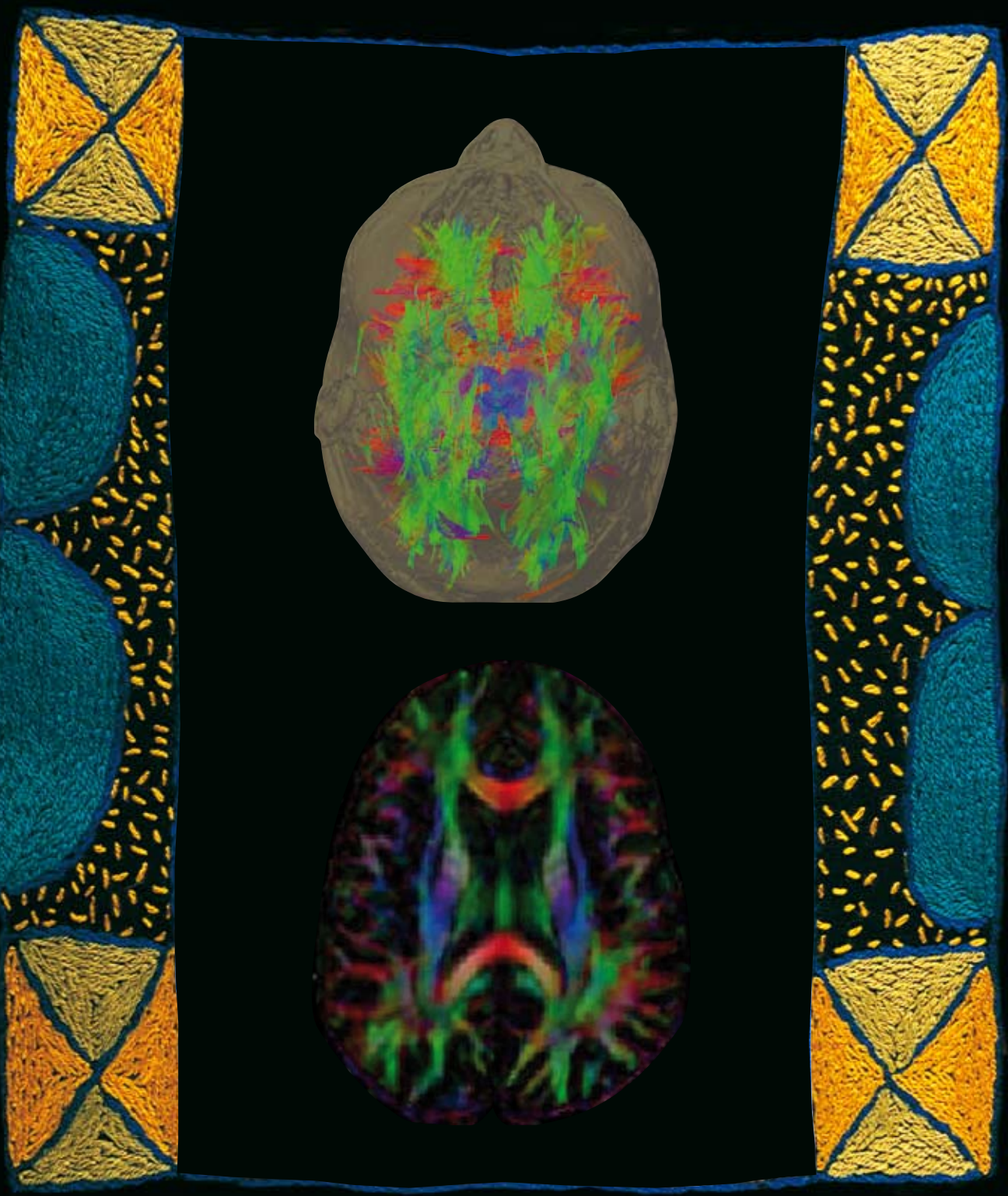
SOUTHERN AFRICAN
# JOURNAL
OF HIV MEDICINE



OCTOBER 2009

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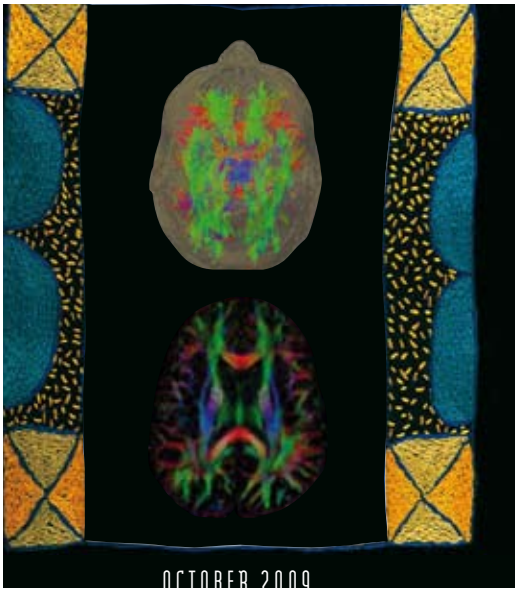
SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE

ISSUE THIRTY-FIVE

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***Cover:*** *These figures are a representation of the white matter tracts in a human brain and were created by an imaging technique known as tractography. Images that capture the self-directionality of water diffusion in the human brain can be acquired by an MRI scanner and are known as diffusion-weighted images (DWI). The direction and integrity of white matter fibres can be calculated from each pixel in a DWI to reconstruct fibres, as shown in the cover images (see article, p. 35).*

*Images courtesy of CUBIC (the Combined Universities Brain Imaging Centre), situated at the Tygerberg campus, Stellenbosch University, and established as an initiative by UCT and Stellenbosch University and Siemens to facilitate neuro-imaging research in Africa.*

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Printed by Tandym Print
ISSN 608-9693

# FROM THE EDITOR

I am delighted to introduce you to our guest editors, who have done a sterling job in pulling together this 'Mental Health in HIV' edition.

They are two Capetonian colleagues who I am also fortunate to consider friends: John Joska is a psychiatrist and Landon Myer is a public health specialist.

John Joska is a senior specialist and lecturer in the Department of Psychiatry and Mental Health at the University of Cape Town. He is head of the Division of Neuropsychiatry, Western Cape provincial programme manager for HIV Psychiatry, and director of the GSH-HIV Mental Health Group. The latter is a newly formed group of mental health professionals who are providing service and investigating the effects of HIV on people living with HIV/AIDS (PLWHA) from a mental health point of view. Current research projects include investigations into neurocognitive disorders in HIV, screening for mental disorders in HIV, and brief psychological interventions in PLWHA with depression.

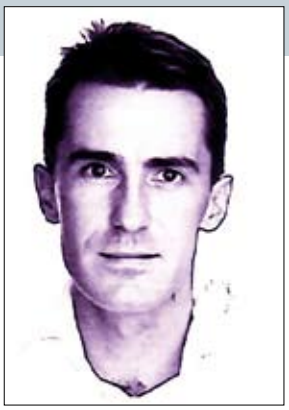
Landon Myer is an associate professor in the School of Public Health and Family Medicine at the University of Cape Town. His research focuses on the roles of HIV/AIDS and other infectious diseases in shaping individual and population health in southern Africa. He is particularly interested in how the HIV epidemic influences other areas of population health, including mental health and women's reproductive health. In investigating these topics, his research incorporates biological mechanisms, individual behaviours and exposures, as well as structural socio-economic and health service conditions.

I am sure you will agree that with their colleagues they have provided a feast of important reading for you all in this edition.

**LINDA-GAIL BEKKER**
*Editor*

# EDITORIAL

## ADDRESSING MENTAL HEALTH IN ROUTINE HIV CARE AND TREATMENT



As this journal's readers are well aware, HIV has complex and wide-ranging impacts on the health of infected individuals. Much of this complexity is due to the nature of host-virus interactions and the pathophysiology of the virus and its sequelae in different organ systems over time. Other aspects are linked to the profound impact an HIV diagnosis has on the life of an infected individual, both through physical morbidity and the psychological and social consequences of a lifelong illness.

The area of mental health is a critical example of the diverse impacts of HIV on patients' health and well-being. The links between HIV and mental health are multiple: risk taking associated with HIV acquisition is more common among individuals with mental disorders; common mental disorders (such as anxiety, depression and alcohol/substance disorders) are often caused in part by the stress of an HIV diagnosis and related stigma; psychotic states are a relatively common presentation of HIV-infected individuals; and neurocognitive manifestations of HIV infection such as HIV-associated dementia emerge later in the course of disease. Taken together, mental disorders may be viewed as their own class of 'opportunistic' conditions affecting HIV-infected individuals in a unique manner.

Dealing with the various mental health impacts of HIV infection is a core component of effective HIV care and treatment. Anxiety and depression among HIV-infected individuals can negatively impact on medication adherence; in these situations, management of mental disorders can help facilitate the management of HIV disease over the long term. The neurocognitive manifestations of HIV disease are a significant cause of morbidity; increasingly we are recognising that these disorders may

be managed effectively, including by early initiation of antiretroviral therapy, to improve the prognosis of affected individuals. In short, basic mental health care is part of good HIV management.

In this context, there is a clear need to make the diagnosis and management of mental disorders more feasible in general HIV care and treatment settings. At the primary and secondary levels of the health care system, medical officers and physicians must be able to identify patients with a possible mental disorder and work up these patients to arrive at a preliminary diagnosis, make management decisions, and follow up patients over time. Support from specialist psychiatrists is necessary in some instances, but most cases do not require specialist referral, and the availability of psychiatric services to support HIV care and treatment is limited in most settings across the region.

This special issue of the journal aims to address this need through a series of focused contributions from leaders in HIV mental health from across South Africa. The first two pieces focus on anxiety and depression in HIV in broad terms (Thom) and post-traumatic stress disorder specifically (Pingo). Following this, the topic of psychotic presentations in HIV is dealt with by an algorithm for the diagnosis and management of psychosis in HIV (Jonsson) and then an extended case study (Boyles) to help reinforce key concepts. The topic of neurocognitive impairment in HIV/AIDS is discussed in detail (Singh) with a short report on the white matter changes that take place in the brain over the course of HIV disease (Hoare) as well as a piece of empirical research investigating the clinical utility of one commonly used tool to identify neurocognitive deficits in HIV (Ogunrin). The final piece deals with cross-cutting issues of prescribing psychotropic medications in the context of HIV infection (Parker). Throughout, these pieces aim to address issues in mental health faced by front-line HIV clinicians on a daily basis, with practical strategies for investigation and management. It is our hope that the contents of this issue may make some contribution towards helping HIV clinicians to better recognise and treat mental disorders in their patients.

**LANDON MYER**
**JOHN JOSKA**
*Guest Editors*

# MESSAGE FROM THE EXECUTIVE

The large International AIDS Society meeting has come and gone from Cape Town. The agenda was dominated by a New Big Idea, an audacious mathematical model by a group of brave World Health Organization modellers showing that giving antiretroviral therapy to everyone with HIV, immediately, could make the epidemic disappear.

We've known for a long time that viral load correlates with infectiousness, whether it is sexual contact, PMTCT or other forms of exposure. ART is so highly effective in reducing viral load that the Swiss created an uproar a year ago by claiming that someone on ART with an undetectable viral load (and no STD) could not transmit HIV sexually.

The WHO researchers essentially argue that if we diagnose HIV quickly and treat everyone who is HIV positive, irrespective of CD4 count, we can arrest sexual transmission early and pretty much eradicate HIV within 10 years. Subsequent papers have even postulated that we could reverse the TB epidemic, as HIV drives this like fuel on a fire. Finally, early economic work has shown 'test and treat' to be cost saving, despite significant initial investment.

There is broad acknowledgment that HIV prevention programmes have been very disappointing, and that even effective interventions such as male circumcision and good PMTCT are unlikely to eradicate the epidemic alone. It is exciting that researchers are thinking creatively, and that models showing we can reverse things are out there.

But to implement this incredibly ambitious model would require a complete restructuring of health systems. We would need to do HIV testing aggressively and provide adequate, easily available ART services, as broadly as possible. The health system would have to be transformed from the lumbering unfriendly giant it is at the moment to a responsive and effective service deliverer. The reality is that we need this anyway, even if the modellers are wrong.

**FRANCOIS VENTER**
*President*

# COMMON MENTAL DISORDERS IN PEOPLE LIVING WITH HIV/AIDS

**Rita Thom,** *MB ChB, DCH, FCPsych, PhD*
*Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg*

The term 'common mental disorders' is an overarching term for conditions that affect a significant number of people in the community. These conditions include depression, anxiety and substance use disorders. In contrast, so-called 'severe mental illnesses' (such as schizophrenia or bipolar mood disorder) are conditions that usually require admission for inpatient treatment and tend both to recur and to be chronically debilitating. Nonetheless, common mental disorders result in a considerable burden to the individual, their families, the community and the economy. Many people with these conditions do not present for treatment, or if they do they usually present to primary care facilities, where these diagnoses are often missed. This is unfortunate, since there is good evidence that these disorders can be effectively treated[1-2] and that much of this treatment can be provided by primary care clinicians.[3]

In South Africa, depressive and anxiety disorders are common in the general population. According to the World Health Organization-led South African Stress and Health (SASH) study, the 12-month prevalence of depressive and anxiety disorders (combined) was 12.6%,[4] while the lifetime prevalence of these disorders was 25.6%.[5] Similarly, the SASH study found a 12-month prevalence of 5.8% and a lifetime prevalence of 13.4% for substance use disorders.[4-5]

## COMMON MENTAL DISORDERS IN HIV-INFECTED INDIVIDUALS

There is good evidence from international research that the prevalence of depression and anxiety in people living with HIV or AIDS is higher than the prevalence of these disorders in HIV-negative controls.[6] One meta-analysis suggests that the prevalence is at least double that in the general community.[7] There is growing evidence that this is true in South Africa and other African countries.[8-13]

The main factors contributing to the increased prevalence of depression and anxiety in individuals living with HIV are:

**Biological,** resulting from both direct and indirect forms of neurotoxicity due to HIV invasion of the central nervous system and the sequelae of immunocompromise. The areas predominantly affected are the sub-cortical areas of the brain, including those within the temporal lobes, which are the seat of emotional/mental disorders.[14] Depressive and anxiety disorders that occur as a result of HIV CNS infection often co-exist with cognitive impairment that is also the result of this infection (see Box 1). Opportunistic conditions such as herpes simplex infection and various malignancies, as well as certain medications used to treat these conditions and antiretroviral medications, can also cause depression or anxiety.[15-16]

**Psychological.** The prevalence of depression and anxiety in people living with HIV or AIDS is similar to that in people suffering from other serious, chronic and life-threatening medical illnesses.[17] A major factor is the psychological reaction to having such an illness. The individual is faced with the reality of serious illness and possible death at an early age. In many cases there are additional stressors related to the stigma associated with HIV/AIDS and lack of social support for the infected individual (see Box 2).

**Primary psychiatric disorder.** Some individuals may be particularly vulnerable to depression and anxiety as a result of genetic loading or early childhood adversity.[18] Some HIV-infected individuals may already have a history of such mental disorder, or the stress of the illness (and the psychosocial consequences) may precipitate a depressive illness and/or an anxiety disorder. In addition, the time of first onset and presentation with primary psychiatric disorders is generally in young adulthood, and this is also the time when most people infected with HIV present for treatment or are diagnosed with the infection. Depressive or anxiety disorders may be completely unrelated to HIV status, or the underlying mental disorder may have contributed to the events associated with acquiring HIV infection (e.g. alcohol abuse and sexual risk taking).

**TABLE I. CLINICAL PRESENTATIONS OF COMMON MENTAL DISORDERS IN PRIMARY HIV/AIDS CARE SETTINGS**

| Presentation | Features |
|---|---|
| Somatic | Headache, backache, abdominal pain - may be atypical, or show limited response to somatic treatments |
| Insomnia | Common presentation; an important depressive symptom |
| Other neuro-vegetative symptoms | Fatigue, weight loss, loss of energy and libido |
| Low mood or depression | May be expressed differently, such as 'stress' or tension |
| Substance abuse | This commonly coexists with depression, and may be a presenting feature |

Several of the most frequently observed presentations of common mental disorders are listed in Table I. Identifying depression in a medically ill individual can be difficult owing to the overlap in somatic symptoms (e.g. loss of appetite or weight, sleep disturbance, pain, fatigue, poor concentration). It is important to consider mood and affect, particularly if alterations in these are constant, unvarying and more severe than is warranted by the individual's circumstances, as well as anhedonia (loss of pleasure in usually enjoyable activities) and functional impairment caused by the symptoms that are present. It is also suggested that an inclusive approach should be used when considering the criteria for making a diagnosis of depression in a medically ill individual.[17] The relationship between substance abuse, mood and anxiety disorders and HIV infection is complex, and all these disorders may play a role in increasing the risk of being infected with HIV, as well as contributing to the burden of disease, poor adherence and disease progression.

**BOX 1**

Mrs K is a 50-year-old woman living in a rural area. Her husband died of AIDS a year ago. She presents at the clinic with severe oral thrush. She is HIV positive and has severe weight loss. She looks depressed and is very tearful, complaining of fatigue and poor sleep and appetite. She has psychomotor retardation and her memory is poor. She is not on antiretroviral therapy. Her CD4 count is 150 cells/µl.

What possible diagnoses should you consider? How would you approach her treatment?

