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Neuro AIDS

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- Professor Kevin R. Robertson, Director of Neuropsychology, University of North Carolina at Chapel Hill
- Professor Ned Sacktor, Johns Hopkins University School of Medicine
- Professor Colin Hall, Vice Chair, Department of Neurology, University of North Carolina at Chapel Hill
- Dr Richard Price, Professor of Neurology, San Francisco General Hospital
- Professor Girish Modi, Chief and Chair of the Division of Neurology, Academic Head of the Department of Neurosciences at the University of the Witwatersrand, South Africa
- Dr Gretchen Birbeck, Chikankata Epilepsy Care Team, Mazabuka, ZAMBIA

Part one: Intro and HIV dementia

By Theo Smart

HIV dementia and other HIV-related neurological problems may be common in Africa according to a recent Ugandan study published this week in *Neurology* (see

<http://www.aidsmap.com/en/news/3FB04917-EF5B-425B-B2D0-CF363BF4B4FC.asp>). In fact, a growing number of studies suggest

that the burden of neurological problems caused directly by HIV could be grossly under-appreciated in resource-constrained settings.

One reason is that healthcare workers in resource-limited settings don't know how to recognise HIV-related neurological conditions.

"It's surprising how many people have clinical difficulty with the relatively common neurological complications of HIV infection," said Dr Steve Miller, in a presentation on the management of the key HIV-related neurological diseases at the Botswana International Conference on HIV/AIDS held last September in Gaborone. But he acknowledged that, for a variety of reasons, diagnosing HIV-related neurological conditions in resource-limited settings isn't always easy.

The neuropsychiatric presentation of a person with HIV can be very complex. Diagnoses can be complicated by a variety of psychiatric factors, including ongoing illicit drug or alcohol abuse, and clinical depression or post-traumatic stress disorder, which could be pre-existing or related to the HIV seroconversion (or the disclosure of it) — and which could be equally important to diagnose and manage. In addition, there are a wide variety of inherited or acquired conditions which may vary by settings and demographics, including poor nutrition, endemic infections (such as malaria), medications (including antiretrovirals) and, of course, opportunistic infections (OIs) and neoplasms. Several of these factors at the same time may contribute to the neurological presentation observed in a person with HIV.

"The relative importance of HIV dementia in sub-Saharan Africa has been considered small in comparison to the burden of CNS OIs," according to Dr Ned Sacktor of Johns Hopkins University School of Medicine, who was senior author of the Ugandan study.

Furthermore, neurocognitive changes are often overlooked in very ill patients. "In countries that have few if any neurologists, and where HIV infection often presents with an overwhelming

opportunistic infection such as tuberculous or cryptococcal meningitis, it is no surprise that what can seem to be mild cognitive deficits are underrecognised or considered unimportant (much the same can be said for depression)," wrote Brew and González-Scarano in an editorial also in this week's *Neurology*.

However, that appears to be changing and in addition to the Ugandan study, HIV dementia is now the focus of an international meeting, the Assessment of NeuroAIDS, the second of which was held last July in Tanzania, as well as ACTG 5199, a large multicentre international study (see Part 2).

Part of the shift in focus, is due to the increasing access to antiretroviral therapy (ART) which can potentially halt and even reverse the neurological problems caused by HIV. However, it is not clear exactly this will play out in resource-limited settings.

"Studies in the developed world indicate that while the incidence of HIV-dementia in sub-Saharan Africa may...decrease after the widespread introduction of HAART, its prevalence may increase as HIV-positive patients live longer. This increase could create a "second epidemic" of cognitively impaired individuals in the region," wrote Wong et al. in the recent paper in *Neurology*.

Furthermore, if ART treatment is not begun soon enough in someone developing HIV-related neurological impairment, it may not be possible to completely reverse all the neurological damage that HIV can cause and the improvements seen on ART might only be transient, with degeneration eventually continuing again even while people are otherwise responding to treatment (see below).

