to the three groups. The nucleotide/nucleoside reverse transcriptase inhibitors lamivudine and stavudine, for example, have a rank score of 0.5. Of the non-nucleotide/nucleoside reverse transcriptase inhibitors, nevirapine has a score of 1 and efavirenz 0.5. These drugs are the first line treatments in South Africa. While several studies have shown that regimens with a relatively high CPE rank (>2) resulted in better neurocognitive outcomes[4], it is not well known whether these regimens may produce neurotoxicity by virtue of their penetration, whether the benefits will persist, or if the HAART-related improvements to date have been observed in individuals with poor baseline neuropsychological performance or worse levels of immunosuppression. Long term studies which examine both the neurocognitive profile, CPE rank, as well as potential measures of antiretroviral neurotoxicity will be needed to resolve these issues. In a well known study, the addition of abacavir to an existing HAART regimen was not associated with improved neurocognitive outcomes.[7] First line treatments in South Africa achieve acceptable CPE ranks scores of between 1.5 and 2. Using a nevirapine-based regimen, a score of 2 is reached by adding the rank scores of lamivudine (0.5), stavudine (0.5) and nevirapine (1).

Second, whether or not less severe forms of HAND result in, or progress to HIV-D, are less clear. Different patterns of HIV-D have now been proposed.[15] It is suggested that some more acute and fulminant forms may be more sensitive to treatments. Nonetheless, only a small proportion of individuals will recover complete neuropsychological function. If, however, HAART could be initiated at higher CD4 counts, where less severe HAND is present, it is possible that progression to less reversible deficits may be prevented. Once HIV-D is present, effective HAART regimens should be used in the first instance. Prospective studies of these issues are sorely needed.

The issue of antiretroviral toxicity has been addressed to a limited extent in the literature, and is based on theories of systemic toxicity, scanty magnetic resonance imaging (MRS) studies, and in vitro evidence.[51-53] This type of antiretroviral neurotoxicity is independent of the phenomenon of neuroIRIS (immune reconstitution syndrome), which is thought to be rare but may result in worsening neurocognitive function despite HAART use.[54] NeuroIRIS may occur from between two and six weeks of HAART, and reflects an inflammatory response following cellular immune reactivation. IRIS is most consistently associated with opportunistic infections (OI's), such as Cryptococcus, tuberculosis or JC-virus. In a small number of individuals, clinical neurological deterioration occurs in the absence of OI's, and is thought to reflect a direct HIV-related immune response.

Adjuvant treatments for HIV-D are less well established. Treatment trials of known drugs such as memantine, an N-methyl-D-asparate (NMDA) receptor antagonist, and lithium, a complex mood stabiliser with glycogen synthase kinase-3 (GSK-3) function, have been conducted with some promising results.[11,55] While lithium may not be an ideal agent in South Africa, and particularly in PLWHA, due its narrow therapeutic index, its beneficial effects may be considered as therapeutic possibilities for other drugs. Putative treatments, based on theories of HIV neurotoxicity include chemokine receptor blockers, anti-oxidants, caspase inhibitors and entry inhibitors, but any novel agent would need to penetrate the blood brain barrier.

Outcomes in HIV-D

The effective use of HAART has clearly been associated with a significant reduction in the disease burden of HIV-D, as noted above. The incidence of HIV-D has decreased substantially.[7] In untreated HIV-D the mean survival is about six months.[56] With HAART, this has increased to two years, even in PLWHA with low CD4 counts at baseline.[57] Given that more than 20% of individuals in primary care in the Western Cape have HIV-D, there are significant implications for care.[19]

Nath and colleagues have proposed a number of subtypes of HIV-D that have emerged in the HAART era, including a subacute progressive type, a chronic inactive type, a chronic active type and a reversible type.[15] Other groups have reported ''reversibility'' or ''treatment response'' in about 30% of PLWHA with HIV-D.[58] The converse is true that more than half have persistent deficits. This means that on the one hand, a substantial number of PLHWA with HIV-D will improve, and that the use of HAART is imperative, but also that a larger number will require additional treatment support. The implications for PLWHA who are economically or socially active are enormous. To date, there are no published cohort studies in South Africa, and this is needed.

