HAART & the molecular biology of AIDS dementia complex

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The era of highly active antiretroviral therapy (HAART) has led to a considerable decline in the HIV disease progression rates and HIV-1-related opportunistic infections especially in developed countries. Unfortunately, antiretroviral treatment for almost 90 per cent of the HIV-infected population is not available because of cost concerns. Although a number of studies have shown uniform impact of HAART on disease progression, its effect on treating HIV infection of the brain and its manifestations, such as AIDS dementia complex (ADC), remains unclear. Along with the reasons why AIDS dementia complex continues to be a problem in the era of HAART, this review also discusses the changes in ADC patterns with HAART and its relevance in developing countries such as India. In addition, an overview of various biological, molecular and therapeutic aspects that may influence HIV dementia (HIV-D) is provided.

Key words AIDS dementia complex - antiretroviral therapy - central nervous system - HIV - HIV dementia

Human immunodeficiency virus type 1 (HIV-1) has been recognized for its ability to target the immune system and nervous tissue. AIDS dementia complex (ADC) or HIV-assosiated dementia (HIV-D) develops in about 20 per cent of HIV infected patients who progress to AIDS. The actual underlying mechanisms of the pathogenesis of ADC in adults and progressive encephalopathy in infants and children still remain obscure. In approximately 30 per cent of immunosuppressed HIV infected patients, the entry of virus into the central nervous system (CNS) initiates a syndrome which is characterized by progressive motor signs and behavioural abnormalities. In contrast, paediatric HIV encephalopathy often occurs prior to clinically obvious immunosuppression. Although the virus infects the brain at an early stage of HIV infection, the neurological disease or complications including dementia, sensory neuropathy and myelopathy tend to occur at advanced stage of HIV disease. HIV affects the CNS either directly, producing distinct neurological symptoms, or indirectly, by causing immunodeficiency resulting into susceptibility to opportunistic infections and HIV-related malignancies.
The current HIV epidemic has seen all categories of individuals (men, women, infants and injecting drug users) becoming infected with HIV, yet most neurological studies have focussed on gay men from developed countries. As the HIV-associated syndromes do not develop until the onset of advanced HIV disease, data on their development, prevalence, manifestation, intervention and management, especially in developing countries, are scanty. Similarly, women and injecting drug users from developed countries have not been studied in greater details for HIV-dementia (HIV-D).

Generally, patients have AIDS-defining illness prior to the appearance of neurological symptoms, but in some very rare cases HIV-dementia develops without profound immunosuppression in apparently healthy individuals with high CD4+ and CD8+ T cell count and below detection viraemia (Saksena et al unpublished observations). There is a good correlation between symptomatic and asymptomatic phases of HIV disease and their association with the development of HIV-D. Miller et al showed HIV-D at only 0.4 per cent in asymptomatic individuals as opposed to 16 per cent in persons with symptomatic phase of HIV disease. Before the introduction of antiretroviral therapy, the overall risk of developing HIV-D in HIV positive individuals was estimated to be at 15-20 per cent, but the exact figures in the era of highly active antiretroviral therapy (HAART) are just beginning to emerge. Some of the most intriguing questions remaining are (i) Why HIV-D continues to prevail in the era of HAART, despite considerable success of HAART regimens and protease inhibitors in particular; and (ii) Are there changes in ADC patterns in the era of HAART? We provide an overview of various mechanisms involved in the causation of HIV-D, drug penetration and distribution in the CNS and its implications on HIV-D, changing features of HIV-D in the era of HAART and effect of compartmentalisation on HIV. Further, it would also be discussed how neurological disease will affect patients in developing countries, and what measures should be taken to prevent occurrence of psychological manifestation.

Possible mechanism of HIV-1 entry and causation of HIV-D: Biological mechanisms

In the brains of patients with HIV-D, HIV is found at highest concentrations in the basal ganglia (especially globus pallidus), subcortical regions and frontal cortex as demonstrated by immunohistology, quantitative PCR and virus isolation. Thus, high HIV loads in the brain appear to be important in the development of advanced ADC but there is little correlation between severity of HIV-D and viral load. Further, the neuropathology of ADC also shows loose correlation between the extent of multinucleated giant cell formation and severity of HIV-D. Hence, there is also likely to be variability in other pathogenic mechanisms such as the individual viral strain and host cell responses to HIV infection. There is now general agreement that the cells supporting productive infection in brain are the microglial cells and macrophages, whereas the neurons and oligodendrocytes are relatively rarely infected. The route of CNS infection appears to involve circulating activated monocytes (CAM), which increase in proportion as the disease stage of an individual.