Given the burden of HIV disease in the developing world, it is crucial that the assessment and management of HIV-related neurological problems receives better attention both in research and in the clinic.

"It is time to formally study and include HIV associated dementia and its related cognitive problems as important complications that should influence the timing of introduction of antiretroviral therapy," wrote Brew and González-Scarano.

Mental health services and research are neglected in most resource-limited settings

But this may be easier said than done. Research into HIV related neurological problems may be difficult in parts of the world where mental health services have long been neglected.

For example, a mental health profile of Zambia published in 2004 claimed that the mental health system in that country was in a state of total disarray — which in turn made it next to impossible to assess the true burden of mental illness there (Mayeya).

According to the Zambian report, the situation evolved in that country, because infrequent reporting of mental illness led to the field being ranked low in the nation's list of health priorities: "Mental health services were subsequently overlooked.... The result was that delivery of the country's mental health services deteriorated. Potential funding agencies and cooperating partners were not keen to put money into mental health and district health management teams stopped prioritizing mental health."

While each country is, of course, unique, the Zambian paper demonstrates the sorts of the public health, psychosocial, and economic factors that commonly influence the mental health services and policy in resource poor countries. It describes a host of primarily psychosocial stress factors such as widespread poverty, unemployment, homelessness, the loss of family members (or parents) to AIDS and other diseases, alcohol or drug abuse that affect the mental health of the population. Like many other

developing countries, there are also large numbers of extremely traumatised refugees from conflicts in neighbouring countries, victims of ethnic or political violence; and hundreds of thousands of people have also been displaced internally because of natural (droughts or floods) and manmade disasters.

In addition, rape and other violence against Zambian women is epidemic. Women, who are disproportionately at risk of HIV infection, are also “forced by circumstances to continue living in abusive relationships to the detriment of their mental well-being,” wrote Mayeya et al. “Some men and women believe that in order to show not just how superior a man is to his wife, but how much he loves her, he should beat her—at least occasionally.”

Given such pressures, one would expect that a lot of people would have trouble coping and that mental illness would be rife. Yet relatively few Zambians ever seek out mental health services. One reason (and a factor that inevitably leads to the under-reporting of mental illness in the country) is the stigma attached to mental illness. For example, “to a large extent in Zambia, people who are mentally ill are stigmatized, feared, scorned at, humiliated and condemned... There are a variety of cultural beliefs about the cause of mental illness in Zambia. Some believe that it is a form of spirit possession or social punishment. Others, that it is caused by witchcraft and can only be treated through traditional means and not conventional medicine.”

In another report from Zambia from the first NeuroAIDS conference, Dr Gretchen Birbeck and colleagues, who were investigating the incidence of HIV dementia in the general populace, reported that stigma rendered one particular neuroassessment tool, the Neuropsychiatric Inventory (NPI) (which involves interviewing family members about a subject’s mental health) virtually useless (Birbeck). “The cultural unacceptability of the NPI became apparent when family members refused to discuss issues of aggression, agitation, hallucinations or depression in any abstract terms (Robertson).”

According to the Zambia mental health profile, when help is sought, it is usually from traditional healers who “are initially consulted by about 70–80% of people with mental health problems,” rather than medical doctors. Communication between such traditional practitioners and the medical establishment is rare and contributes to the under-reporting of these conditions.

Even when care is sought at the local clinic or hospital, the staff may not be well equipped to diagnose the condition. Finding or adapting culturally and resource- appropriate tools for the assessment of neuropsychiatric health has been a major challenge because most screening tools were designed for Americans or Western European norms (Robertson). Recently, with the development of the simple International HIV Dementia Scale (see below), it may be possible to perform some basic screening even at the primary health care level and then refer patients suspected of having a psychiatric or neurological problem.

However, in many settings there may simply be nowhere to refer patients to. In many countries, there is a severe shortage of staff trained to diagnose or manage neurological complaints at the referral level. Most countries have few if any neurologists. And in Zambia “referral services used to be available (1975–1990) but have collapsed due to lack of coordination,” wrote Mayeya et al.