**BOX 2**

Mr M is a 29-year-old man who was recently diagnosed HIV positive when he presented to health services with a severe upper respiratory tract infection. His CD4 count is 250 cells/µl. He comes for a follow-up appointment in a dishevelled state, smelling of alcohol. He recently lost his job as a clerk in an office, his wife is unemployed and they have a young child. He starts crying in your office and voices suicidal ideation.

What would your immediate management be? And in the longer term?

**BOX 3**

Ms B is a 24-year-old woman who was diagnosed HIV positive during antenatal screening. She had PMTCT and her baby was delivered safely 2 weeks ago. She is living with the father of the child, who is aware of her status and has also tested HIV positive. They are both currently asymptomatic. He is very supportive and it is their first child. She is extremely anxious about the well-being and HIV status of her baby. She complains that she is not sleeping and that she gets very irritable with the baby at times. Sometimes she finds herself just bursting into tears for no reason.

What could be going on here? What are the risks in this situation? How would you manage her?

## SCREENING FOR COMMON MENTAL DISORDERS IN HIV PRIMARY CARE SERVICES

Because the presentation of depression and anxiety can be unclear and because many people do not volunteer information about substance use disorder, it is critical that people who are infected with HIV should be screened for these disorders. A range of screening instruments have been validated in South Africa and are recommended for use.[19-21] Some of these are self-report instruments, while others are administered by the health worker. Once an individual is identified through screening, they should receive a more thorough assessment by a trained clinician.

The Substance Abuse and Mental Illness Symptoms Screener (SAMISS) is a 13-item screening questionnaire developed for use in HIV-positive individuals that can easily be applied in a busy primary care setting (Box 4). The SAMISS was found to have a sensitivity of 86% and specificity of 95% in diagnosing DSM-IV-defined substance use and depressive/anxiety disorders,[22] and validation of this tool in South Africa is underway. The advantages of using this instrument are that it is reasonably quick to administer and that it covers all the common mental disorders including substance use disorders.

**BOX 4. THE SUBSTANCE ABUSE AND MENTAL ILLNESS SCREENER**

**Substance use items:**

1. How often do you have a drink containing alcohol? (Alcoholic drinks include one beer, one glass of wine, *a mixed drink of hard liquor, or one wine cooler. Each of these counts as one drink, unless they have double shots, which would equal two drinks.)* (If you do not drink, go to question 4.)
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

2. How many drinks do you have on a typical day when you are drinking?
0 - 1 or 2
1 - 3 or 4
2 - 5 or 6
3 - 7 to 9
4 - 10 or more

3. How often do you have four or more drinks on one occasion?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

4. In the past year, how often did you use non-prescription drugs to get high or change the way you feel?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

5. In the past year, how often did you use drugs prescribed to you or to someone else to get high or change the way you feel?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

6. In the last year, how often did you drink or use drugs more than you meant to?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

7. How often did you feel you wanted or needed to cut down on your drinking or drug use in the last year, and not been able to?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

Patient considered positive for substance use symptoms if any of the following criteria are met:
a) The sum of responses for questions 1 - 3 is ≥5
b) The sum of responses for questions 4 - 5 is ≥3
c) The sum of responses for questions 6 - 7 is ≥1

**Mental health items:**

*Medications/antidepressants*
8. During the past 12 months, were you ever on medication/antidepressants for depression or nerve problems?
1 - Yes
2 - No

*Major depression*
9. During the past 12 months, was there ever a time when you felt sad, blue or depressed for 2 weeks or more in a row?
1 - Yes
2 - No

10. During the past 12 months, was there ever a time lasting 2 weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?
1 - Yes
2 - No

*Generalised anxiety disorders*
11. During the past 12 months, did you ever have a period lasting 1 month or longer when most of the time you felt worried and anxious?
1 - Yes
2 - No

*Panic disorder*
12. During the past 12 months, did you have a spell or an attack when all of a sudden you felt frightened, anxious or very uneasy when most people would not be afraid or anxious?
1 - Yes
2 - No

13. During the past 12 months, did you ever have a spell or an attack when for no reason your heart suddenly started to race, you felt faint, or you couldn't catch your breath? [If respondent volunteers 'only when having a heart attack or due to physical causes', mark 'No'.]
1 - Yes
2 - No

Patient considered positive for symptoms of mental illness if he/she responded yes to any mental health question.

## PREVENTION OF COMMON MENTAL DISORDERS IN HIV PRIMARY CARE SERVICES

Given the increased risk of common mental disorders in HIV-infected individuals, it makes sense to put basic preventive services into place in HIV treatment services. These include support groups, counselling, psycho-education, social work and occupational therapy interventions, as available. It is important to note that services of this kind are commonly available as part of HIV primary care services (particularly in the context of antiretroviral therapy), but are usually focused on treatment initiation and adherence; however, such types of psychosocial support have important additional benefits in promoting mental health. Individuals who provide this kind of psychosocial support should be trained to identify patients who may have a common mental disorder (e.g. using the SAMISS), and to refer them for appropriate assessment and intervention. Ideally, psychiatric and mental health care services should be offered on site in HIV treatment services, but this may not always be possible and specialist services are not required to effectively diagnose and manage many common mental disorders. Alternatively, it would be important to identify referral resources and establish good links and communication channels between the HIV treatment service and the psychiatric/mental health services.

## MANAGEMENT OF COMMON MENTAL DISORDERS

Treating common mental disorders has direct benefits on the quality of life and well-being of affected individuals. In addition, there is evidence from international research that untreated depressive and anxiety disorders lead to poor antiretroviral adherence[23] and may speed HIV disease progression.[24-26] The management of mental disorders requires a holistic approach with attention to biological as well as psychosocial factors.

### BIOLOGICAL MANAGEMENT

#### Identify and treat any underlying or associated general medical condition

HIV infection itself is associated with features of depression and apathy. Other chronic conditions such as peripheral neuropathy, or intra-cranial secondary infections or tumours, may produce depression. These include progressive multifocal leuco-encephalopathy or vasculopathy. Usually a careful history, physical examination and routine investigations (e.g. serological testing for syphilis) are adequate to rule these out as causes of psychiatric symptoms, and special investigations (such as lumbar puncture or computed tomography of the brain) are not necessary in many primary care settings.

#### Assess cognitive impairment

Cognitive impairment often co-exists with depressive disorders, and may be a confounding variable. It is sometimes difficult to assess whether there is depression in the presence of dementia, and depressive illness may also present with cognitive features consistent with dementia. If there are other features and markers of late-stage HIV infection, the need for antiretroviral medication should be considered, as this is an important treatment for HIV-associated dementia (see related article by Singh in this edition).

#### Assess for suicidality

Suicidal ideation is common in HIV-infected individuals. In a study in South Africa,[27] 22.5% of a sample of HIV-infected individuals attending HIV treatment sites had experienced suicidal ideation in the past, and 8.6% had current suicidal ideation; 69% of the participants with past suicidal ideation had experienced this as a result of their diagnosis. The period after diagnosis is therefore a period of high risk. In the same study, suicidal ideation was strongly associated with the presence of a depressive disorder. It is important to ask patients who are at high risk about thoughts of suicide, as these may not be volunteered. A thorough risk assessment should be conducted, and the need for inpatient admission should always be considered.

#### Treat depressive or anxiety disorders with medication when necessary

Antidepressant medication is effective in treating both depressive and anxiety disorders in HIV-infected people, even in the presence of cognitive impairment (for more detail on specific medications and their use, see the article in this edition on psychotropic prescribing in HIV-infected individuals). Antidepressant medication can be used safely in combination with antiretroviral medication, as long as one is aware of several specific drug interactions and monitors the patient, adjusting medication when necessary. Generally antidepressant medication should be used for 6 months to 1 year to treat a single episode of a depressive illness. People with recurrent episodes should remain on long-term treatment. Anxiety disorders are best managed with a combination of psychosocial interventions and judicious use of medication. Benzodiazepines should be avoided, only being used in acute crisis situations for short periods of time (less than 2 weeks). Should medication be needed to manage anxiety, the selective serotonin reuptake inhibitors (SSRIs) should be used.

#### Manage substance withdrawal and provide rehabilitation for substance use disorders

The initial intervention in terms of substance use disorders is safe medical detoxification, followed by assess-

ment of the need for and possibilities of rehabilitation. Motivational interviewing is a useful tool for engaging people with substance use disorders in treatment of their addictive behaviour. Rehabilitation usually consists of group and individual psychotherapy, and can usually be managed on an outpatient basis. Support groups, where available, are useful in keeping people sober and drug-free.

### INTERPERSONAL, COGNITIVE-BEHAVIOURAL PSYCHOTHERAPY

There is evidence of benefit from interpersonal psychotherapy for the treatment of depressive disorders in HIV-infected individuals.[28] Cognitive-behavioural therapy (CBT) has been shown to have benefit in depressive illnesses in general primary health care.[28] Supportive therapy and support groups are not sufficient where individuals are depressed, but support group facilitators should be trained to identify people who may be depressed. An adaptation of CBT for people living with HIV, called cognitive-behavioural stress management (CBSM), has been found to be effective when conducted in group settings in HIV clinics in the USA.[28] This intervention includes didactics on physiological effects of stress, stress management strategies, CBT interpretation of stress and emotions (addressing cognitive distortions, automatic thoughts), coping skills training, assertiveness training, anger management, identification of social supports, and group support. This is a structured intervention that could be implemented in HIV clinics or primary care settings where group treatment can be used to treat a number of depressed individuals at the same time, and it deserves attention in South Africa.

Most common mental disorders can be managed effectively in primary care, but there are several specific indications for referring a patient to specialist psychiatric and mental health services (Box 5).

**BOX 5**

Indications for referring a patient to specialist psychiatric and mental health services:

1. Any patient who requires inpatient treatment should be referred for a psychiatric assessment.
2. Any patient who presents with suicidal ideation should be referred for a psychiatric assessment.
3. Failure to respond to primary care interventions as outlined above.
4. Patients who fail to respond to an equivalent dose of fluoxetine or citalopram of 20 mg per day for a depressive or anxiety disorder should be referred for a psychiatric assessment or opinion.

## DISCUSSION OF CASE SCENARIOS

Mrs K (Box 1) has stage 3 or 4 HIV disease. She may have neurocognitive impairment and she may also have a depressive disorder. Assessment should include physical examination, and assessment of her cognitive status. She is clearly a candidate for antiretroviral therapy, which should be started as soon as possible. One would re-assess her mental state regularly, and if her mood did not lift once she has recovered physically, one would consider starting her on an SSRI.

A suicide risk assessment should be carried out on Mr M (Box 2). Because he is intoxicated, he would need to be supervised until he became sober. His wife could be called into the clinic to discuss the situation with her. It would be important to educate him about alcohol abuse and its consequences in terms of his HIV status as well as his mood. Another important consideration would be when to start antiretroviral treatment. A social work referral should be made for assistance or advice regarding the couple's financial situation, as well as referral to a support group or a psychologist depending on his condition. His mood should be monitored over time and if it remains low one would consider starting him on an antidepressant.

Ms B (Box 3) could be suffering from postpartum depression. It is important to assess her mental state and do a risk assessment with regard to self-harm as well as possible harm to her baby. One could call her husband in and discuss the situation with them both. If she has features of a depressive disorder, she should be started on an SSRI. It is also important to make sure that there is adequate support and supervision for her and her baby. If the safety of either is a concern, she should be admitted to hospital.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# FROM THE EDITOR

I am delighted to introduce you to our guest editors, who have done a sterling job in pulling together this 'Mental Health in HIV' edition.

They are two Capetonian colleagues who I am also fortunate to consider friends: John Joska is a psychiatrist and Landon Myer is a public health specialist.

John Joska is a senior specialist and lecturer in the Department of Psychiatry and Mental Health at the University of Cape Town. He is head of the Division of Neuropsychiatry, Western Cape provincial programme manager for HIV Psychiatry, and director of the GSH-HIV Mental Health Group. The latter is a newly formed group of mental health professionals who are providing service and investigating the effects of HIV on people living with HIV/AIDS (PLWHA) from a mental health point of view. Current research projects include investigations into neurocognitive disorders in HIV, screening for mental disorders in HIV, and brief psychological interventions in PLWHA with depression.

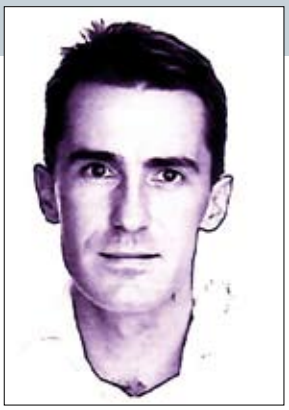
Landon Myer is an associate professor in the School of Public Health and Family Medicine at the University of Cape Town. His research focuses on the roles of HIV/AIDS and other infectious diseases in shaping individual and population health in southern Africa. He is particularly interested in how the HIV epidemic influences other areas of population health, including mental health and women's reproductive health. In investigating these topics, his research incorporates biological mechanisms, individual behaviours and exposures, as well as structural socio-economic and health service conditions.

I am sure you will agree that with their colleagues they have provided a feast of important reading for you all in this edition.

**LINDA-GAIL BEKKER**
*Editor*

# EDITORIAL

## ADDRESSING MENTAL HEALTH IN ROUTINE HIV CARE AND TREATMENT



As this journal's readers are well aware, HIV has complex and wide-ranging impacts on the health of infected individuals. Much of this complexity is due to the nature of host-virus interactions and the pathophysiology of the virus and its sequelae in different organ systems over time. Other aspects are linked to the profound impact an HIV diagnosis has on the life of an infected individual, both through physical morbidity and the psychological and social consequences of a lifelong illness.

The area of mental health is a critical example of the diverse impacts of HIV on patients' health and well-being. The links between HIV and mental health are multiple: risk taking associated with HIV acquisition is more common among individuals with mental disorders; common mental disorders (such as anxiety, depression and alcohol/substance disorders) are often caused in part by the stress of an HIV diagnosis and related stigma; psychotic states are a relatively common presentation of HIV-infected individuals; and neurocognitive manifestations of HIV infection such as HIV-associated dementia emerge later in the course of disease. Taken together, mental disorders may be viewed as their own class of 'opportunistic' conditions affecting HIV-infected individuals in a unique manner.

Dealing with the various mental health impacts of HIV infection is a core component of effective HIV care and treatment. Anxiety and depression among HIV-infected individuals can negatively impact on medication adherence; in these situations, management of mental disorders can help facilitate the management of HIV disease over the long term. The neurocognitive manifestations of HIV disease are a significant cause of morbidity; increasingly we are recognising that these disorders may

be managed effectively, including by early initiation of antiretroviral therapy, to improve the prognosis of affected individuals. In short, basic mental health care is part of good HIV management.

In this context, there is a clear need to make the diagnosis and management of mental disorders more feasible in general HIV care and treatment settings. At the primary and secondary levels of the health care system, medical officers and physicians must be able to identify patients with a possible mental disorder and work up these patients to arrive at a preliminary diagnosis, make management decisions, and follow up patients over time. Support from specialist psychiatrists is necessary in some instances, but most cases do not require specialist referral, and the availability of psychiatric services to support HIV care and treatment is limited in most settings across the region.

This special issue of the journal aims to address this need through a series of focused contributions from leaders in HIV mental health from across South Africa. The first two pieces focus on anxiety and depression in HIV in broad terms (Thom) and post-traumatic stress disorder specifically (Pingo). Following this, the topic of psychotic presentations in HIV is dealt with by an algorithm for the diagnosis and management of psychosis in HIV (Jonsson) and then an extended case study (Boyles) to help reinforce key concepts. The topic of neurocognitive impairment in HIV/AIDS is discussed in detail (Singh) with a short report on the white matter changes that take place in the brain over the course of HIV disease (Hoare) as well as a piece of empirical research investigating the clinical utility of one commonly used tool to identify neurocognitive deficits in HIV (Ogunrin). The final piece deals with cross-cutting issues of prescribing psychotropic medications in the context of HIV infection (Parker). Throughout, these pieces aim to address issues in mental health faced by front-line HIV clinicians on a daily basis, with practical strategies for investigation and management. It is our hope that the contents of this issue may make some contribution towards helping HIV clinicians to better recognise and treat mental disorders in their patients.

**LANDON MYER**
**JOHN JOSKA**
*Guest Editors*

# MESSAGE FROM THE EXECUTIVE

The large International AIDS Society meeting has come and gone from Cape Town. The agenda was dominated by a New Big Idea, an audacious mathematical model by a group of brave World Health Organization modellers showing that giving antiretroviral therapy to everyone with HIV, immediately, could make the epidemic disappear.

We've known for a long time that viral load correlates with infectiousness, whether it is sexual contact, PMTCT or other forms of exposure. ART is so highly effective in reducing viral load that the Swiss created an uproar a year ago by claiming that someone on ART with an undetectable viral load (and no STD) could not transmit HIV sexually.

The WHO researchers essentially argue that if we diagnose HIV quickly and treat everyone who is HIV positive, irrespective of CD4 count, we can arrest sexual transmission early and pretty much eradicate HIV within 10 years. Subsequent papers have even postulated that we could reverse the TB epidemic, as HIV drives this like fuel on a fire. Finally, early economic work has shown 'test and treat' to be cost saving, despite significant initial investment.

There is broad acknowledgment that HIV prevention programmes have been very disappointing, and that even effective interventions such as male circumcision and good PMTCT are unlikely to eradicate the epidemic alone. It is exciting that researchers are thinking creatively, and that models showing we can reverse things are out there.