Since the emergence of a subset of circulating monocytes during HIV-1 disease appears to correlate with cognitive impairment, it has been hypothesized that diagnostic protein profiles may be obtained from
this monocytic subset especially for patient at risk for HIV-D\textsuperscript{17}. Wojna \textit{et al}\textsuperscript{17} with the help of sophisticated proteomic techniques (surface enhance laser desorption/ionization-time of flight protein chip assay) have elegantly shown with a case study seven unique proteins between 3 and 20 kD in monocyte-derived macrophages (MDM) from patients with HIV associated dementia (HAD), which were absent in the control group. Further, all these proteins were abrogated after HAART. Recently, Sun \textit{et al}\textsuperscript{17} have also shown that there is loss of macrophage-secreted lyzozyme in HIV-D as shown by SELDI-TOF mass spectrometry. Thus, both studies confirm macrophage dysfunction as a significant consequence to HAD and both emphasize the utility of MDM profiling for the diagnosis and monitoring of HIV-D.

Cell types, other than macrophages also get infected with HIV-1. Non-productive infection of astrocytes with the expression of \textit{nef} and \textit{rev} in infants with HIV-related encephalopathy has been reported\textsuperscript{19,20}. Hence the observed neuronal dysfunction and loss of neurons in advanced HIV-D (20-40% in the frontal lobe) must be due to indirect factors such as neurotoxins and cytokines. Astrocytosis induced during brain infection may also be a critical event in HIV-D, as dopamine system may be damaged, which may have profound consequences in clinical manifestation of HIV-D.

Viral determinants of ADC: molecular mechanisms

The underlying molecular mechanisms governing ADC remain controversial and poorly understood. As in HIV infection in general, variability in viral and host factors almost certainly determine the likelihood of ADC in HIV-1-infected patients. Neurologic disease is often caused by single amino acid changes in the surface proteins\textsuperscript{21}. Characteristic changes in the env gp120 V3 loop and the macrophage phenotype associated with macrophage tropism are also associated with microglial tropism\textsuperscript{22,23}. They are also involved in influencing the infectivity of macrophages and T-lymphocytes\textsuperscript{23-28}. It is thought that characteristic changes within the V3 loop of the envelope and the macrophage phenotype correlate with progression to severe ADC\textsuperscript{3,29}. Two independent studies\textsuperscript{24,25} have shown association between molecular changes in the envelope V3 loop region and the development of HIV-D. Two mutations specifically of residues 305 and 329 were shown to correlate with HIV-D\textsuperscript{23,24} and these changes were absent in non-demented patients. Although several studies\textsuperscript{24-27} have found differences between blood and brain-derived strains from patients with ADC, these have failed to show similar consistent changes in residues 305 and 329, which would be correlated to ADC in HIV infected individuals. Further, our detailed studies\textsuperscript{28,29} also failed to show any evidence for consistent molecular changes that segregate demented and non-demented patients. Thus, it is likely that single amino acid changes or the biological nature of infecting strains may be accountable for the neurologic disease manifestation in HIV infected individuals\textsuperscript{29}.

Chemokine receptor usage and neurotropism

CCR5 and CXCR4 are the two major chemokine co-receptors used by HIV together with CD4 receptor for gaining entry into the target cells. The entry of HIV into the brain and its interaction with recently discovered chemokine receptors still remain obscure. Classically, the entry of HIV into the brain is either across the blood-brain barrier or from the cerebrospinal fluid (CSF). It is now accepted that the T-cell line tropic HIV-1 strains use the chemokine receptor CXCR4 [previously known to be stromal-cell derived factor (SDF-)1], a powerful leukocyte chemoattractant\textsuperscript{30}. By contrast, CC-chemokine receptor CCR5 is utilized primarily by macrophage-tropic non-syncytium inducing HIV-1 strains\textsuperscript{30}. CCR5 is known to be a key player in the initial infection by macrophage tropic strains of HIV-1.