Approaches to detection, treatment and research in resource-limited settings

Given that South Africa has the largest HIV epidemic in the world, and that despite putative clade differences in neurotoxicity, it is likely that a substantial proportion of individuals entering late stage HIV/AIDS will develop HIV-D. Our approach should be three-fold:

(1) Wide-spread screening programmes:

This will involve the use of screening tools for HIV-D being integrated into primary health care. This is in order to detect covert cases of HIV-D in busy clinics, where awareness of milder HIV-D may be low. Several instruments exist, including the HIV Dementia Scale and the Brief Cognitive Neuroscreen.[59,60] A brief tool that has been validated for use in Uganda, and that can be taught to non-neurologist staff, is the International HIV Dementia Scale (IHDS).[61] Using a cut-off score of 10, the IHDS has a sensitivity and specificity of 80% and 55% respectively. The integration of the IHDS will involve training in its use, and information regarding what to do with positive screens. At clinics, where more extensive neuropsychological testing is not available, patients who screen positive may be evaluated by more experienced clinicians on a referral basis, and then initiated on HAART. Additional treatment support and follow-up should be considered. Where additional neuropsychological resources are available, referral may be an option. We recommend the use of a test battery containing tests of the following domains: attention and concentration, verbal memory, psychomotor function and executive function. Tests within these domains may include the digit symbol coding test for attention, the Hopkins auditory verbal learning test for verbal memory, the grooved pegboard test for

psychomotor speed, and the color trails tests 1 and 2 for executive function. These tests are widely used and are readily taught to technical staff with a minimum of necessary equipment.

(2) Consideration of offering HAART to individuals with higher CD4 counts

There is debate as to whether HAART should be started in PLWHA with higher CD4 counts. What is known, is firstly, that mild neurocognitive disorders (MND) are common, occurring in about 20-30% of PLWHA, depending on disease stage.[13] Secondly, the presence of MND correlates with neuropathological changes similar to HIV-D.[39] Thirdly, the presence of MND is likely to produce significant functional impairment.[62] Whether or not MND predicts progression to HIV-D is less clear. We propose that PLWHA with documented MND and functional impairment are at risk of this deterioration, and should be initiated on HAART. Prospective cohort studies are needed to define the outcomes more clearly.

(3) Prospective cohort treatment effects studies

To date, there have been no published cohort treatment effect studies in South Africa, and relatively few in Africa. Studies of PLWHA entering ARV care should be conducted with a view to describing the course and progression of neuropsychological impairment, the impact on function, and the effect of anti-retrovirals on cognition. Careful clinical characterisation may further allow for the development of predictive variables and potential biomarkers of HIV-D. In this way, a greater understanding of potential risk factors may be developed. The effect of anti-retrovirals on cognition is receiving greater attention and these studies should carefully document these.[15]

Conclusion

The involvement of the CNS in HIV- known as ''neuroAIDS''- has profound implications in South Africa where the largest number of infected people lives. Several clinical implications emerge from this review. Screening for HAND should be routinely performed in all individuals entering care, and in those with higher CD4 counts in whom a neurocognitive disorder is suspected. They should be followed up in order to describe the course and impact of neuroAIDS. In this way, we can begin to address the massive burden that dementia-associated with HIV infection poses.

Locally relevant research directions should include investigations into either ''mechanisms'' or ''treatments''. Prospective cohorts in South Africa should be studied, with a view to gathering not only data on neurocognitive problems and their course, but also the underlying host-viral interactions, such as clade-specific differences. Treatment programme research needs to consider ways of addressing the burden of disease of neurocognitive disorders, and may involve studies of epidemiology, but also of providing supportive and therapeutic approaches to individuals with neurocognitive problems. The problem of HIV dementia will not abate with widespread HAART, and novel solutions to address this burden are urgently needed.

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