But to implement this incredibly ambitious model would require a complete restructuring of health systems. We would need to do HIV testing aggressively and provide adequate, easily available ART services, as broadly as possible. The health system would have to be transformed from the lumbering unfriendly giant it is at the moment to a responsive and effective service deliverer. The reality is that we need this anyway, even if the modellers are wrong.

**FRANCOIS VENTER**
*President*

# COMMON MENTAL DISORDERS IN PEOPLE LIVING WITH HIV/AIDS

**Rita Thom,** *MB ChB, DCH, FCPsych, PhD*
*Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg*

The term 'common mental disorders' is an overarching term for conditions that affect a significant number of people in the community. These conditions include depression, anxiety and substance use disorders. In contrast, so-called 'severe mental illnesses' (such as schizophrenia or bipolar mood disorder) are conditions that usually require admission for inpatient treatment and tend both to recur and to be chronically debilitating. Nonetheless, common mental disorders result in a considerable burden to the individual, their families, the community and the economy. Many people with these conditions do not present for treatment, or if they do they usually present to primary care facilities, where these diagnoses are often missed. This is unfortunate, since there is good evidence that these disorders can be effectively treated[1-2] and that much of this treatment can be provided by primary care clinicians.[3]

In South Africa, depressive and anxiety disorders are common in the general population. According to the World Health Organization-led South African Stress and Health (SASH) study, the 12-month prevalence of depressive and anxiety disorders (combined) was 12.6%,[4] while the lifetime prevalence of these disorders was 25.6%.[5] Similarly, the SASH study found a 12-month prevalence of 5.8% and a lifetime prevalence of 13.4% for substance use disorders.[4-5]

## COMMON MENTAL DISORDERS IN HIV-INFECTED INDIVIDUALS

There is good evidence from international research that the prevalence of depression and anxiety in people living with HIV or AIDS is higher than the prevalence of these disorders in HIV-negative controls.[6] One meta-analysis suggests that the prevalence is at least double that in the general community.[7] There is growing evidence that this is true in South Africa and other African countries.[8-13]

The main factors contributing to the increased prevalence of depression and anxiety in individuals living with HIV are:

**Biological,** resulting from both direct and indirect forms of neurotoxicity due to HIV invasion of the central nervous system and the sequelae of immunocompromise. The areas predominantly affected are the sub-cortical areas of the brain, including those within the temporal lobes, which are the seat of emotional/mental disorders.[14] Depressive and anxiety disorders that occur as a result of HIV CNS infection often co-exist with cognitive impairment that is also the result of this infection (see Box 1). Opportunistic conditions such as herpes simplex infection and various malignancies, as well as certain medications used to treat these conditions and antiretroviral medications, can also cause depression or anxiety.[15-16]

**Psychological.** The prevalence of depression and anxiety in people living with HIV or AIDS is similar to that in people suffering from other serious, chronic and life-threatening medical illnesses.[17] A major factor is the psychological reaction to having such an illness. The individual is faced with the reality of serious illness and possible death at an early age. In many cases there are additional stressors related to the stigma associated with HIV/AIDS and lack of social support for the infected individual (see Box 2).

**Primary psychiatric disorder.** Some individuals may be particularly vulnerable to depression and anxiety as a result of genetic loading or early childhood adversity.[18] Some HIV-infected individuals may already have a history of such mental disorder, or the stress of the illness (and the psychosocial consequences) may precipitate a depressive illness and/or an anxiety disorder. In addition, the time of first onset and presentation with primary psychiatric disorders is generally in young adulthood, and this is also the time when most people infected with HIV present for treatment or are diagnosed with the infection. Depressive or anxiety disorders may be completely unrelated to HIV status, or the underlying mental disorder may have contributed to the events associated with acquiring HIV infection (e.g. alcohol abuse and sexual risk taking).

**TABLE I. CLINICAL PRESENTATIONS OF COMMON MENTAL DISORDERS IN PRIMARY HIV/AIDS CARE SETTINGS**

| Presentation | Features |
|---|---|
| Somatic | Headache, backache, abdominal pain - may be atypical, or show limited response to somatic treatments |
| Insomnia | Common presentation; an important depressive symptom |
| Other neuro-vegetative symptoms | Fatigue, weight loss, loss of energy and libido |
| Low mood or depression | May be expressed differently, such as 'stress' or tension |
| Substance abuse | This commonly coexists with depression, and may be a presenting feature |

Several of the most frequently observed presentations of common mental disorders are listed in Table I. Identifying depression in a medically ill individual can be difficult owing to the overlap in somatic symptoms (e.g. loss of appetite or weight, sleep disturbance, pain, fatigue, poor concentration). It is important to consider mood and affect, particularly if alterations in these are constant, unvarying and more severe than is warranted by the individual's circumstances, as well as anhedonia (loss of pleasure in usually enjoyable activities) and functional impairment caused by the symptoms that are present. It is also suggested that an inclusive approach should be used when considering the criteria for making a diagnosis of depression in a medically ill individual.[17] The relationship between substance abuse, mood and anxiety disorders and HIV infection is complex, and all these disorders may play a role in increasing the risk of being infected with HIV, as well as contributing to the burden of disease, poor adherence and disease progression.

**BOX 1**

Mrs K is a 50-year-old woman living in a rural area. Her husband died of AIDS a year ago. She presents at the clinic with severe oral thrush. She is HIV positive and has severe weight loss. She looks depressed and is very tearful, complaining of fatigue and poor sleep and appetite. She has psychomotor retardation and her memory is poor. She is not on antiretroviral therapy. Her CD4 count is 150 cells/µl.

What possible diagnoses should you consider? How would you approach her treatment?

**BOX 2**

Mr M is a 29-year-old man who was recently diagnosed HIV positive when he presented to health services with a severe upper respiratory tract infection. His CD4 count is 250 cells/µl. He comes for a follow-up appointment in a dishevelled state, smelling of alcohol. He recently lost his job as a clerk in an office, his wife is unemployed and they have a young child. He starts crying in your office and voices suicidal ideation.

What would your immediate management be? And in the longer term?

**BOX 3**

Ms B is a 24-year-old woman who was diagnosed HIV positive during antenatal screening. She had PMTCT and her baby was delivered safely 2 weeks ago. She is living with the father of the child, who is aware of her status and has also tested HIV positive. They are both currently asymptomatic. He is very supportive and it is their first child. She is extremely anxious about the well-being and HIV status of her baby. She complains that she is not sleeping and that she gets very irritable with the baby at times. Sometimes she finds herself just bursting into tears for no reason.

What could be going on here? What are the risks in this situation? How would you manage her?

## SCREENING FOR COMMON MENTAL DISORDERS IN HIV PRIMARY CARE SERVICES

Because the presentation of depression and anxiety can be unclear and because many people do not volunteer information about substance use disorder, it is critical that people who are infected with HIV should be screened for these disorders. A range of screening instruments have been validated in South Africa and are recommended for use.[19-21] Some of these are self-report instruments, while others are administered by the health worker. Once an individual is identified through screening, they should receive a more thorough assessment by a trained clinician.

The Substance Abuse and Mental Illness Symptoms Screener (SAMISS) is a 13-item screening questionnaire developed for use in HIV-positive individuals that can easily be applied in a busy primary care setting (Box 4). The SAMISS was found to have a sensitivity of 86% and specificity of 95% in diagnosing DSM-IV-defined substance use and depressive/anxiety disorders,[22] and validation of this tool in South Africa is underway. The advantages of using this instrument are that it is reasonably quick to administer and that it covers all the common mental disorders including substance use disorders.

**BOX 4. THE SUBSTANCE ABUSE AND MENTAL ILLNESS SCREENER**

**Substance use items:**

1. How often do you have a drink containing alcohol? (Alcoholic drinks include one beer, one glass of wine, *a mixed drink of hard liquor, or one wine cooler. Each of these counts as one drink, unless they have double shots, which would equal two drinks.)* (If you do not drink, go to question 4.)
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

2. How many drinks do you have on a typical day when you are drinking?
0 - 1 or 2
1 - 3 or 4
2 - 5 or 6
3 - 7 to 9
4 - 10 or more

3. How often do you have four or more drinks on one occasion?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

4. In the past year, how often did you use non-prescription drugs to get high or change the way you feel?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

5. In the past year, how often did you use drugs prescribed to you or to someone else to get high or change the way you feel?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

6. In the last year, how often did you drink or use drugs more than you meant to?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

7. How often did you feel you wanted or needed to cut down on your drinking or drug use in the last year, and not been able to?
0 - Never
1 - Monthly or less
2 - 2 - 4 times a month
3 - 2 - 3 times a week
4 - 4 or more times a week

Patient considered positive for substance use symptoms if any of the following criteria are met:
a) The sum of responses for questions 1 - 3 is ≥5
b) The sum of responses for questions 4 - 5 is ≥3
c) The sum of responses for questions 6 - 7 is ≥1

**Mental health items:**

*Medications/antidepressants*
8. During the past 12 months, were you ever on medication/antidepressants for depression or nerve problems?
1 - Yes
2 - No

*Major depression*
9. During the past 12 months, was there ever a time when you felt sad, blue or depressed for 2 weeks or more in a row?
1 - Yes
2 - No

10. During the past 12 months, was there ever a time lasting 2 weeks or more when you lost interest in most things like hobbies, work, or activities that usually give you pleasure?
1 - Yes
2 - No

*Generalised anxiety disorders*
11. During the past 12 months, did you ever have a period lasting 1 month or longer when most of the time you felt worried and anxious?
1 - Yes
2 - No

*Panic disorder*
12. During the past 12 months, did you have a spell or an attack when all of a sudden you felt frightened, anxious or very uneasy when most people would not be afraid or anxious?
1 - Yes
2 - No

13. During the past 12 months, did you ever have a spell or an attack when for no reason your heart suddenly started to race, you felt faint, or you couldn't catch your breath? [If respondent volunteers 'only when having a heart attack or due to physical causes', mark 'No'.]
1 - Yes
2 - No

Patient considered positive for symptoms of mental illness if he/she responded yes to any mental health question.

## PREVENTION OF COMMON MENTAL DISORDERS IN HIV PRIMARY CARE SERVICES

Given the increased risk of common mental disorders in HIV-infected individuals, it makes sense to put basic preventive services into place in HIV treatment services. These include support groups, counselling, psycho-education, social work and occupational therapy interventions, as available. It is important to note that services of this kind are commonly available as part of HIV primary care services (particularly in the context of antiretroviral therapy), but are usually focused on treatment initiation and adherence; however, such types of psychosocial support have important additional benefits in promoting mental health. Individuals who provide this kind of psychosocial support should be trained to identify patients who may have a common mental disorder (e.g. using the SAMISS), and to refer them for appropriate assessment and intervention. Ideally, psychiatric and mental health care services should be offered on site in HIV treatment services, but this may not always be possible and specialist services are not required to effectively diagnose and manage many common mental disorders. Alternatively, it would be important to identify referral resources and establish good links and communication channels between the HIV treatment service and the psychiatric/mental health services.

## MANAGEMENT OF COMMON MENTAL DISORDERS

Treating common mental disorders has direct benefits on the quality of life and well-being of affected individuals. In addition, there is evidence from international research that untreated depressive and anxiety disorders lead to poor antiretroviral adherence[23] and may speed HIV disease progression.[24-26] The management of mental disorders requires a holistic approach with attention to biological as well as psychosocial factors.

### BIOLOGICAL MANAGEMENT

#### Identify and treat any underlying or associated general medical condition

HIV infection itself is associated with features of depression and apathy. Other chronic conditions such as peripheral neuropathy, or intra-cranial secondary infections or tumours, may produce depression. These include progressive multifocal leuco-encephalopathy or vasculopathy. Usually a careful history, physical examination and routine investigations (e.g. serological testing for syphilis) are adequate to rule these out as causes of psychiatric symptoms, and special investigations (such as lumbar puncture or computed tomography of the brain) are not necessary in many primary care settings.

#### Assess cognitive impairment

Cognitive impairment often co-exists with depressive disorders, and may be a confounding variable. It is sometimes difficult to assess whether there is depression in the presence of dementia, and depressive illness may also present with cognitive features consistent with dementia. If there are other features and markers of late-stage HIV infection, the need for antiretroviral medication should be considered, as this is an important treatment for HIV-associated dementia (see related article by Singh in this edition).

#### Assess for suicidality

Suicidal ideation is common in HIV-infected individuals. In a study in South Africa,[27] 22.5% of a sample of HIV-infected individuals attending HIV treatment sites had experienced suicidal ideation in the past, and 8.6% had current suicidal ideation; 69% of the participants with past suicidal ideation had experienced this as a result of their diagnosis. The period after diagnosis is therefore a period of high risk. In the same study, suicidal ideation was strongly associated with the presence of a depressive disorder. It is important to ask patients who are at high risk about thoughts of suicide, as these may not be volunteered. A thorough risk assessment should be conducted, and the need for inpatient admission should always be considered.

#### Treat depressive or anxiety disorders with medication when necessary

Antidepressant medication is effective in treating both depressive and anxiety disorders in HIV-infected people, even in the presence of cognitive impairment (for more detail on specific medications and their use, see the article in this edition on psychotropic prescribing in HIV-infected individuals). Antidepressant medication can be used safely in combination with antiretroviral medication, as long as one is aware of several specific drug interactions and monitors the patient, adjusting medication when necessary. Generally antidepressant medication should be used for 6 months to 1 year to treat a single episode of a depressive illness. People with recurrent episodes should remain on long-term treatment. Anxiety disorders are best managed with a combination of psychosocial interventions and judicious use of medication. Benzodiazepines should be avoided, only being used in acute crisis situations for short periods of time (less than 2 weeks). Should medication be needed to manage anxiety, the selective serotonin reuptake inhibitors (SSRIs) should be used.

#### Manage substance withdrawal and provide rehabilitation for substance use disorders

The initial intervention in terms of substance use disorders is safe medical detoxification, followed by assess-

ment of the need for and possibilities of rehabilitation. Motivational interviewing is a useful tool for engaging people with substance use disorders in treatment of their addictive behaviour. Rehabilitation usually consists of group and individual psychotherapy, and can usually be managed on an outpatient basis. Support groups, where available, are useful in keeping people sober and drug-free.

### INTERPERSONAL, COGNITIVE-BEHAVIOURAL PSYCHOTHERAPY

There is evidence of benefit from interpersonal psychotherapy for the treatment of depressive disorders in HIV-infected individuals.[28] Cognitive-behavioural therapy (CBT) has been shown to have benefit in depressive illnesses in general primary health care.[28] Supportive therapy and support groups are not sufficient where individuals are depressed, but support group facilitators should be trained to identify people who may be depressed. An adaptation of CBT for people living with HIV, called cognitive-behavioural stress management (CBSM), has been found to be effective when conducted in group settings in HIV clinics in the USA.[28] This intervention includes didactics on physiological effects of stress, stress management strategies, CBT interpretation of stress and emotions (addressing cognitive distortions, automatic thoughts), coping skills training, assertiveness training, anger management, identification of social supports, and group support. This is a structured intervention that could be implemented in HIV clinics or primary care settings where group treatment can be used to treat a number of depressed individuals at the same time, and it deserves attention in South Africa.

Most common mental disorders can be managed effectively in primary care, but there are several specific indications for referring a patient to specialist psychiatric and mental health services (Box 5).

**BOX 5**

Indications for referring a patient to specialist psychiatric and mental health services:

1. Any patient who requires inpatient treatment should be referred for a psychiatric assessment.
2. Any patient who presents with suicidal ideation should be referred for a psychiatric assessment.
3. Failure to respond to primary care interventions as outlined above.
4. Patients who fail to respond to an equivalent dose of fluoxetine or citalopram of 20 mg per day for a depressive or anxiety disorder should be referred for a psychiatric assessment or opinion.

## DISCUSSION OF CASE SCENARIOS

Mrs K (Box 1) has stage 3 or 4 HIV disease. She may have neurocognitive impairment and she may also have a depressive disorder. Assessment should include physical examination, and assessment of her cognitive status. She is clearly a candidate for antiretroviral therapy, which should be started as soon as possible. One would re-assess her mental state regularly, and if her mood did not lift once she has recovered physically, one would consider starting her on an SSRI.

A suicide risk assessment should be carried out on Mr M (Box 2). Because he is intoxicated, he would need to be supervised until he became sober. His wife could be called into the clinic to discuss the situation with her. It would be important to educate him about alcohol abuse and its consequences in terms of his HIV status as well as his mood. Another important consideration would be when to start antiretroviral treatment. A social work referral should be made for assistance or advice regarding the couple's financial situation, as well as referral to a support group or a psychologist depending on his condition. His mood should be monitored over time and if it remains low one would consider starting him on an antidepressant.