The physical infrastructure has also been neglected in many countries. “The buildings lack maintenance, most of the lavatories are non-functional...” according to the Zambian report. Moreover, access to working neuroimaging equipment, which is very useful for the differential diagnosis of several neurological conditions, may be extremely limited (perhaps to only a few facilities within a country).

For example, neurologists from Mali stressed at the NeuroAIDS conference that they had no access to MRIs in the country (although they could perform CT scans) (Traore).

According to Dr Birbeck, “Even CT technology is largely unavailable to the vast majority of people in sub-Saharan Africa. There are two CT scanners in Zambia and at any point in time neither may be working...even if one were fortunate enough to have geographical access to the scanner. There is no MRI in Zambia or Malawi. I don’t think Uganda has one. And one has to remember that even if a scanner exists, geographical and financial barriers prevent the vast majority of people from being able to access the technology.” (Birbeck 2000, Birbeck and Munsat).

As a result of all these issues, the lion’s share of neuropsychiatric problems in many resource-constrained countries probably go unrecognised, under-reported, undiagnosed and untreated.

Therefore, concluded the Zambian report, “a comprehensive picture of the incidence and prevalence of mental and neurological disorders per 10,000 population is not well known.” However, records from one referral hospital there suggest that acute transient psychotic states are more commonly encountered, followed by schizophrenia, substance misuse, epilepsy and dementia.

Given the high HIV prevalence in Zambia (over 20%), one might presume that many of the mental disorders observed would be HIV-associated. However, in another study evaluating risk factors associated with a first episode of psychoses among 160 subjects admitted to Chainama Hills College Hospital, in Lusaka, clinical evidence of HIV/AIDS was found in only 9%. What was far more striking was that most cases were men (male to female sex ratio was 2.5:1), and that alcohol and other drug abuse were common in these psychotic males (56%) (Mbewe). Thus, neurological problems related to other social ills or demographic conditions may be at least as prevalent as those caused by HIV.

Psychiatric problems in the HIV-infected population commonly go unaddressed, may overlap with neurological problems that HIV causes directly

Furthermore, many of the mental illnesses first observed in a person with HIV are likely to be psychiatric disorders, rather than neurological disease caused by HIV infection — and these can be severe enough to impair someone’s ability to function.

For example, clinical depression (with a high risk of suicide), anxiety disorders (especially post-traumatic stress disorder (PTSD)), substance abuse, and psychoses have all commonly been associated with HIV infection. Some of these conditions may actually precede infection (and could be what puts a person at risk of HIV acquisition in the first place) while others develop subsequent to, or as a result of HIV infection.

Reports from the developed world suggest that people with HIV are more likely to experience these mental health problems, not least because the vulnerable groups most affected by HIV: gay men, refugees, sex workers and migrants and drug users, are already more likely to have mental health problems. These observations are likely to hold true wherever such marginalised and oppressed groups are most affected by HIV, but it is not clear whether the same exact patterns will bear out in the more generalised epidemics in sub-Saharan Africa.

However, given the increased vulnerability of women to violence, it is not surprising that there appears to be a high rate of PTSD

among HIV-infected women in South Africa. For example, in one study from researchers at the University of Stellenbosch, twenty-two out of 149 people (14.8%) diagnosed with HIV/AIDS recently (on average within the past six months) met criteria for PTSD (Olley 2005).

"In some cases," the authors noted, "PTSD is secondary to the diagnosis of HIV/AIDS but in most cases it is seen after other traumas." Those with PTSD were significantly more likely to be suffering from concurrent psychiatric conditions including major depressive disorder, suicidal ideation and social anxiety disorder. They were also more likely to be women and to have a history of sexual violation within the past year. In another study from the same team, after six months longer follow-up, there was a new onset of PTSD in several cases, for a total prevalence of 20%. Overall, the second study found a high baseline prevalence of psychiatric disorders, in 56% of patients.