The chemokine receptors could also play a major role in viral entry into the brain. He \textit{et al}\textsuperscript{31} reported that the microglial cells in brain express CXCR4, CCR3 and CCR5. This infection of microglia is predominantly supported by macrophage-tropic HIV-1 strains, and to a much less extent with T-cell tropic strains. In addition, other studies have shown that certain HIV-1 isolates preferentially grow on microglia, and not on macrophages, suggesting that
strains infecting macrophages may differ. Because HIV-1 infection of microglial cells is one of the most important steps in HIV infection of the brain and the development of neurocognitive disorders/impairment\textsuperscript{32}, both CCR5 and CCR3 could play a critical role in HIV neuropathogenesis. The exact role of CCR3 remains controversial because of the unavailability of \textit{in vitro} data confirming the previous observations by He and colleagues\textsuperscript{31}. We have conclusively shown that brain-derived isolates predominantly use only CCR5\textsuperscript{29}.

In our studies we have demonstrated greater heterogeneity in HIV genotypes from different regions of the brain, and high homogeneity in viral strains from blood of the same patient with AIDS dementia complex\textsuperscript{38,33}. These data suggest that viral strains evolve independently after they cross the blood-brain barrier. We have also dissected the biology of each of these strains from both demented and non-demented patients and found evidence that the biological nature has more to do with influencing the disease manifestation than the envelope genotype of infecting strains\textsuperscript{29}. These biological differences had immense influence on tropism of viral strains, with tropism for monocytes, T cells and macrophages in strains from non-demented patients, as opposed to largely M-tropic strains from patients with dementia\textsuperscript{29}. Thus the biological nature of HIV-1 strains residing in the CSF and brain, along with the host factors, may influence the manifestation of neurologic symptoms.

\textbf{Drug resistance, viral compartmentalization and HIV-D}

Strict adherence to HAART is critical in determining its success. Incomplete adherence, non-compliance, sub-optimal dosing and pharmakokinetic drug interactions can rapidly lead to the emergence of drug resistance\textsuperscript{14}. There is a evidence showing significant correlation between cognitive impairment on HAART and adherence. Thus, drug resistance emergence in the CSF, blood and the CNS may have remarkable impact, because the positive effects of certain antiretroviral agents, which penetrate the blood-brain barrier efficiently, may be compromised\textsuperscript{35}.

A serious concern is that in the era of HAART, HIV-D continues to be a problem. Thus, the degree of regional compartmentalization of drug resistant viral variants during HAART suggests that poor and perhaps differential penetration of antiretroviral drugs may occur in the CNS. This may encourage the independent development of HIV quasispecies in regions of the brain with characteristic resistance profiles through a milieu of sub-therapeutic drug concentrations. This phenomenon may further be accentuated by the varied tropism of HIV variants arising as a consequence of selection pressures imposed on HIV in each of the local areas, and also by cellular differences in the CNS that may display differential permissibility to antiretroviral drugs. A great concern arises in that mutations conferring resistance to multiple antiretroviral drugs may predominate in brain regions where drug levels are sub-optimal\textsuperscript{36}. Hence the CNS may become a source and a reservoir for multiple drug resistant viral strains that may emerge systemically at the failure of therapy.

We also reiterate that, in addition to resistance mutations, we have also observed a marked absence of drug resistant mutants in certain areas of the CNS in almost all patients\textsuperscript{35}. Presently, there is no clear explanation for the notable absence of resistance in certain regions\textsuperscript{35}, but several studies have shown that drug concentrations \textit{in vivo} can vary considerably from one tissue type to another, or one organ to another, during therapy\textsuperscript{37,38}. In addition, some compartments including the CSF\textsuperscript{39}, genital secretions\textsuperscript{40}, and lymphoid tissue\textsuperscript{41} have been shown to be poorly accessible to different antiretroviral drugs. In rhesus monkeys a dramatic difference in the levels and concentration-time profiles of lamivudine (3TC) between lumbar and ventricular CSF was observed\textsuperscript{42}. Therefore, the sub-optimal therapeutic drug levels in the CNS, and poor penetration of these drugs in various regions of the CNS, may be a more likely explanation for the independent evolution of drug resistant variants in diverse areas of the CNS. Cumulatively, the spectrum of primary and secondary resistance mutations in diverse areas of the CNS, which develop as a consequence of the administration of ART or HAART, may significantly influence the outcome of therapy both in the CNS and systemic circulation\textsuperscript{35}. In our study a detailed analysis of drug resistant HIV-1 genotypes regionally compartmentalised in diverse
regions of the CNS during antiretroviral therapy is reported. Our data have clarified that, both primary and secondary resistance mutations are regionally distributed in diverse areas of the CNS, which may be significantly important in a clinical context. It remains unknown which cell types in the CNS may harbour resistant virus and permit their active replication and propagation, and whether poor penetration of drugs and sub-optimal drug concentrations have some role in encouraging viral replication of independently evolving viral quasispecies in diverse areas of the CNS. Nonetheless, further clarification of these aspects may have important implications for future design of antiretroviral treatment strategies for treating CNS infection and will allow a greater understanding of the correlation between drug resistant genotypes and HIV-D.