Ms B (Box 3) could be suffering from postpartum depression. It is important to assess her mental state and do a risk assessment with regard to self-harm as well as possible harm to her baby. One could call her husband in and discuss the situation with them both. If she has features of a depressive disorder, she should be started on an SSRI. It is also important to make sure that there is adequate support and supervision for her and her baby. If the safety of either is a concern, she should be admitted to hospital.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# THE MANAGEMENT OF TRAUMA AND POST-TRAUMATIC STRESS DISORDER IN HIV-INFECTED INDIVIDUALS

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Women are disproportionately affected by the HIV epidemic and also carry a higher burden of early childhood trauma, other life traumas (e.g. rape and partner violence) and post-traumatic stress disorder (PTSD).[1,2] Yet PTSD and other common psychiatric disorders (e.g. depression, alcohol abuse) are commonly under-detected in HIV care settings. For many HIV-infected individuals in South Africa, HIV clinical care is the primary point at which mental illness can be identified and an intervention can be administered.[3] When one considers the high prevalence of trauma and PTSD in infected patients, and its potential effects on antiretroviral therapy (ART) adherence, disease progression and quality of life, it is clear that correctly identifying and treating these conditions can significantly contribute to optimal patient care.

## HIV, TRAUMA AND PTSD INTERFACE

Post-traumatic stress disorder (PTSD) is a complex psychological and physiological response to serious, life-threatening trauma. The prevalence of PTSD in HIV-infected individuals varies across studies, ranging from 30% to 64%[4-6] depending on the various methods of assessment, sample characteristics and diagnostic criteria used. In one South African study of recently diagnosed HIV/AIDS patients (*N*=149), 14.8% met current criteria for PTSD at baseline, and 26.2% met criteria at 6-month follow-up.[7,8] Rates of PTSD appear to be significantly higher among HIV-infected individuals than in the general population.

Many studies show that a history of trauma, particularly physical and sexual abuse, is common among HIV-positive individuals and exceeds that in the general population.[9] In one study in the USA, 95% of the women in primary care had experienced some form of sexual abuse in their lifetime, and 83% had experienced significant physical abuse.[10] Another study found that 72.5% of the participants had experienced at least two types of traumatic events during their lifetime, and 53.5% had some sexual and/or physical abuse history in their lifetime.[11] The association between HIV infection and trauma exposure may be causal (for example, childhood sexual abuse has been linked to higher rates of sexual and drug use risk behaviours that increase the risk of HIV) or may reflect of the concentration of HIV infection in socio-economically deprived populations who are at high risk of trauma exposures.[12]

Traumatic life events, especially multiple traumatic events, are strongly associated with poorer treatment adherence, HIV risk behaviours, a history of alcohol abuse and depression, more hospitalisations, and faster HIV disease progression.[9,11-14] Furthermore, there is a dose-response relationship with the odds of non-adherence to antiretroviral therapy (ART) increasing with each additional lifetime traumatic exposure.[14] Prior trauma may affect adherence through a variety of pathways, including: (*i*) PTSD or other mental health problems (as well as substance misuse); (*ii*) subjective experiences of and trust in the health care system; (*iii*) individual coping styles and self-efficacy mechanisms; and (*iv*) the availability of social support.[14,15]

## ASSESSMENT OF TRAUMA AND PTSD

There are essentially three core aspects to consider in the assessment for PTSD in people living with HIV/AIDS (PLWHA): (*i*) identification of patients who are predisposed to the disorder (i.e. at risk); (*ii*) careful assessment of all traumatic events that a patient has experienced; and (*iii*) understanding of the diagnostic criteria for PTSD.

HIV-infected patients with PTSD can present a special challenge to the primary care physician as they com-

monly complain of vague somatic symptoms that may be the somatic expression of their disorder, be exacerbated by their PTSD, or be unrelated.[16] Patients with PTSD also suffer from psychiatric co-morbidities such as depression, other anxiety disorders and substance abuse. Many patients use alcohol or drugs in an attempt to self-medicate their PTSD symptoms. In addition, patients with PTSD are at an increased risk of gastro-intestinal, cardiac, respiratory and neurological problems.[17]

## RISK FACTORS FOR PTSD

Risk factors in both infected and uninfected individuals associated with the development of PTSD are listed in Table I.

In PLWHA, additional factors such as stigma may be contributory. For example, a study of 102 HIV-infected women that examined risk factors for PTSD symptomatology found that PTSD was associated with a higher degree of perceived stigma, more HIV-related physical symptoms, less perceived social support, more pre-HIV trauma, and more negative life events.[19] Stigma was the strongest individual predictor of PTSD, which highlights its importance in assessing for PTSD co-morbidity in infected individuals.

## TRAUMATIC LIFE EVENTS

PLWHA who have PTSD are typically unaware of the connection between a past traumatic experience and their current symptoms. At the same time, primary care physicians are often reluctant to ask about trauma for fear of upsetting or offending patients or because of their own discomfort around hearing patients' trauma narratives. Asking HIV-positive patients about trauma with a simple question such as 'Have you ever been physically, sexually or emotionally harmed?' may be useful in helping patients understand the relationship between trauma and its effects (i.e. in providing psycho-education), eliciting any underlying disorder/s, and then managing patients appropriately.[16]

## THE DSM-IV CRITERIA FOR PTSD

There are six criteria (A - F) for the diagnosis of PTSD according to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, text revision (DSM-IV-TR).[20] Criterion A defines the PTSD-qualifying event/stressor as one that involves actual or threatened death or injury and evokes a response of intense fear, horror or helplessness. Traumatic events that give rise to PTSD include childhood abuse, rape, domestic violence, violent physical assault, motor vehicle accidents, military combat, and natural and man-made disasters.[20] Although being given a diagnosis of a life-threatening disease such as HIV may be considered as 'traumatic', there is some controversy about whether it classifies as an event that is capable of giving rise to PTSD.[21,22]

It is crucial to ask patients whether a traumatic experience is ongoing or in the past (e.g. 'Is this dangerous/life-threatening experience continuing in your life now?').[16] This should be followed up with questions including 'Some people who have had extremely traumatic experiences develop symptoms (e.g. nightmares, sleep disturbances, flashbacks) like the one you describe', or 'Some people who have had traumatic experiences like you also have symptoms of ... [e.g. chronic pain]. Have you ever thought that there might be a connection between your traumatic experience and your symptoms?'[16]

Criteria B - D refer to the three symptom clusters of PTSD: intrusive recollections, avoidance/numbing, and hyper-arousal. Intrusive recollections include recurrent distressing memories and nightmares of the event, acting or feeling as if the traumatic event were recurring,

**TABLE I. FACTORS ASSOCIATED WITH THE DEVELOPMENT OF PTSD[18]**

**Pre-traumatic factors**
- Previous psychiatric disorder
- Female gender
- Personality (external locus of control greater than internal locus of control)
- Lower socio-economic status
- Lack of education
- Minority status/race*
- Previous trauma
- Family history of psychiatric disorders

**Peri-traumatic factors**
- Severity of trauma
- Perceived threat to life
- Peri-traumatic emotions
- Peri-traumatic dissociation

**Post-traumatic factors**
- Perceived lack of social support
- Subsequent life stress

*The effect of race/minority status has been documented primarily in US samples.

and intense psychological and physiological distress on exposure to internal or external cues that remind one of a certain aspect of the event.

Avoidance/numbing symptoms refer to avoiding thoughts, feelings, conversations, activities, people or places that arouse recollections of the trauma, inability to recall important aspects of the trauma, lack of interest or participation in significant activities, feelings of detachment from others, restricted range of affect, and a sense of a foreshortened future.

Hyper-arousal symptoms include difficulty falling or staying asleep, irritability or outbursts of anger, difficulty concentrating, hyper-vigilance, and an exaggerated startle response.

Criterion E refers to the duration of the symptoms (lasting more than 1 month), and criterion F refers to the functional significance of symptoms (whether there is clinically significant distress or impairment in social, occupational or other important areas of functioning).

Lastly, one needs to specify whether the symptoms are acute (less than 3 months) or chronic, and whether symptom onset is delayed (onset of symptoms at least 6 months after the trauma).

## SCREENING

While a detailed diagnostic interview such as the Clinician Administered PTSD Checklist (CAPS) is the 'gold standard', such an interview is lengthy and may be impractical for use in primary care settings. Brief and simple-to-complete screening tools may be more feasible. The four-item Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD) is one such measure that assesses symptoms specific to the core domains of PTSD.[23] The PC-PTSD asks the patient 'In your life have you ever had any experience that was so frightening, horrible or upsetting that, in the past month, you ...'

- Have had nightmares about it or thought about it when you did not want to
- Tried hard not to think about it or went out of your way to avoid situations that reminded you of it
- Were constantly on guard, watchful, or easily startled
- Felt numb or detached from others, activities or your surroundings.

Three or more 'yes' responses to these questions is highly suggestive of PTSD, requiring further evaluation of symptoms and other trauma-related problems by a mental health care practitioner if need be. A cut-off of 3 on the PC-PTSD yields a sensitivity of 78% and specificity of 87% compared with the gold-standard CAPS.[23] The PC-PTSD is simple to administer and may be easily used in a busy clinical setting alongside the SA-MISS (see related article in this issue on common mental disorders in HIV).

## MANAGEMENT OF PTSD

PLWHA who have PTSD are often fearful and highly sensitive to physical sensations (e.g. a physical examination can remind some patients of their traumatic experience), and in turn may be ambivalent about medical treatment. Being supportive, enhancing a sense of personal safety, and recommending self-care strategies (e.g. an activity that is enjoyable and self-fulfilling) can help patients manage their anxiety and reduce risk-taking and self-destructive behaviours.

In clinical practice, the majority of adults with PTSD derive most benefit from a combination of treatment approaches encompassing psychopharmacology and psychotherapy.[17] The management principles discussed below are illustrated in the form of a case study (see box).

### PHARMACOLOGICAL TREATMENT

Medication has been shown to be significantly more effective than placebo across all three symptom clusters in PTSD, and has also been shown to be effective in reducing co-morbid symptoms and improving quality of life.[24-30] Medication should be considered from the beginning if the patient prefers it, if the symptoms are severe and persistent, if there is co-morbid depression and anxiety, and if functioning is severely disrupted. PLWHA who have PTSD may be highly sensitive to physical symptoms and to medication side-effects. Adherence may be enhanced by starting medication at low doses with gradual increases based on tolerability.

- **Selective serotonin reuptake inhibitors (SSRIs)** are the most studied medications for PTSD and are widely considered as first-line agents for this condition. In South Africa fluoxetine is easily available and can be used as a first-line agent. SSRI treatment is most helpful in the long term if it is continued for at least 12 months after remission of symptoms. More on the use of SSRIs can be found in the article on psychotropic prescribing in HIV infection.
- **If there is no response in 8 weeks,** the primary care physician should refer the patient for psychiatric care. Further indications for referral to specialised psychiatric care are shown in Table II.[31]
- **Benzodiazepines should be avoided or used with caution.** While they reduce anxiety and promote sleep, controlled trials have not shown them to be superior in efficacy to placebo; with the risk of drug dependence, benzodiazepines are not recommended.

## TABLE II. WHEN TO REFER FOR SPECIALISED PSYCHIATRIC CARE

- If the patient has other serious psychiatric problems which are not improving on treatment
- If the patient has suicidal thoughts/behaviour
- If there are persistent problems with medication side-effects
- If PTSD symptoms are not responsive to an adequate trial ((8 weeks at an average therapeutic dose) of at least one medication
- If there are co-existing substance abuse problems
- If the patient is experiencing other life stressors and/or poor social support

### PSYCHOLOGICAL TREATMENTS

Psychological treatments are widely used to treat PTSD as they have been shown to significantly reduce symptoms.[32] All patients willing to attend should be referred for psychological treatment, depending on the available services. Trauma-focused cognitive-behavioural therapy (CBT) is recommended as it has been extensively studied in PTSD.[33] CBT consists of anxiety management (teaching patients skills to cope with stress, such as relaxation training, breathing training, assertiveness training, etc), cognitive therapy (modifying unrealistic assumptions, beliefs and automatic thoughts), and prolonged exposure therapy (learning to confront situations associated with the trauma).[25]

### SUPPORTIVE INTERVENTIONS

When a patient has recently experienced an extremely traumatic event, time should be taken to educate the patient and his or her family about acute stress reactions and PTSD, and to reassure the patient that it is normal to be upset and distressed shortly after a trauma. The family should be encouraged to talk about the traumatic event with the patient and provide the necessary support, where possible.[33] In instances of domestic violence, for example, the physician will need to assess whether reporting is required and should inform the patient of the limits of confidentiality. Involvement of social workers should be considered to ensure that ongoing abuse does not occur.

### CASE STUDY

A 26-year-old HIV-positive woman with a CD4 count of 180 cells/µl is referred to her local ARV clinic to initiate antiretroviral therapy. In the initial interview the HIV clinician notices that she appears to be a little anxious and withdrawn, and seems tired.

The patient says that she was diagnosed with HIV 3 years ago after she was sexually and physically abused by her boyfriend at the time. A year ago she left her family and friends in the Eastern Cape to find work in Cape Town. She has Grade 10 education, and is currently a casual employee at a fast-food restaurant and living with a friend.

The HIV clinician becomes concerned, as this patient has a history of previous trauma, comes from an impoverished background and has little social support, and enquires further about her symptoms of anxiety and tiredness. The patient says that about 2 months ago she was mugged on the way home from work, physically assaulted and threatened with a knife. Since then she's had difficulty sleeping, occasionally experiences nightmares of the event, can't recall certain aspects, feels constantly on guard, and feels as if her emotions are numbed. She has taken a number of days off work recently as she's afraid she will be mugged again, and her supervisor has already warned her that she may lose her job.

The HIV clinician makes the diagnosis of post-traumatic stress disorder, and explains the treatment options available. At the patient's request, fluoxetine 20 mg daily is prescribed and a referral is made to the clinic psychologist to initiate cognitive-behavioural therapy. The patient is also started on ARVs and warned of possible side-effects, and regular follow-up is arranged to monitor her progress.

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# ASSESSMENT AND TREATMENT OF PSYCHOSIS IN PEOPLE LIVING WITH HIV/AIDS

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The pathophysiology of psychosis and other forms of severe mental illness in HIV infection is complex, and multifactorial causation is likely in most instances. Severe mental illness has been identified as a risk factor for the acquisition of HIV infection and occurs as both a manifestation of opportunistic infections and a result of the neurotropic effects of the virus.[1] A full psychiatric assessment in people living with HIV/AIDS (PLWHA) presenting with psychosis is important but may prove difficult in many parts of South Africa. This paper presents a variety of algorithms to simplify the assessment and management of an HIV-infected patient with psychosis.

## APPROACH TO PLWHA AND PSYCHOSIS (FIG. 1)

A comprehensive history from the patient and/or caregiver is needed. There should be special focus on the history of the current complaint, past psychiatric history, past and present substance abuse history, full medical history and sexual risk history and the patient's adherence to previous treatment regimens. Of equal importance is identification of social support systems.

A mental status examination will need to be conducted. In the psychotic patient one needs to focus specifically on the behaviour and appearance of the patient. His or her speech and speed of thoughts should be assessed, and mood symptoms, affect, suicidality and neuro-vegetative symptoms evaluated. Perceptual disturbances, thought form, thought content and finally insight and judgement also need to be assessed.

A comprehensive and meticulous physical and neurological examination should be performed to exclude any organic causes for the presenting psychiatric symptoms. A useful hierarchical approach has been suggested by Ambrosino *et al.*[2] One should first examine for signs of delirium and rule out HIV-associated cognitive disorders. Medical diagnoses should first be considered and only after that should a psychiatric diagnosis be entertained. The differential diagnosis needs to consider the course of the HIV infection, the presence of a pre-existing psychiatric illness, use of illicit substances and the presence of cognitive impairment.[3]

## PSYCHOTIC DISORDERS IN PLWHA (FIG. 1)

A useful delineation may be to divide psychosis in the PLWHA into: (*i*) psychiatric disorders predating HIV infection; (*ii*) new-onset psychotic disorders; and (*iii*) disorders associated with medical conditions (delirium) or substance intoxication or withdrawal, and those that are likely to be complications of treatment (i.e. antiretrovirals or antituberculosis drugs).[4]

### PSYCHOTIC DISORDERS PREDATING HIV INFECTION

Major psychiatric disorders presenting with psychosis and predating HIV infection include schizophrenia, bipolar mood disorder and major depressive disorder with psychotic features. These disorders present with significant impairment of functioning and follow a chronic course.[5] Substance abuse may predispose and/or precipitate a substance-induced psychotic disorder. There are a multitude of substances that may cause psychotic symptoms or psychotic disorders, and a clear collateral history is vital.