Depression was the most common mental illness observed (diagnosed in close to 35% of PLHIV evaluated (Olley 2006)). Over a longer course of HIV infection, an even greater number of people can be expected to develop clinical depression as a result of poor health or simply of being HIV-positive, particularly in settings where having HIV is so highly stigmatised.

Some of the symptoms of depression, such as trouble concentrating, confusion or forgetfulness and of severe anxiety related to PTSD, such as agitation or psychoses, may be difficult to distinguish from neurological illnesses that HIV can cause directly. For example, cognitive impairment is one of the core signs of HIV-associated brain disease, but at least one longitudinal study in gay men found that in earlier disease severe depression could actually impair cognitive performance to a similar extent (Baldewicz).

In this study, researchers compared cognitive performance in 59 HIV-positive and 55 HIV-negative men every 6 months for 8 years. While fine motor speed and speed of information processing was more impaired in those with AIDS, compared to the asymptomatic HIV-positive and HIV-negative men (combined), on several cognitive indicators, the asymptomatic HIV-positive men actually performed worse than the men with AIDS. The cause for this appeared to be severe depression.

However, as the study's findings suggest, the cognitive impairment caused by HIV itself rather than by depression tends to be coupled with other progressively degenerative neurological problems caused by the virus — particularly motor problems.

HIV dementia and its nomenclature

According to a presentation by Dr Colin Hall at the NeuroAIDS conference, it is this combination of cognitive and motor dysfunction that makes HIV dementia or brain disease a clinically unique syndrome, and it is often accompanied by the two other primary HIV-related neurological conditions: peripheral neuropathy and myelopathy (spinal cord disease) (both to be discussed in a future HATIP article).

There are several terms used for HIV-related brain disease including:

- AIDS dementia complex, because of its significant cognitive derangement;
- HIV-associated minor cognitive or motor deficit disorder (MCMD), generally less severe impairment albeit associated with functional disability;
- sub acute HIV encephalitis, largely a histological and CSF description of the condition;

- or simply HIV-associated dementia (HAD) or HIV dementia (HIV-D). (Some neurologists use either of the two later terms to refer to HIV-related CNS disease overall, while others use it only for later stage disease).

"The fact that it has all these synonyms gives one a clue [about] the clinical manifestations but also points to the fact that we don't really have the full picture of what this condition is about," Dr Miller said in the Botswana meeting. "Typically in clinical situations, we find patients with those conditions have behavioural changes, memory impairment and motor dysfunction. But the changes one sees may be subtle or they may be very overt and one can see one or more of these characteristics in combination."

HIV-D (MCMD) begins with slight changes in behaviour, intellect and co-ordination. Friends and family notice forgetfulness, changes in personality and symptoms normally characteristic of depression, such as loss of appetite and motivation. Tasks that require concentration or complex thought become difficult. These symptoms could be interspersed with sharp mood swings or mania. Motor skills gradually deteriorate: hands become clumsy, movement is slow and unsteady and eye movements become jerky.

The more subtle signs seen with MCMD may occur with CD4 cells as high as 300, but without ART, generally progress to HIV-D if the patient survives long enough (Stern). This could justify using the diagnosis of MCMD as an indication for immediately going on ART rather than waiting for CD4 cells to fall below 200 — and for classic HIV-D to develop.

"Classic" HIV dementia accompanies late-stage immune suppression (CD4 <200/cells/mm³ in most) and has the following characteristics (from Dr Hall's presentation):

- Early concentration/memory difficulty
- Losing track of conversation
- Progress to difficulty with written material
- Apathetic appearance, indifference
- Generally not depressed, occasionally manic, psychotic
- Often marked response slowing
- Generally progressive motor dysfunction with slowing (several reports stress difficulty with fine finger movement)
- Gait ataxia, difficulty turning
- Progress to cane-wheelchair
- Bladder/bowel incontinence
- Hyperreflexia, increased jaw jerk and snout, abnormal saccades (ability of the eyes to track/pursue movement between two points)

Once the symptoms of HIV-D become unmistakable, there is a very poor prognosis — and without treatment, death usually follows within months or even weeks (Hall).