**Distribution and penetration of antiretroviral agents in the CNS**

The CNS is highly delicate and evolutionarily built to protect against intrusive chemicals. The downside is that the same mechanisms, which protect brain against intrusive chemicals, also render it a difficult compartment for therapeutic intervention. Many pharmaceutical agents struggle to penetrate the CNS effectively and are poorly sustained within the CNS compartment.

The CNS is a key anatomical reservoir of HIV-1 in both treated and untreated patients. Independently evolving HIV variants have been detected in diverse areas of the CNS, which are genetically distinct from those found in the blood of the same patient. As a consequence, it has been hypothesized that the CNS may act as a sanctuary site for HIV and render the virus less susceptible to antiretroviral treatment. Pathological studies have suggested that macrophages and macrophage-related microglial cells are the primary CNS sites of HIV infection. Other studies have also provided evidence that macrophages and microglial cells are the primary source of HIV in the CNS, and a non-syncytium inducing, macrophage tropic phenotype is more common in HIV variants from this compartment. CSF serves as an independent compartment for viral replication, a feature that may be related to differences in HIV viral load dynamics between the peripheral blood and CSF.

Unique anatomical structures limit the distribution of anti-HIV drugs into the CNS. These structures are the blood-brain barrier located between the blood and brain tissue, and the blood-CSF barrier primarily formed by the choroid plexus. High plasma protein binding of protease inhibitors (PIs) and their unidirectional efflux by P-glycoprotein membrane proteins in the blood-brain barrier limit the penetration and absorption of antiretrovirals into the CNS. As a result, the CNS (which also encompasses the retina) represents a site in which ongoing viral replication may occur. Further, a greater concern arises in that mutations conferring resistance to multiple antiretroviral drug classes may predominate in compartments where drug levels are sub-optimal. Hence, the CNS may in some cases be a source of ongoing replication for multiple drug resistant HIV strains. As systemic treatment may not reduce the CNS viral load due to inadequate penetration of drugs, investigation into new methods of delivery is of paramount importance. So far, nucleoside analogs are the most characterized of the antiretroviral agents in terms of CNS distribution.

**Distribution of nucleoside reverse transcriptase inhibitors (NRTI) in the CNS:** Currently, there are five available nucleoside analogs: zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T) and lamivudine (3TC). AZT crosses the blood-CSF barrier and its distribution into the CNS is the most studied among the NRTIs. As a consequence, it has been hypothesized that the CNS may act as a sanctuary site for HIV and render the virus less susceptible to antiretroviral treatment. Pathological studies have suggested that macrophages and macrophage-related microglial cells are the primary CNS sites of HIV infection. Other studies have also provided evidence that macrophages and microglial cells are the primary source of HIV in the CNS, and a non-syncytium inducing, macrophage tropic phenotype is more common in HIV variants from this compartment. CSF serves as an independent compartment for viral replication, a feature that may be related to differences in HIV viral load dynamics between the peripheral blood and CSF.

Previous studies have shown that AZT crosses both the blood-brain and blood-CSF barriers by passive
diffusion, a process recently demonstrated using a bilateral in situ brain perfusion technique\textsuperscript{64}. While it is not metabolized to any discernible extent in the brain, the effectiveness of AZT treatment may be reduced by the efflux of this drug from the CNS through active transport mechanisms\textsuperscript{55,61}.