### NEW-ONSET PSYCHOTIC DISORDERS

New-onset psychosis in the HIV-infected patient is the development of psychotic symptoms (delusions, hallucinations, disorganised behaviour, negative symptoms or altered form of thought), either acutely or subacutely, in the absence of concurrent substance abuse, opportunistic infections, space-occupying lesions, cognitive impairment or various medications. It is hypothesised that this is caused by subcortical neurodegeneration and the direct neurotropic effects of HIV on the central nervous system (CNS), or is a manifestation of

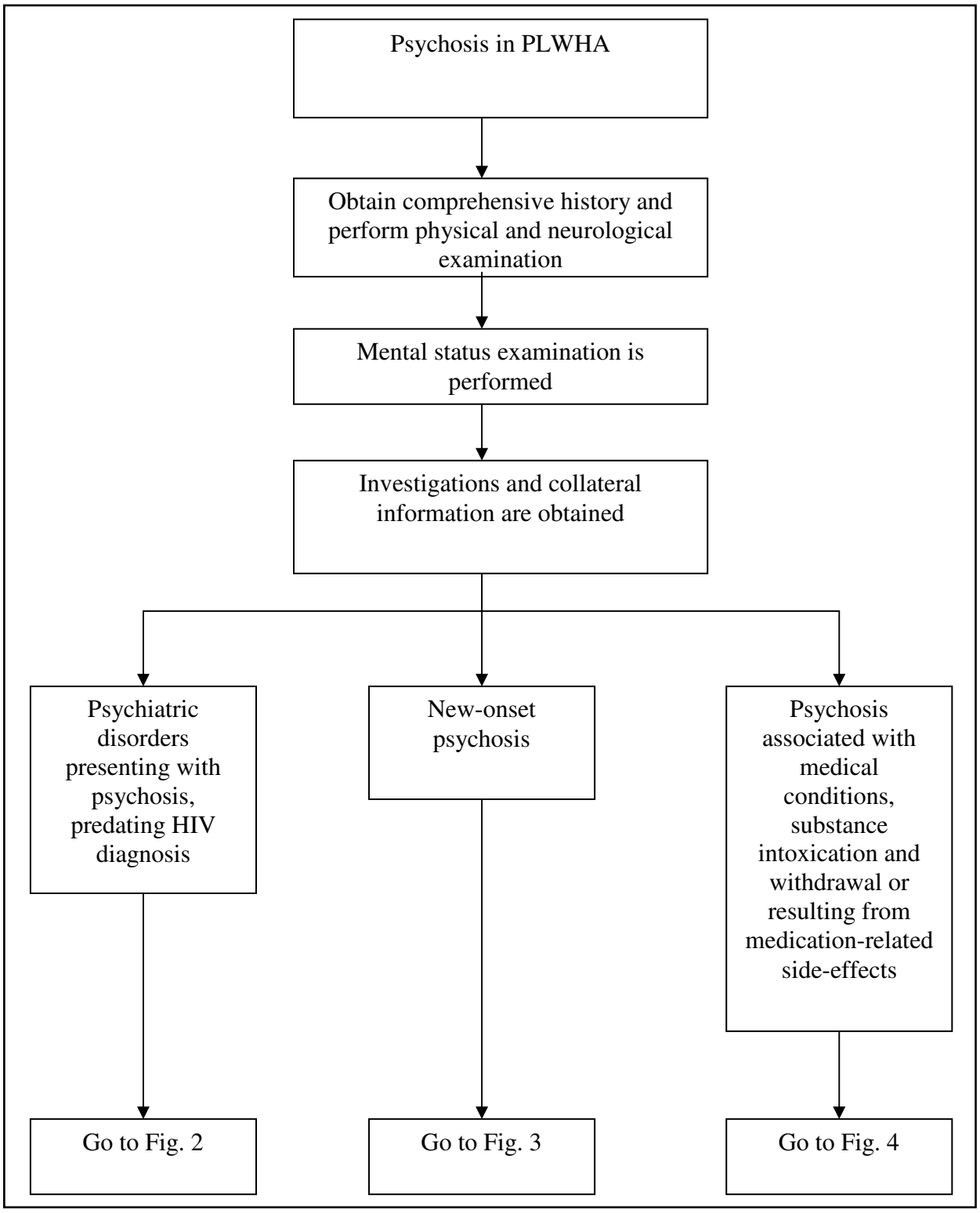


*Fig. 1. Approach to the assessment of psychosis in PLWHA.*

HIV-associated encephalopathy in the absence of severe HIV-associated dementia. Some suggest that it is due to an increase in intracellular free calcium.[6] Rates of new-onset psychosis in HIV-positive patients have been reported to range from 0.5% to 15%.[7]

Psychotic symptoms may also occur in the presence of major HIV-related mood disorders. In a Ugandan study in which HIV-negative patients with primary mania and patients with HIV-related secondary mania were compared, the patients with secondary mania were more irritable, aggressive and disruptive and had a higher rate of psychotic symptoms than those with primary mania.[8] Finally, new-onset psychotic symptoms may also occur in the presence of HIV related-cognitive disorders.[9]

## PSYCHOSIS ASSOCIATED WITH MEDICAL CONDITIONS, SUBSTANCE INTOXICATION, SUBSTANCE WITHDRAWAL OR AS A COMPLICATION OF MEDICATION

### Delirium

Delirium often has multifactorial causation and manifests with an acute presentation of disturbance in consciousness, change in cognition and development

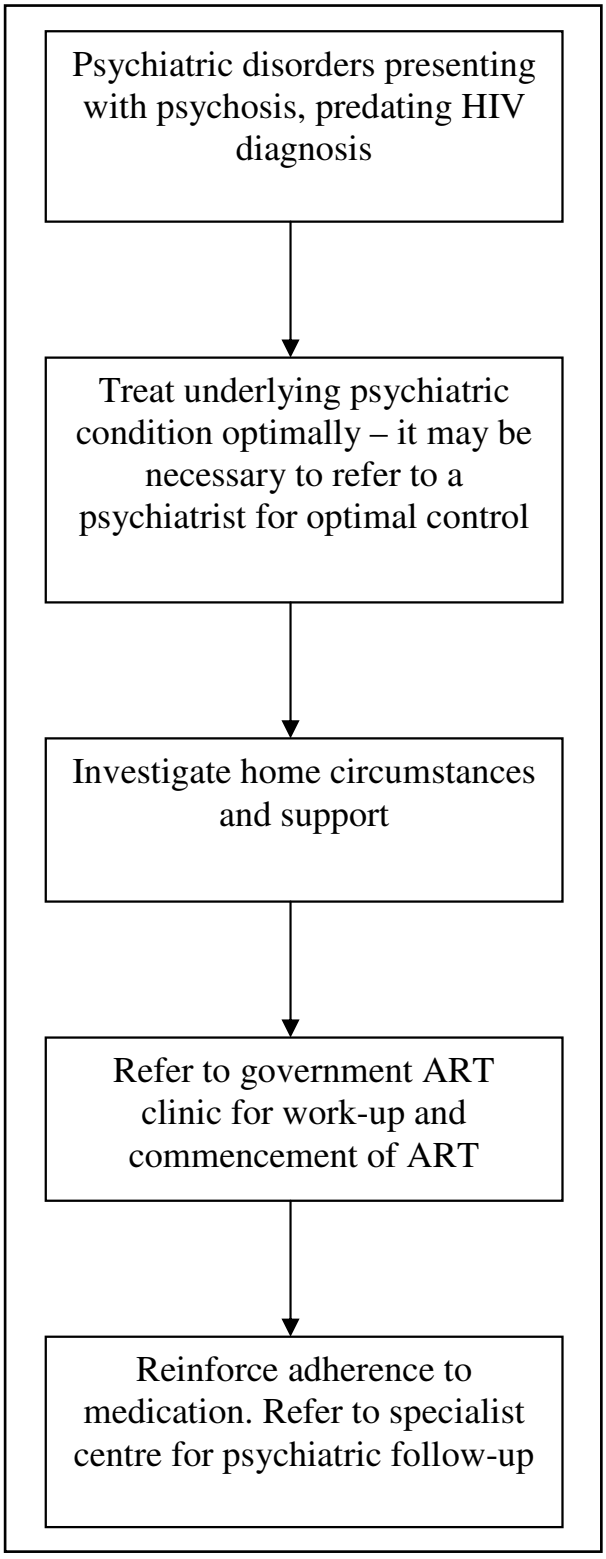


*Fig. 2. Psychotic disorders predating HIV infection.*

of perceptual disturbances, with a fluctuating course.[10] It may be due to the presence of CNS opportunistic infections, metabolic disorders, neuropsychiatric side-effects of various drugs, or substance intoxication or withdrawal. Studies from before the era of highly active antiretroviral therapy (HAART) reported a prevalence of delirium of 12 - 29% among individuals with AIDS.[11] The diagnosis of delirium depends on accurate diagnosis of the underlying cause. A comprehensive physical examination, diagnostic work-up (biochemical and microbiological parameters, cerebrospinal fluid examination) and brain imaging (computed tomography) are needed to help make the diagnosis. Hospitalised patients with HIV should be assessed early and frequently for delirium, and treatment for the underlying cause should be initiated as soon as possible.

### Substance intoxication or withdrawal

Substance intoxication and withdrawal are reversible substance-specific syndromes and may present with a delirium-type picture. HIV-infected individuals have a high prevalence of substance abuse, with lifetime rates as high as 50%.[12] HIV-positive drug abusers are reported to have higher rates of both HIV-associated dementia and HIV encephalopathy than HIV-infected people who do not abuse drugs.[13] Drug abuse may increase the risk of developing delirium. Furthermore, it may not only affect disease progression but also be associated with reduced adherence to antiretroviral therapy (ART) and is therefore a very important co-morbidity to consider in the patient with 'triple diagnosis' disorders, i.e. psychiatric disorders, HIV infection and substance abuse disorders.[14]

### Psychosis as a complication of medical treatment

Some medications used to treat HIV or the medical complications of HIV/AIDS may cause psychiatric disorders presenting with psychotic symptoms. Efavirenz has been associated with a wide range of neuropsychiatric side-effects. Psychotic symptoms associated with the commencement of efavirenz therapy are reported to occur early on and may necessitate its discontinuation.[15]

Other medications commonly used in HIV medicine that can be associated with mental state changes and psychotic symptoms include corticosteroids; other antiviral agents, e.g. ganciclovir; antifungal agents, e.g. amphotericin B; and some antibacterials, e.g. antituberculosis drugs, dapsone and sulphadiazines.[4,16]

These 'psychotoxic' reactions, which may manifest as psychosis, mania or delirium, have been associated with the commencement of treatment with isoniazid, ethionamide, ethambutol and some of the fluoroquinolones. A study in Peru found that severe psychiatric syndromes associated with isoniazid occurred in approximately 1% of patients with tuberculosis between 1991 and 1999.[17] A careful history is therefore necessary to determine the temporal relationship between the development of psychotic symptoms and commencement of the drug, as this has very important implications in terms of management.

## TREATMENT OF HIV-ASSOCIATED PSYCHOSIS

When a patient presents with psychotic symptoms in the presence of HIV infection it is essential to exclude life-threatening medical causes of the psychotic symptoms. This may be extremely difficult in the agitated,

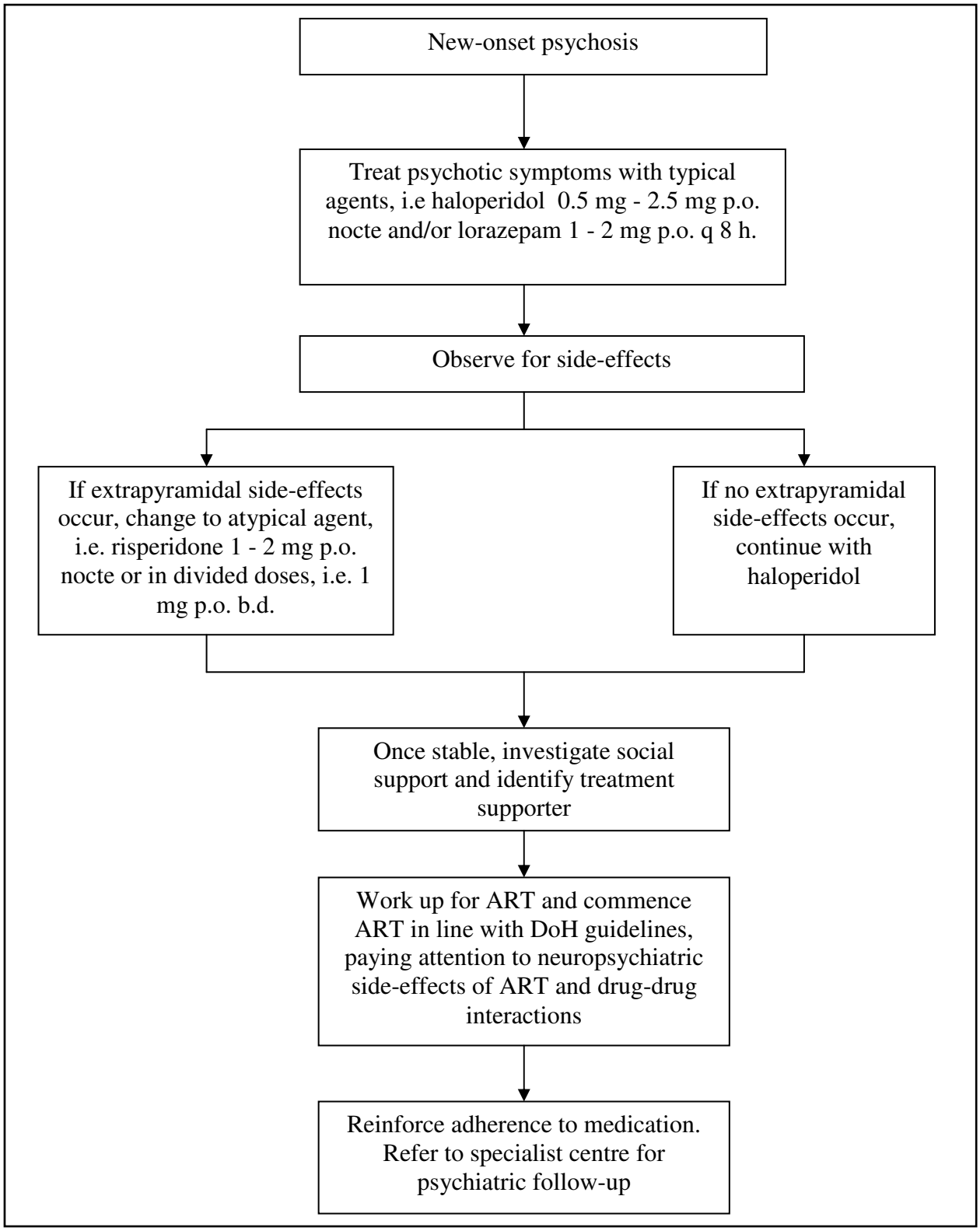


*Fig. 3. New-onset psychosis.*

disorganised or violent patient, and antipsychotic medications may need to be instituted before a thorough work-up is completed. Antipsychotic medications are safe and effective in the presence of HIV disease, but treatment modifications may be necessary and conservative dosing strategies may need to be implemented. Antipsychotic medication should always be used at the lowest possible dose for the shortest possible duration.

The choice of antipsychotic drugs depends largely on the patient, presenting symptoms, past response, potential side-effect profile, possible drug interactions, cost, and pill burden of the chronically ill patient. Many patients with new-onset psychosis or psychosis associated with various medical conditions may only require short-term treatment with antipsychotic medication. However, some patients may require long-term maintenance treatment with antipsychotic agents, and here special attention must be paid to the follow-

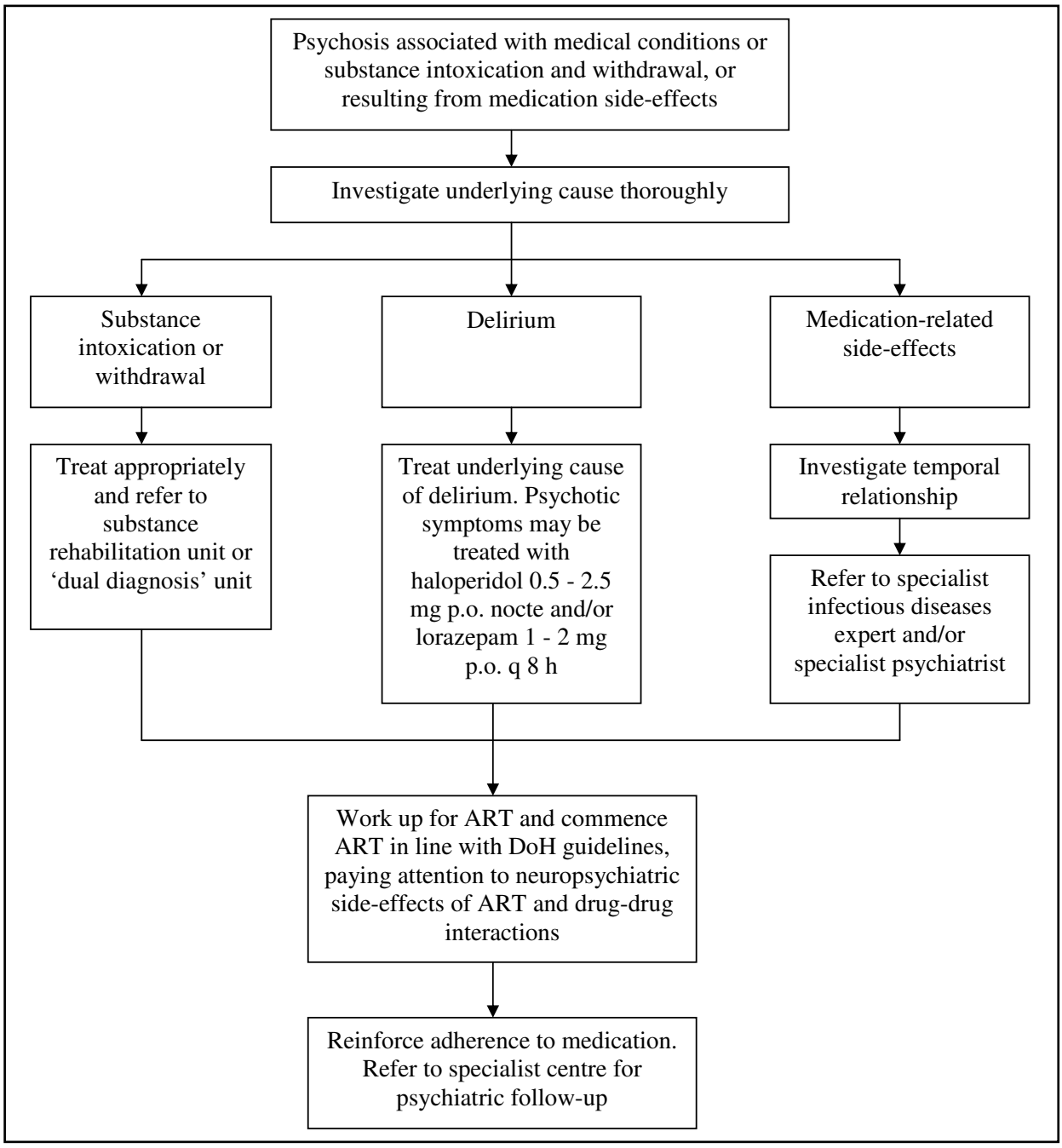


*Fig. 4. Psychosis associated with medical conditions or substance intoxication/withdrawal, or resulting from medication-related side-effects.*

ing factors. The typical antipsychotics are commonly used in resource-constrained settings. Here low doses of haloperidol (0.5 - 2.5 mg) and chlorpromazine (25 - 50 mg) have proven effective and safe. Vigilance is required with regard to extrapyramidal side-effects with haloperidol and anticholinergic side-effects with chlorpromazine.