The pathogenesis of HIV neurological damage isn't well understood

Although it is clear that HIV invades the central nervous system early in the course of infection — and remains sequestered there — "we don't really know what causes it in terms of the molecular mechanisms," said Dr Miller. Although studies show that HIV does cross the blood-brain barrier, infecting macrophages or microglial cells, there is no evidence that it can productively infect neurons (Hall, Robertson).

One possibility is that interactions between viral proteins such as gp120 or tat may lead to nerve cell damage, as could local changes in immune or inflammatory activity in response to the infection (Shui, Brana). For example, there is considerable evidence of imbalances of cytokines such as tumour necrosis factor and some of the interleukins in the CNS of people with HIV. Altered chemokine MCP-1 metabolism has also been blamed (Gonzalez).

Alternatively, viral products or inflammation could cause neurotransmitter problems, such as those between glutamate and calcium transport. More recently, there has been evidence of profound and progressive disturbance of dopamine transport in people with HIV-related CNS problems (Wang).

Regardless, around the time of HIV seroconversion, some people develop an acute syndrome phase with encephalitis, with a presentation similar to mononucleosis, or some other neurological symptom. These will usually get better on their own, although there are rare reports of coma and death (Hall 2004). However, development of this acute HIV encephalitis could suggest a predilection for the neurological disorders developing later in the course of disease.

Studies give widely varying estimates of incidence and prevalence in developed countries

Whether HIV-related neurological damage is gradual and ongoing from that point or mostly occurs in later stage disease (at higher viral loads) is unclear. But by the time of death, close to 90% of people with AIDS have evidence of CNS damage attributable to HIV, according to autopsy studies conducted before the advent of antiretroviral therapy (ART) in the developed world — even though changes in behaviour may not have been observed during the patient's lifetime (Elder and Server, 1998).

Also, pre-ART, it was estimated that anywhere between 40-70% of people with HIV developed some degree of cognitive impairment (Robertson, Wilson). ADC was less common, generally evolving only once CD4 cell counts fell to less than 200 cells/mm³. According to an analysis of the MACS cohort study, ADC developed in 15% of people with HIV (McArthur 1993). A later analysis, conducted when mono and dual nucleoside therapy was in use, reported that only 7% of people with HIV developed dementia annually (though 15-20% would develop it cumulatively) (Sacktor 2001).

Since the use of ART, HAD seems to have become much less common — developing in around 1% of people with HIV per year (Hall 2004). However, some reports suggest that HAD might only be delayed in people on ART and that, with increased survival, neurological problems are increasing in prevalence (Dore 1999, 2002; Ives 2001). This may be increasingly likely in older patients (Becker 2004; Cherner 2004; Valcour 2004a,b).

In contrast to the pattern seen pre-ART, people on ART may develop HIV related-brain disease at much higher CD4 cell counts (possibly up to 300), but tend to progress much more slowly. (Dore 2002) (More on the impact of ART below).

Prevalence of HIV-related brain disease in resource-limited settings

But these are findings reported in developed countries. "Very little is known about the prevalence of ADC and milder neuropsychological dysfunction in HIV-infected people in resource-limited settings," wrote Dr Kevin Robertson and colleagues in a report on the first conference on the Assessment of NeuroAIDS in Africa held in 2004. Different studies have produced dramatically different results. For example, in one study in the late 1980's, researchers reported that

the prevalence of ADC in Sub-Saharan Africa was as low as 3% (Belec) while another published the same year claimed it was as high as 54% of 200 people with AIDS in Tanzania (Howlett). Then a few years later, another study in people with HIV in Zaire found dementia in only 9% (Perriens).

To some extent this could be due to differences in assessment methods (or the appropriateness of assessment tools to different settings) (Robertson). So in a later study, WHO conducted an investigation into HIV-related cognitive impairment using standardised assessment screening procedures on 602 HIV-positive and 353 HIV-negative individuals from Thailand, Zaire; Kenya and Brazil. The study found rates of neurological impairment ranged between 13-19% in symptomatic patients. When the same individuals were given a neurological examination, a substantially greater proportion of symptomatic individuals were reported to have neurological impairments (41% Zaire, 40% Kenya, 66% Thailand and 54% Brazil) (Maj).