Uptake and penetration of ddI into the CNS is poor\textsuperscript{65,66} and its mechanism of entry is probably passive diffusion. The efflux of ddI from the CNS is prominent and similar to that of AZT, and occurs through an active transport process. The CNS distribution of ddC is similar to that of ddI in humans. The low uptake of ddC in the CNS is partially due to limited penetration of the blood brain barrier, a factor related to its octanol/water coefficient and high solubility in water\textsuperscript{67}. The entry of ddC may be mediated, at least in part, by a nucleoside transporter\textsuperscript{50}, and it is believed that there may likewise be an active efflux mechanism of ddC from the CNS. Only a limited number of studies have been conducted on the penetration and effect of 3TC in the CNS. These have shown that its distribution in the CNS is poor\textsuperscript{68}. Since 3TC is structurally related to ddC, it is hypothesized to have similar absorption and efflux properties in the CNS. Some studies have suggested the existence of a dynamic efflux transport system in the blood-CSF barrier and possibly the blood-brain barrier\textsuperscript{42}. Other studies on both humans and animal models have indicated that d4T penetrates into the CNS to a substantial degree\textsuperscript{69,70}. It is thought to enter the CNS via passive diffusion\textsuperscript{50}, but further studies are required to confirm this, and to clarify whether d4T is actively transported out of the CNS.

**Distribution of non-nucleoside reverse transcriptase inhibitors (NNRTI) in the CNS:** Few studies are available regarding the CNS distribution of NNRTIs, which are potent anti-HIV agents. These drugs act by binding directly to the active site of the RT and so prevent the replication of HIV.

Resistance is a major problem in this class of drugs, limiting their effectiveness\textsuperscript{71}. Approved and commonly used drugs in this class include nevirapine, delavirdine and efavirenz. Nevirapine has been shown to have the best blood-brain barrier permeability among anti-HIV agents including nucleoside analogs (AZT, ddI, ddC and d4T) and protease inhibitors (saquinavir, indinavir and amprenavir) in an in vitro study using bovine cerebral endothelial cells\textsuperscript{72}. In the same study, delavirdine was found to have undetectable blood-brain barrier permeability. A study using an experimental NNRTI drug (atevirdine) in the treatment of AIDS dementia complex showed improved neurologic function in four of five patients who completed the trial, no firm correlation was found between this clinical response and the atevirdine level in CSF\textsuperscript{73}.

**Distribution of protease inhibitors (PIs) in the CNS:** Little data are available concerning the CNS penetration of PIs. In rats the penetration of indinavir into the CNS was limited\textsuperscript{49}, and it is thought the extent of CNS distribution of other PIs is likely to be limited and poor. The reduced CNS distribution of saquinavir, ritonavir and nelfinavir may relate to the fact that these PIs are highly protein-bound in the plasma (over 98%). In contrast, the protein binding of indinavir is only 60 per cent\textsuperscript{49}. In addition, most PIs are substrates of P-glycoprotein (P-gp) which acts as an efflux pump limiting the extent of the PI distribution in the CNS. Nonetheless, some PIs have been found to have a favourable effect on the treatment of ADC, producing stabilization or near complete regression in white matter disease correlating with cognitive improvement\textsuperscript{74}. An experimental compound, amprenavir, in combination with AZT and 3TC resulted in CSF viral loads below detection (<400 copies/ml) within 32 wk after initiation of treatment. Amprenavir was the second best anti-HIV agent in terms of uptake in cerebral endothelial cell lines, in the study conducted by Glynn and Yazdanian\textsuperscript{72}. The drug crosses the blood-brain barrier well. In individuals treated with HAART, the incidence of AIDS and HIV-D has decreased\textsuperscript{75}. However, antiretroviral treatment is not always effective, or universally available, and the long-term effects of even transient viral replication in the CNS are not clear\textsuperscript{76}. Thus the role of HIV infection and replication in the CNS, and its correlation with the development of CNS disease and dementia remains an important and unresolved issue. It has been hypothesized that the CNS may act as a sanctuary for HIV and render the virus less susceptible to antiretroviral treatment\textsuperscript{43,77}. As a result of inadequate drug...
penetration into the CNS, systemic antiretroviral treatment may fail to prevent viral replication and have little effect in reducing the viral burden of this compartment.