Among the atypical antipsychotics, risperidone (1 - 4 mg/d) is commonly used, if available. This may be used in patients who present with or pose a risk of developing extra-pyramidal side-effects. The atypical antipsychotics are generally better tolerated than the typical antipsychotics, but they are associated with longer-term metabolic side-effects and the potential development of drug-drug interactions. Development of the metabolic syndrome, weight gain, abnormal lipid profiles and diabetes mellitus are well described with some of the atypical antipsychotics (olanzapine and clozapine). The lipodystrophy syndrome described in HIV-positive patients on ART predisposes these patients to the development of diabetes mellitus and coronary artery disease. The atypical antipsychotics with a propensity to develop metabolic syndrome and certain ART regimens (protease inhibitors (PIs) and the nucleoside reverse transcriptase inhibitors (NRTIs) in particular), taken together, may have serious long-term adverse effects.[18,19]

Many psychotropic medications and ART (especially the PIs and NNRTIs) share the same cytochrome P450 (CYP) iso-enzymes for metabolism, and competition between the two is prominent.[18,19] Interactions resulting in a decreased plasma concentration-time curve

for olanzapine may be clinically important.[20] For other important interactions, see the article in this issue on psychotropic prescribing.

It may be necessary to make use of benzodiazepines in the agitated, aggressive patient when antipsychotics alone do not provide sufficient containment. The use of benzodiazepines with few or no active metabolites is crucial. Lorazepam in small divided doses may be necessary, i.e. 1 - 2 mg orally every 8 hours. Caution is needed when using lorazepam in the patient with delirium, as one study found it to be ineffective and associated with significant adverse effects.[21] However, this agent may be the only drug available in certain resource-limited settings, and benefit versus risk will need to be ascertained for each individual patient.

Psycho-education is imperative throughout all stages of treatment. Psychosocial interventions and regular follow-up with the multidisciplinary team (psychiatrist, psychiatric nurse, social worker, occupational therapist and psychologist) are important. Adherence should consistently be reinforced and improved. Referral to an occupational therapist who uses various activity groups, support groups and food garden/nutrition security groups to help improve adherence may be considered. Supportive therapy is vitally important as the patient recovers. Temporary placement in an appropriate facility may be necessary for patients who are difficult to treat and those who require longer in-patient care.

Ongoing viral replication in the brain is a risk factor for neuropsychiatric disorders, and in combination with degree of immunodeficiency and other factors that lower the threshold for developing psychosis (family history, substance abuse) these constitute a stress-within-a-stress diathesis model. It is often not realistic to start ART in a psychotic patient without antipsychotics as adherence is likely to be poor, but once the patient has reached a state of relative stability ART should be started as soon as possible to decrease the contribution of HIV replication in the brain. In patients with psychosis related to immunosuppression and brain dysfunction, treatment with antipsychotics and ART simultaneously may be necessary from the time of initial presentation. It is vitally important that the patient be monitored closely, either as an inpatient if difficult to contain, or very closely by caregivers to ensure intensive adherence. Adherence counselling at all stages of recovery is imperative to ensure understanding of the need for ART and adherence to prevent possible resistance.

It is difficult to recommend a time frame with regard to duration of antipsychotic medication, as there is a relative paucity of literature. A possible option is to wean the patient slowly off antipsychotics after psychotic symptoms have remitted for 6 months, then take a watch-and-wait approach. This must only be done if good follow-up is possible so that antipsychotic medication can be reintroduced the moment symptoms recur.

In order to simplify the management of psychosis in the HIV-positive patient, three algorithms are presented. Fig. 2 describes the management of psychotic disorders predating HIV infection, Fig. 3 details the treatment and referral procedure for new-onset psychosis, and Fig. 4 describes the process for the assessment, management and referral of psychosis associated with medical conditions, substance intoxication/withdrawal and symptoms resulting from medication-related side-effects.

## COMMENCEMENT AND CHOICE OF ARV DRUGS FOLLOWING COMPREHENSIVE WORK-UP AND REMISSION OF PSYCHOTIC SYMPTOMS

Commencement of ART may be initiated in accordance with the Department of Health guidelines.[22] Department of Health first-line regimens are used, but special attention needs to be paid to co-existing antituberculosis treatment, liver toxicity, drug-drug interactions and possible neuropsychiatric side-effects of various ARTs. Ideally commencement of ART in the patient with psychosis should be instituted in a multidisciplinary setting. Adherence is an important concern in preparing patients for lifelong ART, but it is also crucial not to exclude patients with serious mental illness from receiving ART because they may 'possibly' be non-adherent. Involvement of a treatment supporter is essential to assist with adherence, with the patient's consent or assent. Intensive pretreatment education and adherence counselling of the patient and treatment partner are vital in order to assess treatment appropriateness and commitment to long-term neuropsychiatric follow-up.

## CONCLUSION

It is imperative to exclude an underlying medical cause for psychotic symptoms in the HIV-infected patient, and a careful differential diagnosis needs to be established based on the criteria set out above. Psychotic symptoms respond well to antipsychotic medication, but medication side-effects and drug-drug interactions must be vigilantly watched out for. It is important to remember that patients with mental illness are at an increased risk of being infected with HIV and of transmitting the virus. Prevention strategies, testing and referral of patients with mental illness and HIV/AIDS is vital. The algorithmic approach offered here serves to simplify and unite the assessment and treatment of psychosis in the HIV-positive patient at all levels of health care.

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# NEUROCOGNITIVE IMPAIRMENT IN PLWHA: CLINICAL FEATURES AND ASSESSMENT

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Neurocognitive impairment (NCI) occurs in 10 - 60% of people living with HIV/AIDS (PLWHA), depending on the severity of the NCI and the stage of the disease. The clinical features and definitions have evolved over the past two decades. HIV-associated neurocognitive disorder (HAND) is a new term used to describe the spectrum of neurocognitive impairment seen in HIV/AIDS. The earliest to most advanced stages are asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND) and HIV dementia (HAD), respectively. People with HAND have impairment on multiple cognitive domains, including attention, concentration, memory, executive function, motor functioning and speed of information processing, and sensory perceptual/motor skills deficits. The milder forms of HAND are easily missed. Diagnosis can be made on clinical grounds in the most severe cases; however, milder forms and confirmation of the diagnosis require neuropsychological testing. Screening tests have limited utility, especially in the milder forms of HAND. Individual subtests derived from longer neuropsychological batteries may be complementary in the diagnosis of HAND. Highly active antiretroviral therapy (HAART) has led to a 40% decline in the incidence of HAD. In the post-HAART era, HAD runs a more chronic course, is milder and is reversed in about a third of cases. However, HAART is not universally successful because incident cases occur in people on HAART. Overall HAART has been shown to be of benefit, and screening for HAND should be the standard of care for PLWHA. HAD is an AIDS-defining illness and patients qualify for HAART irrespective of their CD4 count. However, the benefit of starting ARVs for people with ANI and MND is currently inconclusive.

HIV infection of the central nervous system occurs almost simultaneously with systemic infection. Primary neurological disorders can affect the brain (e.g. HIV-associated dementia), spinal cord (e.g. HIV- associated vacuolar myelopathy) and meninges.[1] HIV-associated dementia (HAD) has also been referred to as HIV encephalopathy or AIDS dementia complex. These terms have been used interchangeably and describe a syndrome that includes the symptom triad of psychomotor slowing, memory impairment and behavioural problems. We now understand that neurocognitive impairment (NCI) in HIV is a spectrum of disorders.[2] In addition to HAD, lesser forms of NCI have also been described, namely HIV-associated minor cognitive-motor deficit (now called mild neurocognitive disorder) and asymptomatic neurocognitive impairment (ANI).[3] These disorders now fall under the new term HIV-associated neurocognitive disorder (HAND) (Table I). The diagnosis of HAND requires a history, clinical examination, appropriate investigations and neuropsychological testing. This review presents the clinical features, diagnostic criteria and tools to help diagnose HAND.

## PATHOGENESIS

HIV neuropathogenesis is not fully understood. It is unclear whether the cognitive decline seen in HIV-infected people is partly or wholly due to the direct effects of HIV, to secondary effects from the chronic hyperimmune activation, to other immunological factors (e.g. cytokines, chemokines and tumour necrosis factor) in the CNS, or to other factors such as hepatitis co-infection and clade diversity. However, it is understood that:[4]

- HIV does not infect the neurons and oligodenrocytes but the monocytes, microglia, astrocytes and endothelial cells.
- Once in the CNS the virus persists and evolves into different strains independent of the systemic reservoir.
- HIV is not evenly distributed in the CNS, and has a predilection for the basal ganglia.
- HIV RNA levels in the cerebrospinal fluid do not correlate with those in the peripheral circulation, especially in advanced HIV disease.

Involvement of the basal ganglia accounts for the clinical distinction between 'subcortical dementia' seen in HAD and the 'cortical dementia' typically seen in Alzheimer's disease.

## EPIDEMIOLOGY

HAD occurs in approximately 10 - 15% of all individuals with HIV/AIDS and is more common in late stages

| TABLE I. CRITERIA FOR HIV-ASSOCIATED NEUROCOGNITVE IMPAIRMENT* | | | |
|---|---|---|---|
| | **Asymptomatic neurocognitive deficit (ANI)** | **Minor neurocognitive disorder (MND)** | **HIV-associated dementia (HAD)** |
| Level of impairment | None | Mild everyday activities: reduced mental acuity, inefficiency in work, homemaking or social activities affected | Marked impairment in day-to-day activities at work, home or social functioning |
| Number SD below population norm on neuropsychological test | 1 | | 2 |
| Number of domains impaired | 2<br>Attention/working memory; verbal/language; abstraction/executive; complex perceptual motor; memory (learning and recall); speed of information processing; sensory perceptual/motor skills | | |
| Exclusion criteria | Absence of criteria for delirium or other causes for dementia. The condition cannot be explained by another co-morbid condition, e.g. substance abuse, infections, pre-existing neurological condition | | |

*Summarised from Antinori *et al.*[3]

of infection.[1] Less severe forms of HAND occur in 30 - 60% of people infected with HIV, depending on the stage of the disease.[1] Approximately 17% of the people attending a highly active antiretroviral therapy (HAART) primary health clinic in Cape Town had some level of NCI, including HAND.[5] The epidemiology of NCI has changed distinctly with the introduction of HAART. In the pre-HAART era HAD was common and more severe, with death likely within 6 months of diagnosis.[6] The introduction of HAART led to a major decline in the incidence of HAD.[1,6,7] However, data from cohorts on long-term HAART in the USA show that incident cases of HAD occur despite HAART, that progression of HAD is variable, and that NCI seems to be milder.[1] The overall prevalence of HAND continues to rise, presumably owing to incomplete reversal or prevention of cognitive impairment, longer survival on HAART and an increasing HIV prevalence.

At present there are no guidelines that recommend specific HAART regimens for the treatment or prevention of HAND. However, epidemiological data suggest at least partial benefit in giving HAART to prevent and reverse HAND.[7-9] HAD is an AIDS-defining illness and people with HAD qualify for HAART irrespective of CD4 counts. There is therefore an urgent need to raise awareness and develop rapid screening tools to detect and monitor HAND.

## CLINICAL FEATURES

Most clinicians can recognise frank HAD, but the more subtle HANDs are easily missed. HAND is: (*i*) a cognitive disorder, accompanied by (*ii*) motor dysfunction and/or (*iii*) behaviour problems.

**Cognitive changes** are problems with memory, decreased attention and concentration. These patients have decreased ability to learn new information and the speed at which they process information and mental tasks is slower than normal. Executive functioning, which includes planning, impulse control, organisation, abstract thinking and judgement, is also affected.

**Motor changes** are more subtle and are often missed. Patients complain of changes in their handwriting, tremor, and 'clumsiness'. They have gait abnormalities in the late stages.

**Behaviour problems** vary and range from aggression or marked isolation to the vegetative state seen in the late stages when patients are mute, immobile and incontinent. The presentation is similar to that of severe depression, because patients appear very apathetic and amotivated, with lack of initiative and psychomotor slowing.

The new classification requires systematic assessment of the following six domains:[3] (*i*) attention-information processing; (*ii*) language; (*iii*) abstraction/executive; (*iv*) complex perceptual motor; (*v*) memory; and (*vi*) sensory perceptual/motor.

Assessment of these domains requires neuropsychological tests that are often not intuitive to the clinician. Most clinicians can test memory with 'bedside' tests; however, assessment of executive functioning and psychomotor speed is more difficult. The challenge is to translate these research criteria and recommend specific tests that can be widely used by non-neuropsychologists. We can recommend a few tests that can assess these various domains (Table II).

The distinction between ANI, MND and HAD depends on: (*i*) the severity of impairment (when compared with population age- and education-appropriate norms for the above domains); and (*ii*) level of functional impairment in everyday activities at work, home or socially.

| TABLE II. SELECTED NEUROPSYCHOLOGICAL TESTS AND THE DOMAINS ASSESSED | | |
|---|---|---|
| **Neuropsychological test** | **Description** | **Domains assessed** |
| Rey Auditory Verbal Learning Test | Recall as many words as possible from a list of 15 words | Memory |
| Grooved peg-board | | Motor |
| Digit span forward | Patient is given an increasing number of random digits. They must repeat digits in the same order | Attention and concentration |
| Digit span backward | Patient is given an increasing number of random digits. They must repeat the digits in reverse order | Attention, concentration and working memory |
| Trail making test A | Join 25 circles with numbers in the correct sequence as quickly as possible. The numbers are distributed across the page and are not in order | Motor and speed of information processing |
| Trail making test B | Join 25 circles with numbers and letters in alternating sequence, i.e. join 1, A, 2, B, 3, C as quickly as possible | Motor and speed of information processing and executive function |

### ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT

This is the mildest form of HAND. The person has no impairment in everyday activities. They may complain of mild slowing in mental acuity and loss of concentration. Abnormalities can only be detected by testing the six domains and comparing against population norms. Patients must have 1 standard deviation (SD) abnormality on two of the six domains. ANI can progress to the next stage in the spectrum of HAND.

### MINOR NEUROCOGNITIVE DISORDER

MND was previously called HIV- associated minor motor-cognitive disorder. MND has the same criteria as ANI, i.e. the patient has 1 SD abnormality on two of the six domains. Unlike patients with ANI, they have impairment in their daily activities, at work or in social functioning or homemaking. This can be by self-report or by observation by someone who knows the patient.

### HIV-ASSOCIATED DEMENTIA

HAD is the most severe form of HAND. By definition patients have at least 2 SD abnormality on two domains, and these deficits cause significant impairment in everyday activities.[3] However, the clinical presentation can vary widely. In early HAD, the patient may appear depressed with apathy, lethargy and social withdrawal. Personality changes are not uncommon, and are often reported more by others than by the patient. In late HAD, psychotic symptoms may be prominent along with severe language dysfunction, verbal memory loss, seizures and mutism. The patient may be incontinent of urine and stool.

Neurological examination may show interruption of smooth ocular pursuit, slowing or inaccuracy of saccades, hyper-reflexia, 'frontal release' signs, slowing of rapid alternating movement of fingers, wrist or feet, and ataxia.

In the post-HAART era the progression of HAD has changed. Based on clinical observation of long-term treatment cohorts, three sub-types of HAD have been defined:[7]

1. **Sub-acute progressive dementia** occurs in ARV-naïve people and has a course similar to that observed in the pre-HAART era.
2. **Chronic active dementia.** These patients are on treatment but have poor adherence leading to viral resistance. They are at risk of developing other neurological complications.
3. **Chronic inactive dementia** occurs in people who are adherent to HAART and have undetectable viral loads. They have some recovery from neuronal injury and are neurologically stable.