More recently, the study by Dr Birbeck had used a variety of tools to assess HIV-related neurological impairment in patients from Lusaka, finding memory problems in 52% of participants, changes in thinking in 33% of the participants and gait problems in 58%.

In the Ugandan study, published this week in *Neurology* and presented in preliminary form by Dr Noeline Nakasujja at the first NeuroAIDS conference, detailed demographic, neuropsychological, neurological, and functional assessments (including using the International HIV Dementia Scale or IHDS as a simple screening tool (see below) were adapted and translated for use in that setting. Twenty-four of 78 (31%) of the HIV-positive patients attending the AIDS clinic were found to have HIV dementia ((see <http://www.aidsmap.com/en/news/3FB04917-EF5B-425B-B2D0-CF363BF4B4FC.asp>).

Since verbal memory, psychomotor, and functional performance worsened with advancing HIV disease, and since the patients were directly compared to normative data obtained by evaluating 100 matched HIV-negative subjects from their community, the findings seem unrelated to underlying poor mental health in that setting.

In contrast, a recent blinded study of HIV-positive (n=73) and HIV-negative (n=87) Ethiopian subjects, found little significant differences between the two groups — using either the IHDS or more involved neurological assessments, according to a presentation by Dr David Clifford at the 2006 NeuroAIDS conference. However, in general, performance on the neurological assessments was lower than Western norms in both the controls and HIV-positive patients. For example, it is telling that peripheral neuropathies were found in around 15% of *both* HIV-positive and HIV-negative study participants. Overall, CNS or PNS abnormalities were detected in 20% of the HIV-negative group and in 34% of the HIV-positive group, but the difference was not statistically significant (p=0.1431). Even so, this is a fair amount of impairment among the HIV-negative group considering that 90% could read and write and 95% were working full time — suggesting that neurological disorders could be under-reported and untreated in Ethiopia, just like in Zambia.

Dr Clifford also suggested that the differences between the Ethiopian and Ugandan study findings could have been due to differences in the level of experience or training in the examiners, differences in the populations' demographics or individual or viral genetics. For instance, Ugandans are primarily infected with HIV-1 clade D, Ethiopians with HIV-1C (which is also more common in Southern Africa. Some researchers believe that there may actually be an important difference in neurotropism between the HIV clades, however, research to clearly demonstrate this has yet to be published.

However, the most obvious explanation is that the patients in Ethiopia had less advanced HIV disease and were drawn from the community, while those in Uganda were drawn from the clinic with lower CD4 cell counts (median 260 in Ethiopia, mean 217 in Uganda) and lower Karnofsky scores (mean 95.7 in Ethiopia, mean 74.8 in Uganda). It should also be noted that the US pilot study for the IHDS screening tool detected neurological impairment in a patient population that generally had a CD4 cell count nadir below 200.

Dr Clifford noted one other potential explanation for why the Ethiopian study (as well as other studies in other resource-limited settings) failed to find as high of a prevalence of neurological problems: “early death may have removed impaired individuals in population.”

Indeed, in many settings, people with HIV often died of other conditions before progression to advanced disease, when neurological symptoms become more overt. However, as HIV diagnosis and the general standard of care for people with HIV improves globally (such as with the rollout of cotrimoxazole prophylaxis), healthcare workers should expect to see more neurological complaints due directly to HIV (Price 2004).

Part 2 of this article – Diagnosis and treatment – follows in a separate email.

Screening for HIV dementia

International HIV dementia scale (from Sacktor 2003)

Memory-Registration – Give four words to recall (dog, hat, bean, red) translated into the local language (in Luganda: kopo, engatto, doodo, myufo) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed:

Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.