Sub-optimal drug penetration also influences the emergence of multiply drug resistant variants, which may also predominate in this anatomical viral reservoir. Discordant changes in peripheral blood and CSF HIV-RNA levels have been reported in response to antiretroviral therapy. Similar and discordant patterns of antiretroviral drug resistance have been detected in the RT and protease genes of isolates from the blood compartment and the CSF of the same patient. A better understanding of the ways in which drug resistant mutations emerge in HIV populations of the CNS, and possibly other anatomic compartments, which have similar barriers to drug penetration such as testes, and the development of more efficacious antiretroviral drugs are of paramount importance to achieve and maintain consummative therapeutic drug levels in the CNS.

**Macrophages and antiretroviral therapy:** Macrophages and cells of macrophage lineage are crucial in HIV infection of the brain. In addition, macrophages may shield HIV from the effect of highly active antiretroviral regimens containing PI, due to the action of P-glycoprotein transporters in their membranes. P-glycoprotein is responsible for the unidirectional transport of selected substrates, including PIs, across key tissue barriers such as the CNS blood-brain barrier and the gastrointestinal tract, limiting the absorption of antiretroviral drugs in these compartments. The resistance of macrophages to the uptake of PIs is likely to result in sub-optimal drug concentrations and increases the likelihood of drug resistance in this compartment.

The overall capacity of this transporter system to reduce drug concentrations in macrophages, and its biological relationship to HIV persistence remains an open area of investigation. The design of agents that inhibit the P-glycoprotein transportation system may be useful, but the use of such a strategy must be approached with caution as many physiological side effects may occur. The extent to which macrophages serve as a long-lived sanctuary for HIV in the face of potent HAART remains to be determined, and until such data are available, it is difficult to conclude whether macrophages serve as a true HIV reservoir *in vivo*.

**Advantages and pitfalls of HAART:** It is now recognized that a potent combination of three or more antiretroviral agents (two NRTIs and one/two PIs or one NNRTI) can allow an extended suppression of HIV replication *in vivo*. This can augment the immune response paving the way for the reconstitution of the host’s immune system. A full recovery of the immune system would require not only replacement of lost T cells, but also the correction of aberrant levels of immune system activation back to normal levels. However, even after extended periods of HAART, immune reconstitution appears incomplete in many cases. Host anti-HIV immunity often gradually declines upon the achievement of viral suppression during therapy, perhaps as a result of the reduced exposure to HIV antigens which may be crucial factors in maintaining immune activation. In other words, while some infected individuals may experience the expected benefits of HAART (low viraemia, sustained rise in CD4+ and CD8+ T cells, and reduction of viral evolution), others remain poor responders and fail to maintain vital host antiviral immune responses. The underlying reasons for poor immune responses during HAART are unclear, and may stem from viral factors (resistance) and/or host factors (P-glycoprotein efflux, adherence, genetics, etc.). Investigation into individualized treatment strategies for such patients seem warranted.

Expansion in the polyclonality of CD4+ and CD8+ repertoires in concomitance with decreasing plasma viraemia and improvements in peripheral blood mononuclear cell (PBMC) production of IL-2 and IL-12 can occur during PI-based HAART, but reports show that virus may rebound to levels above baseline values after stopping therapy.

The toxicity of antiretroviral drugs is a subject of intense debate, and has been a prominent topic at various international forums. As HIV infection becomes a “manageable” disease with greatly reduced morbidity and mortality attributable to reduced immunodeficiency, the identification,
monitoring and clinical management of the adverse effects of antiretroviral therapies assumes proportionally greater importance in the clinical setting. Several adverse effects of individual antiretroviral drugs have been recognized, such as effects related to the CNS (e.g., irritability related to efavirenz), mitochondrial toxicity and hyperlactatemia with NRTIs, and lipoatrophy, cardiac disease and hepatotoxicity from the use of NRTIs and other antiretroviral drugs.

**Changing features of HIV-D in the era of HAART**

The era of combination ART has certainly produced considerable delays in disease progression rates in developed nations, but the prevalence of HIV-D is on the increase in contemporary cohorts of HIV-infected individuals. In the HAART era, the manifestation of neurological disease has certainly become less severe and more manageable. Both newly diagnosed moderate to severe dementia have fallen from 6.6 in 1989 to 1 per cent in year 2000.