## CLINICAL WORK-UP FOR HAND

HAND is a diagnosis of exclusion. Other diseases that affect CNS functioning, i.e. opportunistic infections, neoplasms, metabolic disturbances and iatrogenic complications, have to be systematically ruled out. Delirium and substance use are common in HIV-infected patients. Appropriate first-line investigations, e.g. a full blood count, assessment of kidney, liver and thyroid function, measurement of the vitamin $B_{12}$ level and serological testing for syphilis, are necessary. Lumbar puncture is also useful to exclude other opportunistic infections. The CSF viral load is not useful in the diagnosis of HAND and does not correlate with the severity of the impairment. Neuro-radiological investigations, e.g. computed tomography and magnetic resonance imaging, are necessary to exclude conditions such as progressive multifocal leuco-encephalopathy and primary CNS lymphomas that can mimic HAND. However, in resource-constrained settings these investigations are not readily available and they are not vital in the absence of focal localising signs.

With delirium and medical causes excluded, the diagnosis of HAND requires testing of the six domains using neuropsychological tests. However, these are often impractical or not available in busy clinical settings. Two-stage

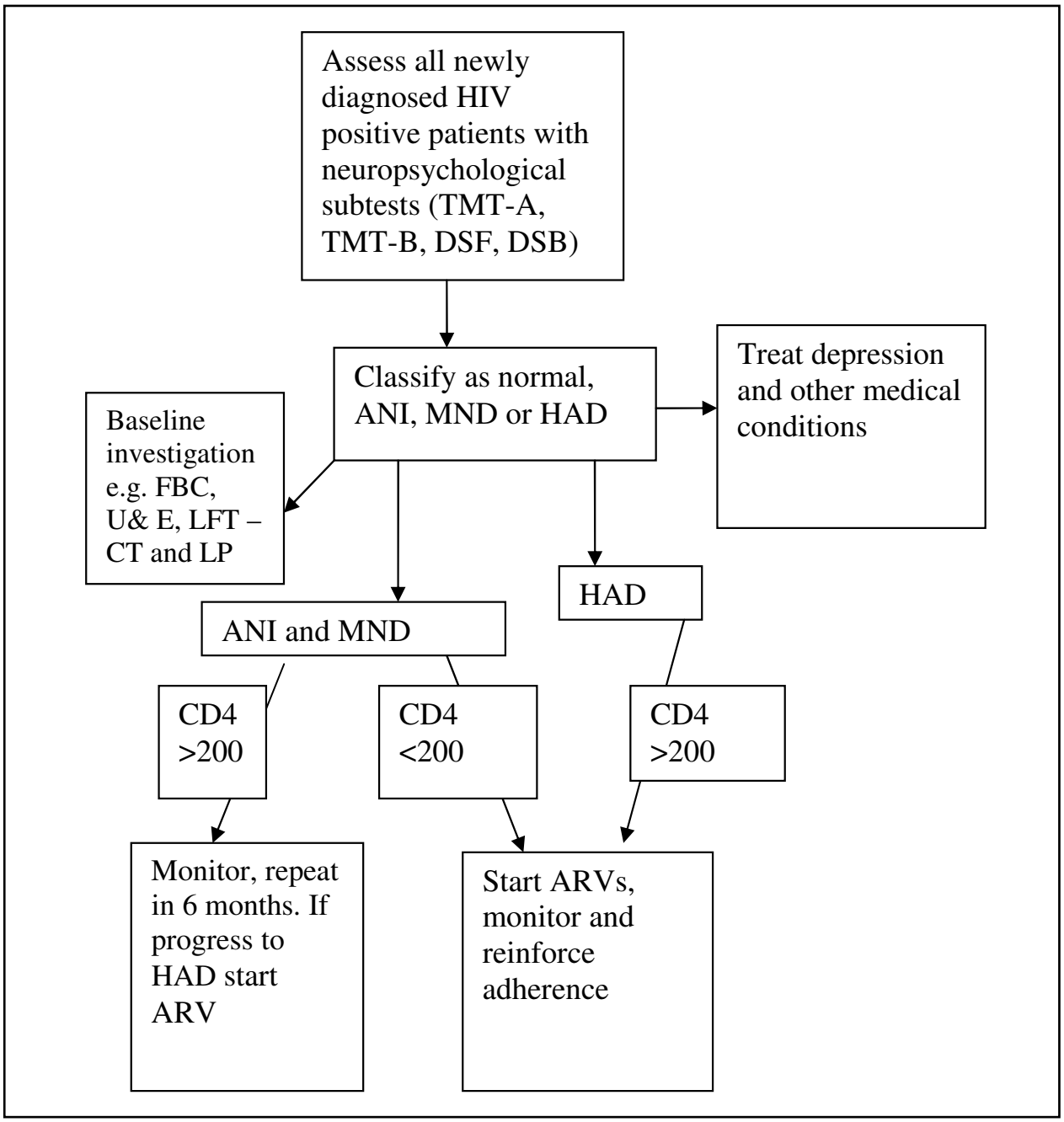


*Fig. 1. Summary assessment and management of neurocognitive function in newly diagnosed PLWHA.*

testing is commonly used in psychiatry. In the first stage a brief, bedside cognitive screening test is administered and people who screen positive can then be subjected to more detailed testing in the form of a neuropsychological battery. See Fig. 1 for algorithm for assessing and managing newly diagnosed patients with HIV.

### COGNITIVE SCREENING WORK-UP

**The Mini-Mental State Examination (MMSE)** was validated for distinguishing Alzheimer's dementia from other dementing disorders.[10] It is loaded with items that are representative of 'cortical' functions. Since HAND is primarily affects sub-cortical processes, the MMSE is not ideal. It is not useful in detecting the milder forms of HAND, and it is affected by age, education and cultural background.[11]

**The HIV Dementia Scale** comprises four items – an anti-saccadic eye movement error task, timed alphabet, verbal memory and copying a cube.[12] Two of these items are timed and therefore more sensitive to sub-cortical functions. This scale has been used in the USA[13] and validated in South Africa.[5] However, observing the anti-saccadic eye movement requires training and is difficult for non-neurologists to administer.[14]

**Mental alternation test.** Patients are asked to count to 20, say the alphabet, and then alternate between the numbers and letters in the following fashion: '1-A, 2-B, 3-C ...'. Progressing from the most recent number or letter to the next letter or number in the sequence is one alternation. The number of correct alternations in 30 seconds, discounting any errors, determines the

score. The maximum score is 52 points, and a score of ≤15 indicates the need for more extensive cognitive testing. This tests a limited number of cognitive domains and is dependent on level of education.[15]

**International HIV Dementia Scale (IHDS).** The IHDS was tested in the USA and Uganda and developed specifically for resource-constrained settings.[14] It has three subtests: timed alternating hand sequence, timed finger tapping, and recall of four items after two minutes. This test has many advantages over its predecessors: it is brief, it can be completed in 2 - 3 minutes, and the patient does not need knowledge of English. It can be performed by non-neurologists and does not require any special equipment other than a stop-watch. The recommended cut-off score of 10 had 80% sensitivity and 55% specificity in the Ugandan study.[14] The specificity declines rapidly with small increment changes in the score, and this may limit its utility. While it has many advantages, validation studies are needed for our local population.

**Neuropsychological battery.** Various neuropsychological test batteries have been proposed. Longer batteries may take as long as 9 hours and brief batteries as little as 1 - 2 hours. Further, the absence of local population norms may limit their utility.[16] Work to develop brief, normed bedside tests is underway (Singh *et al.* – unpublished data) focusing on the separate domains of memory and recall, attention and working memory, speed of information processing, executive functioning, and motor abnormalities. We have collected population norms for the following bedside tests: digit span forward, digit span backwards, trail making test A and trail making test B. While these tests require training to conduct and are likely to be beyond the reach of a busy primary care HIV clinical service, they have an important role to play as part of specialist referral to diagnose HAND.

## TREATMENT

### ANTIRETROVIRAL THERAPY

HAART has lowered the incidence of HAND and improved patient outcomes, but HAART is not universally successful in reversing or preventing HAND.[1] While HAART can effectively suppress viral replication in the systemic circulation, its pharmacodynamics and effects on the virus in the CNS are less clear. ARVs, especially protease inhibitors, do not cross the blood-brain barrier easily and do not achieve significant levels in the CSF. There is some evidence that CNS-penetrating HAART (e.g. abacavir and zidovudine) may be effective in improving neuropsychological functioning.[8,17] Growing evidence suggests that for milder neurocognitive disorders the use of antiretrovirals may slow progression or at least prevent severe forms of HAND.

However, owing to the lack of conclusive evidence that HAART can prevent or reverse neurological damage caused by HIV, the role of initiating HAART in asymptomatic individuals is undefined.


### ACKNOWLEDGMENTS

I would like to thank J Joska for all his assistance in preparing this manuscript. Dinesh Singh was supported by the Fogarty International Centre, NIH, grant 5-D43-TW00231 (AIDS International Training and Research Program, Quarraisha Abdool Karim, PhD, Principal Investigator).


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# THE IMAGING OF HIV-RELATED BRAIN DISEASE

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Advanced HIV disease is strongly associated with an increased occurrence of various neuropsychiatric disorders,[1] and highly active antiretroviral therapy (HAART) is an important aspect of managing these conditions effectively.[2] In addition, there is growing recognition that many HIV-infected individuals will develop neuropsychiatric disorders relatively early in the course of HIV disease, in many cases before CD4 cell counts drop below 500 cells/µl.[3] However, it is not known who in the earlier phases of the disease will go on to develop neurocognitive disorders, or who will respond to treatment.[4,5] New approaches in neuro-imaging have the potential to detect early HIV-associated damage in the brain. Preliminary evidence suggests that the neurotoxic effects of HIV result in damage to white matter tracts in the brain.[6] Once damage is established and related cognitive disorders ensue, the ability of HAART to reverse existing dysfunction is probably limited.[7] Earlier treatment with HAART in at-risk or minimally symptomatic patients may prevent further decline in cognition and delay the course of HIV disease.

## FINDINGS FROM AUTOPSY, CT AND MRI STUDIES

Many individuals infected with HIV eventually present with evidence of neurological involvement, including cognitive deterioration. Autopsy studies of patients with HIV-associated dementia (HAD) demonstrate damage to the deep white matter areas involved in sub-cortical dementia (including the caudate nucleus and basal ganglia).[8] This finding is complemented by results of both computed tomography (CT) and structural magnetic resonance imaging (sMRI), with association between HAD and both diffuse atrophy with ventricular dilatation[9] and deep white matter lesions. Furthermore, a correlation between declining cognitive function and the loss of volume in certain brain structures, including the basal ganglia and caudate nucleus, has also been reported.[10]

Dynamic contrast-enhanced MRI has identified sub-cortical grey and frontal white matter as the principal sites of early metabolic abnormalities in HIV disease.[11] Both increased regional cerebral blood volume and post-contrast enhancement have been reported in the basal ganglia in moderate and advanced HAD, reflecting increased vascularity and blood-brain barrier (BBB) permeability. These findings are consistent with the characteristics of the early neurological deficits, and the known predilection of HIV for the basal ganglia.[12] The degree of neurocognitive impairment in HIV is correlated both with the degree of BBB breakdown in the basal ganglia and with viral load.[13]

## DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI), a recent advance in MRI methods, is uniquely suited to the study of subtle white matter abnormalities that are not detected by traditional MRI. DTI can be used to quantify the magnitude and directionality of tissue water mobility (i.e. self-diffusion). Barriers such as myelin sheaths, membranes, or white matter tracts result in greater self-diffusion along the axis of the barrier and reduced diffusion out of the tract. This type of restricted self-diffusion is termed 'anisotropic'. Fractional anisotropy (FA) is a measure derived from the diffusion tensor imaging that assesses the degree of anisotropic self-diffusion, i.e. the integrity of the white matter tract.[14] The higher the FA the healthier the tract; lower FA indicates damage to its integrity. DTI provides us with information about the large-scale networks that are made up of long tracts connecting distant relay stations in the brain (Fig. 1).[15] These networks are important for the development of higher brain functions such as language, praxis, social behaviour and emotion. Lesions affecting white matter connections lead to dysfunction, and cognitive disorders are sometimes better explained by a disconnection mechanism between distant cerebral regions than by primary damage of those regions themselves.[16]

## DTI IN HIV

DTI studies have revealed central nervous system abnormalities in asymptomatic HIV-positive patients with no cognitive impairment and normal structural

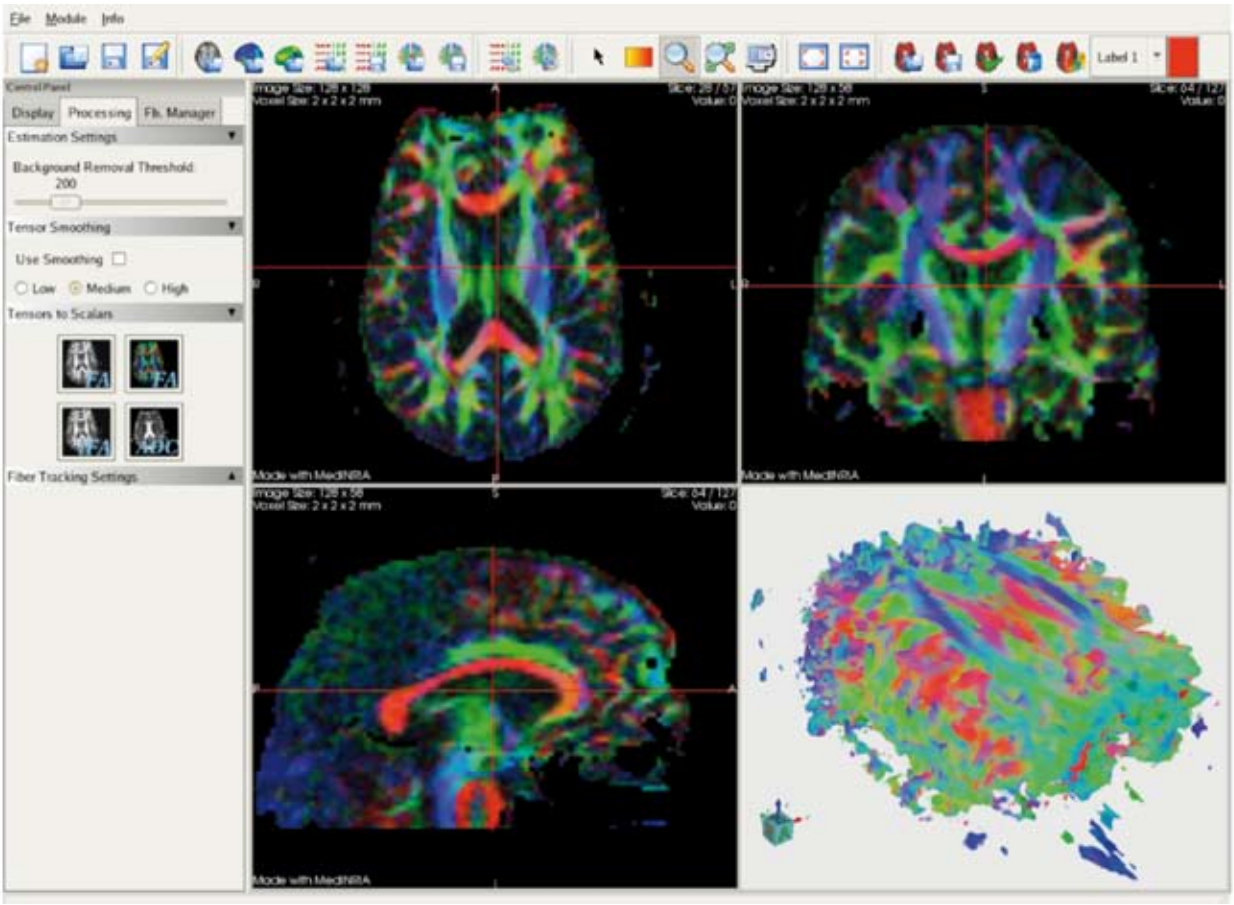

*Fig. 1. DTI tractography showing axial, sagittal and coronal views in an individual patient. Areas shaded green represent white matter tracts from anterior to posterior, those in blue inferior to superior, those in red, from left to right. It is possible to isolate regions of interest, or to detect areas where significant abnormalities in integrity of white matter occur.*

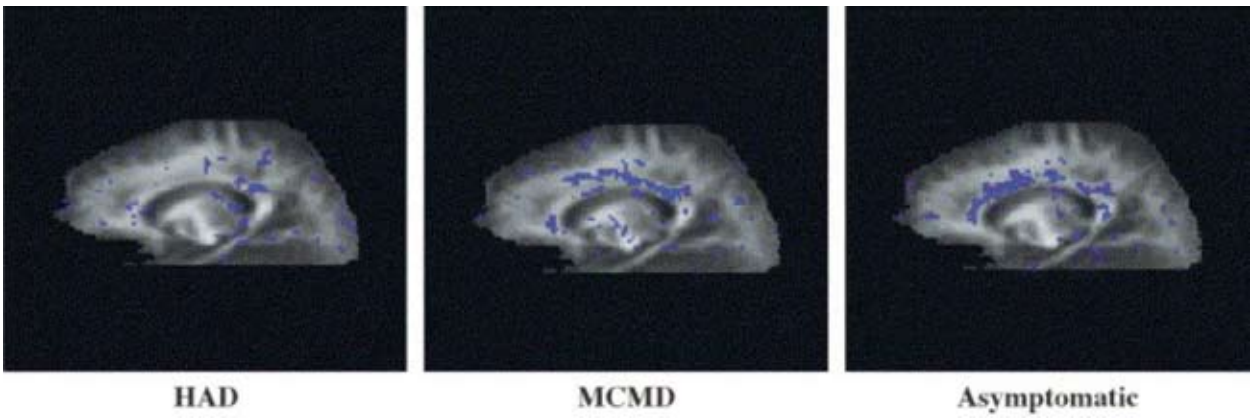


*Fig. 2. DTI images showing changes in FA in three groups of patients by clinical severity. These changes reflect significant differences between the groups compared with HIV-negative controls, and indicate (i) that FA is impaired across the spectrum of HIV-associated neurocognitive disorder, including asymptomatic neuropsychological impairment, and (ii) that different regions may be affected across different severities, with some affected areas being responsible for a greater degree of clinical impairment. The amount of FA does not correspond to the location or severity of FA.*

MR studies. Diffuse damage to cerebral white matter, as evidenced by pallor on DTI, is one of the most frequent neuropathological features of HIV-1 infection and has been found to be particularly prominent in the advanced stages of the disease.[17] The white matter pallor has been found to be more prevalent and severe in patients with HAD.[17]

DTI abnormalities have been reported in the frontal white matter of cognitively asymptomatic patients infected with HIV,[18] and MR spectroscopy studies indicate that this region may be subject to early injury in patients infected with HIV.[19]

Studies utilising DTI have identified sub-cortical white matter and corpus callosum abnormalities in patients with HIV, despite normal-appearing white matter on MR and non-focal neurological examinations[20] (Fig. 2). Patients with the largest anisotropy decreases had the most advanced HIV disease. Interestingly, patients with the lowest viral loads and normal anisotropy were receiving HAART. This has led some to suggest that DTI

could be used as a potential biomarker of brain injury in patients infected with HIV.[21]

## CONCLUSION

DTI and other emerging neuro-imaging technologies may provide markers for early CNS disease in HIV-positive patients, allowing for the earliest possible detection of cognitive impairment. This in turn may facilitate early preventive antiretroviral treatment to reduce long-term damage. Novel imaging techniques such as DTI applied in individuals with mild forms of neurocognitive disorder may be a good place to start. Studies examining response to HAART in patients infected with HIV will be important to determine whether DTI abnormalities reflect reversible or more advanced, irreversible injury. Correlates of white matter damage and neurocognitive decline need to be sought, including whether measures of white matter damage in the central nervous system correlate with viral load, illness duration, age, treatment exposure and treatment adherence. These factors are almost certainly critical in determining the overall impact of HIV on brain function, and in particular on white matter integrity.