- 4 = ³ 15 in 5 seconds
- 3 = 11-14 in 5 seconds
- 2 = 7-10 in 5 seconds
- 1 = 3-6 in 5 seconds
- 0 = 0-2 in 5 seconds

2. Psychomotor Speed:

Have the patient perform the following movements with the non-dominant hand as quickly as possible:

1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.

- 4 = 4 sequences in 10 seconds
- 3 = 3 sequences in 10 seconds
- 2 = 2 sequences in 10 seconds

- 1 = 1 sequence in 10 seconds
- 0 = unable to perform

3. Memory-Recall:

Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).

- Give 1 point for each word spontaneously recalled.
- Give 0.5 points for each correct answer after prompting
- Maximum – 4 points.

Total International HIV Dementia Scale Score

This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of <10 should be evaluated further for possible dementia.

Further assessments and diagnosis of dementia

According to the South African Handbook of HIV Medicine, at the referral level, assessment generally starts by taking a patient's thorough history, and performing a careful physical exam to find any underlying illness and whether any special investigations are needed. “Staging the patient is a crucial step in determining the likely aetiology of a neurological problem.”

Dr Hall also emphasized that the neurological disorders caused by HIV become more common as CD4 cell count fall and with higher plasma or CSF viral loads. A neurological assessment should find the characteristic clinical picture (as describe above).

The International Neurological Study (ACTG 5199 – see below) has assembled a battery of neurological tests that may help trained (and equipped) neurologists assess the functional parameters that are impaired in HIV-D (downloadable as pdf and powerpoint files from the NeuroAIDS conference site

<http://nerve.neurology.unc.edu/ana/archive.htm>). However, in light of the Ethiopian study, which used some of the same performance tests, it is probably advisable for neurologists to establish norms for each indicator among the general population in their local setting.

Diagnosis also requires that viral, bacterial and fungal opportunistic infections of the CNS must be ruled out (this will be discussed in a future HATIP). Although it can be helpful to perform CSF and radiological evaluations (particularly to rule out OIs and neoplasms), the neuroimaging abnormalities typically observed with HIV-D are not always specific to the condition.

“Typically these individuals will have changes on CSF evaluation and on neuroimaging, but there are really no specific or diagnostic features on either of those two investigations that reliably tell you, this is HIV-associated dementia and nothing else. And perhaps this is why it's such a complicated condition to diagnose,” said Dr Miller.

However, he noted that neuroimaging characteristically shows cerebral atrophy. “Some of the features that are associated with HIV dementia on MRI picture are a very enlarged ventricular system, which is a reflection of the brain cell atrophy that occurs, and very high signal intensities at the junction of the gray and white matter are very typical of changes that are seen in people who have this problem.”

Treatment of HIV dementia

The first and most obvious treatment for HIV-related CNS disease is ART – and improvements on treatment may be dramatic (Robertson

2004). This appears to correlate with viral activity in the CNS. For example, a recent autopsy study showed a significant drop in brain tissue viral load in patients treated with ART in the previous three months, and many other studies show sustained improvement in neuropsychological function after several months of ART in both adults and children (Hall 2006).

And recently, Dr Sacktor presented data at the NeuroAIDS conference showing clear improvement in cognitive performance after three months on ART in a study of 23 Ugandan patients (96% of whom had some neurological impairment at baseline). IHDS scores went up from a baseline of 8.0 to 10 at three months and to 12 after six months.

However, Dr Hall stressed that a few large studies now show that significant neurological deficits are still common in treated populations, with an overall current prevalence of 30%, a prevalence 37% in those with CD4 cell counts below 200, and with progressive deficits reported in some treated subjects (Sacktor 2002, McArthur 2003, Albert).

In the first study, an analysis of the Adult AIDS Clinical Trials Group (AACTG), A5001 ("AACTG Longitudinal Linked Randomized Trials (ALLRT) Protocol" which involved 1498 subjects all on ART, 43% were found to be neurologically impaired at baseline (this correlated with a nadir CD4 cell below 200). More than half of these were unimpaired after 52 weeks on therapy, while 19% who were unimpaired at baseline became impaired (Median 93 weeks).