Before the use of HAART, the incidence of HIV-D appeared to be stable among individuals with advanced stage of disease. In pre-HAART era, the mean CD4+ T cell count at the time of the diagnosis of HIV-D was between 50-100 cells/µl blood depending on patient group examined, whereas in the era of HAART this mean CD4+ T cell count has jumped to 160/µl blood. The actual underlying reasons for this elevation upon HAART introduction remain unclear. It has been hypothesized that the failed restoration of specific defect in immune function related to HIV-D, or it may suggest that the HIV disease duration is becoming more critical, or it could be due to both. The mean time to death, which was 6-9 months in pre-HAART era has increased to >44 months in post-HAART era. There are several conditions, which deserve particular attention. These conditions do suggest that HIV-D in the era of HAART appears to be transforming. The basal ganglia hypermetabolism, which was the typical of HIV-D and correlated with neuropathological changes in basal ganglia in the pre-HAART era, does not appear to be a prominent feature of HIV-D in post-HAART era. In contrast, the mesial temporal lobe abnormalities have gained more prominence and relevance in post-HAART era. In pre-HAART era, temporal lobe changes were commonly seen in patients with HIV-D, but now they appear to be less conspicuous as determined by positron emission tomography and neuropathological testing. Before the introduction of HAART, the standard CSF markers, such as beta-2 microglobulin and HIV viral load in the CSF were considered to be important in diagnosis of HIV-D, but now they no longer fully correlate with the presence or severity of HIV-D in HIV patients.

A remarkable change is that most HAART treated patients with neurological manifestation of HIV disease remain more stable. In some cases partial reversal of symptoms with neurological deficits have been observed after a few years on HAART. Although biological reasons for this reversal are unclear, but adherence and compliance to therapy are critical for the management of HIV-D. Drug fatigue usually results in poor adherence, which, in turn, may lead to the development of drug resistance. Further, although speculative, it is likely that many of these patients with few years on HAART may have responded maximally to HAART and may have been left with a fixed deficit, perhaps due to neuronal loss. Thus, intensification of HAART may have little effect in repairing cognitive loss.

As a consequence of HAART, three distinct forms of HIV-D can be observed: (i) A ‘subacute progressive’ dementia in therapy naïve patients with clinical syndrome of severe and progressive dementia comparable to pre-HAART era; (ii) A ‘chronic active’ dementia, in patients, with HAART who show evidence of poor adherence to drug regimen and in some cases the emergence of drug resistance. This group is pre-disposed to risk for neurological disease progression; and (iii) A ‘chronic inactive’ dementia in patients on HAART who adhere to drugs, are fully compliant and show effective suppression of viral burden in both CSF and plasma and have shown signs of recovery from neuronal injury. This group is more stable.

HAART may also be associated with chronic form of AHIV-D. A prospective positron emission tomography (PET)-cerebrospinal fluid (CSF) study has also highlighted that there are changes in ADC.
in the era of HAART. The PET study included patients who developed HIV-D over several years in the presence of below detection viral loads in both plasma and CSF compartments. Patients treated with HAART for two years, who are neuro-asymptomatic, also have shown elevated levels of neopterin and normal levels of HIV CSF RNA copies and beta-2 microglobulin in both blood and the CSF. These data suggest that HAART cannot restore all CSF functional deficits to normal. The reasons could be (i) Partial functional loss prior to initiation of HAART, or (ii) Poor penetration of antiretroviral drugs into the CSF, which are unable to achieve below detection limits of HIV RNA copies. It is clear that various CSF markers of immune activation such as neopterin, beta-2 microglobulin and quinolinic correlate with the severity of HIV-D and they decline with HAART treatment. In pre-HAART era, the levels recorded for all the aforementioned CSF markers were highly elevated in patients with HIV-D as opposed to post-HAART era. Thus, antiretroviral therapy that achieves maximal reduction in CSF HIV-1 RNA would be expected to provide the greatest protection against HIV-D. At this stage, this is speculative and more trials are needed to confirm this.

Although HAART has changed the forms of ADC, the emergence of resistant forms of HIV to both RT and PIs has shown the resurgence in the frequency of HIV encephalitis, and HIV leukoencephalopathy in AIDS patients failing HAART. It is characterized by massive infiltration of HIV-infected monocyte/macrophages into the brain and extensive white matter destruction. Recently, it has been proposed that this condition may be caused by interactions of anti-HIV drugs with cerebrovascular endothelium, astroglial cells and white matter of the brain. These interactions may cause cerebral ischaemia, increased blood-brain permeability and demyelination. This study concluded that with HAART severe forms of HIV encephalitis appear to be emerging as the epidemic matures. The main factor attributing to this is the prolonged survival of HIV patients, which may predispose them to prolonged exposure to virions and viral proteins and selection of more virulent and neurotropic viruses in the face of HAART.