In another study, ACTG 362, of 643 subjects on ART who were followed prospectively for neurological problems. 57 participants had neurological impairment at baseline, 47% of these remained impaired at week 48, while 6% of the unimpaired developed neurological disorders over the course of the study.

According to Dr Hall, ART may not always stop CNS progression because most "antiretrovirals have poor penetrance across the blood-brain barrier." Since the virus remains compartmentalized in the brain, there may be continuing replication in the CNS (in fact, virological failure in the CSF appears to be common) and could cause continuing neurological decline.

Several antiretrovirals, including the nucleoside analogues: AZT, d4T, 3TC and abacavir, and the non-nucleoside analogue reverse transcriptase inhibitors: efavirenz and nevirapine, have been suggested as having better CSF penetration, though it is not clear how this reflects on levels within the actual brain tissue — or even whether this is indeed necessary for clinical response.

"Many people have tried to link this to actual drug penetration into the brain or into central nervous system compartments and look at drug levels. But as yet, I think we can't obviously say that any of that data is meaningful. There's much we don't know about the penetration of antiretrovirals through the blood-brain barrier and the blood CSF barrier and even though actual measurements of certain antiviral drugs looks low in CSF, one nevertheless sees a very good clinical outcome," said Dr Miller.

Nevertheless, Dr Hall stressed that it is "probably reasonable to add these [CNS penetrant antiretrovirals] in neurologically impaired patients."

The International Neurological Study

And of course, with the exception of Dr Sacktor's small study, most of those data again come from developed countries. To address this in a wider number of resource-limited settings, the US National Institutes of Mental Health (NIMH) and NIAID AIDS Clinical Trials Group is conducting a multicentre international study, to explore the effects of antiretroviral therapy on cognitive functioning in

resource-limited settings. ACTG 5199: The International Neurological Study (Robertson, Kumwenda, Supparatpinyo) will enroll a maximum of 880 subjects at 11 sites including Blantyre and Lilongwe, Malawi; Harare, Zimbabwe; Johannesburg and Durban, South Africa; Pune and Chennai, India; Rio de Janeiro and Porte Alegre, Brazil; Lima, Peru and Chiang Mai, Thailand. More information is available online at <http://nerve.neurology.unc.edu/ana>.

Other potential therapies for HIV dementia

Several other adjunctive medications have also been proposed for HIV-D and are being evaluated in clinical trials. For example, calcium channel blockers have been proposed. However, an American trial of one such drug, nimodipine, ACTG 162, was stopped in 1995 after no benefits were seen (Navia).

Dr Miller noted that most recently the old anti-convulsive valproic acid has been suggested as worth investigating due to its affect on dopamine transporters and changes in various transporter proteins involved with that neurotransmitter. However, valproic acid has also been shown to stimulate HIV replication from latently infected cells.

Finally, at the recent NeuroAIDS conference, a couple of presentations suggested a potential role for minocycline, an off-patent antibiotic, a derivative of tetracycline, which readily crosses the blood-brain barrier (Sacktor 2006, Zink). The drug is safe and well tolerated in trials with up to four years of follow-up, and has been on the market for 30 years, used for acne and rheumatoid arthritis. Data from the SIV macaque model suggest that it has an anti-inflammatory and neuro-protective affects, and may even directly inhibit viral replication in the brain (Zink 2005).

Dr Sacktor is primary investigator for a multicentre trial of minocycline for HIV-infected patients with neurological disease. Minocycline is also moving into clinical trials in Uganda.

Development of this particular adjunctive therapy (if it works) might be particularly useful in Africa, because in addition to being cheap, safe and off-patent, according to a presentation by Dr Christine Zink, it may also reduce peripheral neuropathies, and has activity against malaria and other common infections such as chlamydia.

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Resources

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Also presentations from the Assessment of NeuroAIDS conference are available online at:
<http://nerve.neurology.unc.edu/ana/archive.htm>].

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