Conclusions

The antiretroviral treatment is slowly becoming available in India. At present, there are two problems in India and other developing countries regarding HIV-associated neurological disorders: clinical inaccuracy/ unawareness and pathological inaccuracies. To monitor for HIV-D clinically it is really education of health care workers for the correct use of HAART. Therefore, physician awareness and training are two essential components for proper control of HIV and its manifestations.

Recently, it has been reported that persistent neurological abnormalities can be seen in therapy naive HIV infected individuals. Such studies have direct relevance in Indian context. Proton magnetic resonance spectroscopy and neuropsychological tests were performed on HIV patients naive for therapy followed by 3 months of HAART. These data revealed that despite significant improvement in CD4+ T cell counts and suppression of plasma and CSF viraemia, elevated brain metabolites (choline compounds and myoinositol in the frontal lobes) and neuropsychological deficits persisted post-HAART. The persistent abnormalities in the brain suggest an ongoing repair or reactive inflammatory processes in the brain after 3 months on HAART. Regimens with 2 CSF-penetrating antiretroviral agents do not appear to be more effective than just one CSF-penetrating agent. As ADC is under-diagnosed, and the assessment of neurological deficits is poor due to socio-economic segregation of HIV patients in India, such studies on persistent neurological damage on HIV-infected therapy-naive and experienced patients in India are warranted. These will not only shed light on what HIV does to the brain in naïve patients, but will also show some novel features of neuropathological aspects of HIV, which pre-HAART era in the developed countries missed out on. In addition, association of HIV-1 subtype dispersal in geographical locales and its influence on ADC can be determined.

The relevance of these studies in the context of developing countries is enormous, because people living with HIV are growing older. According to the CDC report, rates of persons living with AIDS suggest
that the older adults (>50 yr of age) account for up to 15 per cent of AIDS case load, representing an increase of about 5 per cent from 1997-1999. Studies are also required in older people living with AIDS as antiretroviral therapy has augmented the survival time for HIV patients, some living for at least 10-20 yr more. These trends emphasize a need for basic epidemiological research on HIV and HIV-associated CNS complications in India and other developing countries. Research is also needed to determine the mechanisms at work in an ageing immune system and to determine whether there is a difference in immune reconstitution after HAART between younger and old age categories infected with HIV, and how such differences can influence the manifestation of neurocognitive dysfunction. It remains poorly understood whether the neurocognitive complications in HIV disease are due to the processes typical of functional ageing or whether there is considerable influence of HIV disease on ageing process. Therefore, there is a continued need for reassessment and further refinement of HIV-D in the elderly and its clear effect in the younger age categories. In India, the incidence of HIV-D in asymptomatic subjects appears to be lower compared to HIV-infected individuals in the USA and Europe (1 to 2% in India as opposed to 15 to 30% in USA and Europe).

Though genetic diversity between subtypes is well documented, the subotypic genetic differences have never been attributed to disease manifestation. Subtype C is the most prevalent subtype circulating in India. Recently, Ranga et al95 have targeted Tat protein because of its association with monocyte chemotactic function. Analyses of Tat sequences representing nine subtypes revealed that at least six amino acid residues are differentially conserved in subtype C Tat protein. Of these, cysteine (at position 31) was highly (>99%) conserved in non-subtype C viruses and more than 90 per cent of subtype C viruses encoded a serine. The C-Tat due to the disruption of CC motif was defective for monocyte chemotactic activity without a loss in the transactivation property. While the CC mutant was functionally competent for both the functions, in contrast, the SC mutant was defective in both. Because Tat could influence monocyte chemotactic function and increased monocyte migration of HIV-1 to the brain has been correlated with HIV-D. These analyses conclude that the loss of the C-Tat chemotactic property may underlie the reduced incidence of HIV-D in India. Although not fully conclusive, it points to an important epidemiologic phenomenon, which could be potentially exploited for further research. This should include subtype C viruses from other geographical regions, such as South Africa where subtype C predominates.

References


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