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# PSYCHOTROPIC PRESCRIBING IN HIV

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The use of psychiatric medication in patients with HIV infection is a complex area, but given the high rates of psychiatric disorder in this population – possibly as high as 50%[1] – it deserves further consideration. A number of issues need to be thought about, including the nature of both the psychiatric illness and the HIV infection, the use of antiretroviral therapy (ART), and patient-related factors.

## PSYCHIATRIC ILLNESS IN HIV

The interaction between HIV infection and psychiatric illness is complex, with many authors suggesting that psychiatric disorders in HIV-positive individuals are frequently under-recognised and under-treated.[2,3] It is well established that there is an increase in the prevalence of a number of psychiatric disorders in HIV-infected individuals, internationally[4,5] and in South Africa.[6,7] There may also be changes in the clinical picture in patients with psychiatric disorders after HIV infection[8] and an interactive effect between HIV infection and vulnerability to psychiatric illness.[9]

## ANTIRETROVIRAL THERAPY (ART)

In patients on ART who may require psychotropic medication important considerations include possible side-effects of existing antiretroviral medications, as well as potential interactions between ART and psychotropics. Psychosis, mania, agitation and suicidal ideation have all been associated with ART. The antiretroviral agents most commonly implicated include abacavir, efavirenz and nevirapine.[10] Although in most cases it would appear that the psychiatric adverse effects occurred shortly after initiation of the antiretroviral agent, cases occurring over a year after commencement have also been reported.

Drug interactions between ART and psychotropic medication, as well as with other medications the patient may be receiving, is another area that must be approached with some caution. A number of psychotropic agents that are potent enzyme inducers are contra-indicated for use with almost all antiretroviral agents as they can seriously compromise antiretroviral therapy; these include carbamazepine, phenytoin, primidone and St John's wort. Caution is also advised when using certain selective serotonin re-uptake inhibitors (SSRIs) and benzodiazepines (see below).

With regard to the antiretrovirals, a wide range of interactions with psychotropic agents have been described, and careful observation in the first weeks to months after any change of these medications is required. All the protease inhibitors, as well as the non-nucleoside reverse transcriptase inhibitors, are metabolised by the cytochrome P450 system and may therefore possess enzyme-inducing or inhibiting properties. In the South African setting, the commonly used agents that require the most caution are efaverinz, which may induce or inhibit CYP3A4, and nevirapine, which may induce CYP3A4. Many other antiretrovirals have been reported as interacting with psychotropics, and a more comprehensive list of interactions can be obtained at the HIV InSite Database of Antiretroviral Drug Interactions (http://www.hivinsite.com/[11]).[10]

## PATIENT-RELATED ISSUES

It is also critical to take into account a wide range of psychosocial factors that may adversely affect the individual patient's willingness and capacity to take medication correctly and for the required duration.

- Many HIV-positive patients may already be on complex drug regimens.
- Patients are often going through a complex process of adjustment to and acceptance of a lifelong diagnosis of HIV/AIDS with associated stigmatisation.
- Many of these patients will be suffering from some degree of cognitive impairment.
- In many psychiatric disorders, particularly those associated with psychosis, insight may be lacking or may fluctuate.

When these issues are considered in their entirety, it becomes clear that the importance of selecting the simplest possible regimens, the provision of regular psycho-education and counselling, and the recruitment of family members or others as treatment partners for all the medications the patient may be receiving cannot be emphasised too strongly.

## PSYCHOTROPIC USE IN SPECIFIC DISORDERS

While this review is based as far as possible on the existing evidence base for psychotropic medication use in

HIV/AIDS, it is important to note that empirical evidence is limited in many instances. Data often come from studies outside sub-Saharan Africa, and in turn the applicability of such evidence to South African populations may require interrogation.

## ANXIETY DISORDERS

The vast majority of the existing literature on the treatment of these disorders in HIV-positive patients describes the use of psychotherapeutic approaches rather than medication. As an initial approach, this is perhaps appropriate in general populations.

Benzodiazepines have been shown to provide rapid symptomatic relief from acute anxiety states, but they should be used with caution in post-traumatic stress disorder (PTSD) and panic disorders, and they have severe limitations in terms of their capacity to produce tolerance and dependence.[12] There is no reason to believe that the situation differs in HIV. Further caution must be applied with the use of alprazolam, midazolam and triazolam, which are dependent on CYP3A4 for metabolism, so that inhibitors of this enzyme system may increase the half-life of these drugs, possibly causing over-sedation and respiratory depression. Additionally, CYP3A4 inducers may lower serum levels and reduce the effect of these drugs.[13] Perhaps safer choices are benzodiazepines such as oxazepam, lorazepam, and temazepam, which are metabolised by glucuronidation.[3] However, a cautious approach is required in all cases, with careful titration of initial doses and observation for accumulation.

There is some evidence in support of buspirone as an anxiolytic in HIV-positive individuals, as reported in two small studies.[14,15] However there are also reports of dyskinesias, myoclonus, psychosis and mania in HIV-positive patients.

Lastly, and perhaps of most clinical relevance, it should be noted that the SSRIs are widely recommended as first-line treatment for a variety of anxiety disorders, including PTSD, generalised anxiety disorder (GAD), panic disorder and obsessive-compulsive disorder in the general population.[10] There is little evidence to suggest this is not the case in HIV-infected individuals, and the use of these drugs is discussed below. In using the SSRIs to treat anxiety disorders it is useful to initiate medication at smaller doses than is usual for the treatment of depression, and in some cases the brief use of small doses of benzodiazepines during the initial period may be helpful.

Alternative hypnotics, such as zopiclone and zolpidem, should be used with caution as interactions with CYP3A4 have been reported. Beta-blockers are sometimes used in the treatment of GAD, but in the context of HIV, consideration must be given to the possibility of respiratory disorders and peripheral neuropathies, in which case these agents are best avoided.

## DEPRESSION

Depressive disorders and their treatment in HIV-positive populations have received far more attention than other psychiatric disorders. A particular area of concern has been raised by studies indicating poor adherence to ART regimens[16] and increased morbidity[17] in HIV-positive patients with untreated depression. Despite this, a systematic review and meta-analysis of controlled trials to examine efficacy of antidepressant treatment among HIV-positive depressed individuals[18] identified only seven studies, almost all of which involved white males in First-World populations. Of these, only three (involving fluoxetine, paroxetine and imipramine) reported significant effects.

Looking more broadly at the literature on tricyclic antidepressants (TCAs), there is evidence to suggest that response rates are similar to those in HIV-negative populations[19] and that these agents are as effective as SSRIs in depressed HIV-positive patients.[20] It would therefore seem that TCAs are an appropriate choice in this context. It is, however, important to consider a number of issues relating to the side-effects of these drugs, particularly anticholinergic effects (which may lead to dry mucous membranes and an increased vulnerability to mucocutaneous candidiasis), alpha-adrenergic blockade (which can result in problematic postural hypotension, particularly in patients with neuropathies and other systemic illnesses), and prolongation of the QTc interval. Other issues such as the potential for sedation and weight gain may be problematic or beneficial, depending on the particular circumstances.

With regard to the SSRIs, although the best evidence for efficacy to date favours fluoxetine and paroxetine, these agents are potentially problematic in conjunction with ART (in particular nevirapine and ritonavir) as both are metabolised by CYP2D6, while fluoxetine also inhibits CYP3A4; there is therefore an increased risk of serotonin syndrome, as well as of changes in levels of antiretrovirals. Although the quality of evidence for the efficacy of both citalopram and sertraline in HIV-positive populations is less compelling, some evidence does exist[21,22] and there is little to suggest interaction with CYP2D6 or CYP3A4. Possible side-effects that may be of concern with this class of drugs include gastro-intestinal disturbances and increased anxiety. These can, however, be mitigated by initiating therapy with low doses and slowly increasing to therapeutic levels.

There is weak evidence to support the efficacy of newer-generation antidepressants in treating depression in HIV-infected patients.[23] Mirtazapine has minimal effect on CYP2D6 or CYP3A410 and has proved a popular choice because of its relatively sedating effects and tendency to improve appetite and promote weight gain.[3] There is currently little evidence on the use of venlafaxine and duloxetine in depressed HIV-positive patients,

and metabolism by CYP2D6 and inhibition of this system would argue against their use as a first-line treatment. Bupropion has been studied in one open trial for depression in HIV-positive patients and was found to be effective,[22] but there are concerns that efavirenz, ritonavir and nelfinavir may increase levels by inhibiting bupropion hydroxylation.[3]

A number of alternative agents for the treatment of depression have been studied quite extensively in HIV. Concerns have been expressed about potential interactions between St John's wort and various antiretrovirals,[24] so this is best avoided. Testosterone may be of use in men with hypogonadism, which may occur as a result of HIV infection,[25] but is not broadly effective as an antidepressant. With regard to psychostimulants, their potential side-effect profile, which includes psychosis, mania, weight loss, anxiety, insomnia and cognitive deficits, would mitigate against their use as first-choice agents.

Finally, the use of electroconvulsive therapy should not be overlooked in cases of treatment resistance or where medication has not been tolerated. Although not well studied in HIV, there are reports of its beneficial use[26,27] and it should not be refused simply on the basis of HIV status.

## BIPOLAR DISORDER AND MANIA

Manic episodes, either as part of bipolar disorder or as a secondary complication of HIV infection,[5,28] are well described in HIV. In a first manic episode it may be preferable to avoid the immediate use of a mood stabiliser in favour of an antipsychotic (see 'Psychosis', below), with short-term use of benzodiazepines (see 'Anxiety Disorders', above) if necessary. In established bipolar disorder, recurrent or relapsing secondary mania, or where this initial approach has proven inadequate, the use of mood stabilisers is indicated. In bipolar mania the preferred first-line mood stabilisers are lithium and sodium valproate, with carbamazepine as a second choice.[10] As mentioned earlier, however, the potent enzyme induction attributed to carbamazepine makes it a poor choice in HIV.

There are mixed reports on the use of lithium in HIV-positive patients. Concerns have been expressed regarding possible increased sensitivity to side-effects[29] and worsening of cognitive impairment;[30] however, a recent study[31] demonstrated quite the opposite, with improvements in HIV-associated neurocognitive impairment on lithium. This may be related to its capacity, together with sodium valproate, for the inhibition of glycogen synthase kinase 3 beta (GSK-3 beta), a survival-regulating enzyme.[32,33] Lithium is excreted unchanged in the urine, so interactions with ART are unlikely. Its narrow therapeutic index, however, is of some concern, particularly when diarrhoea is likely, and extreme caution is required with medications that may reduce the glomerular filtration rate. It can therefore be concluded that lithium may be a reasonable choice, provided that it is well tolerated on initiation and that excellent compliance can be guaranteed.

Valproate (available as sodium valproate or valproic acid) is generally considered to be better tolerated than lithium and safer with regard to therapeutic index, but neutropenia, hepatic failure and the potential for teratogenesis in women of child-bearing age remain a concern.[10] Its potential to inhibit CYP3A4 may result in interactions with some antiretrovirals, and caution is advised when using it in combination with nevirapine and efaverinz. It has also been shown to inhibit GSK-3 beta.[33] Early reports raised some concerns that it may increase viral loads by stimulating replication.[34] More recently it was suggested that this effect, in combination with ART, may lead to the possibility of cure by depleting latent viral stores,[35] but unfortunately this has not been substantiated.[36] Whether sodium valproate may lead to cognitive decline in HIV-positive individuals or not is not entirely resolved, however, with some studies showing no decline[37,38] but one study suggesting problems with longer-term use at higher doses.[39] This concern is supported by a fairly extensive literature pointing to adverse neurocognitive effects of valproate in individuals with cognitive impairment, although it should be noted that valproate is not unique in this effect either (e.g. Gualtieri and Johnson[40]). While valproate is therefore probably a reasonable choice of mood stabiliser in this setting, it would seem prudent to exercise caution with higher doses and to monitor cognitive function carefully, shortly after initiation as well as in the longer term.

## PSYCHOSIS

The older 'classic' antipsychotics, haloperidol in particular, have been shown to be safe and effective in studies of HIV-infected patients with schizophrenia[8] as well as those with HIV-associated psychotic disorder.[41,42] However, these patient groups have increased susceptibility to extrapyramidal side-effects (EPSE) and possibly to tardive dyskinesia (TD) and neuroleptic malignant syndrome.[10] Although chlorpromazine may be less likely to produce EPSE and is helpful in restless patients when benzodiazepines are not well tolerated, this is similarly limited to a lower dosage range. Further problems include the well-established side-effects of neutropenia, alpha-adrenergic blockade and anticholinergic effects. It can therefore be concluded that these agents may be useful and, where psychosis or delirium with psychotic symptoms are present, a trial, at initial doses of not more than 1 mg of haloperidol, or the equivalent, is indicated; at higher doses, EPSE can be expected. It is also worth noting that an *adequate* trial of any anti-psychotic requires at least a week of treatment at any dosage increment, if not longer.

Given the high risk of EPSE and TD, the newer, second-generation or 'atypical' antipsychotics may be a

reasonable first-line approach, and are clearly a rational second line when EPSE have become apparent. Theoretically, at least, an additional advantage of these agents is their high potency as serotonin 5HT2A receptor antagonists, which may be a useful effect as pro-phylaxis against, and treatment of, progressive multifocal leucoencephalopathy.[43] Risperidone was shown to be effective in the treatment of HIV-associated psychotic and manic symptoms in one series of 17 cases,[44] where a particularly good response in patients with manic symptoms was noted. EPSE can however be a problem, even in low doses,[45] and severe complications as a result of interactions with ritonavir have been described.[46] There is very little literature of substance on the use of other second-generation agents, other than for short-term, symptomatic use in delirium. Some care must be taken with olanzapine, owing to metabolism by CYP2D6 (the same may be said of clozapine), but the low risk of EPSE and growing evidence of their efficacy as mood stabilisers[10] make these agents compelling choices. The use of clozapine may be considered in HIV-positive patients with treatment-resistant schizophrenia, but given this drug's association with neutropenia it is best used as a last resort in settings where CD4 counts remain high and white cell counts can be closely monitored.

## DELIRIUM

As mentioned at the outset, the most critical step in managing delirium in the setting of HIV infection is to vigorously identify and treat possible causes (see the article on assessment and treatment of psychosis in HIV-infected individuals in this issue). The short-term use of low-dose antipsychotics and/or benzodiazepines may be considered if clinically indicated to manage behavioural disturbance.

## HIV-ASSOCIATED DEMENTIA

As described elsewhere in this issue, the mainstay of treatment of HIV-associated dementia is ART, but short-term, symptomatic use of antipsychotics and mood stabilisers may be helpful.

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CASE STUDY

# THE BEHAVIOURALLY DISTURBED PATIENT WITH HIV/AIDS

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While HIV invades the brain early in the course of HIV infection,[1] severe mental illness probably only occurs later in the disease.[2] In many instances this may be the first presentation of a psychiatric illness in a younger person. In addition, the clinical syndrome may include manic and/or psychotic features, together with neurocognitive disturbance. These patients are at risk of secondary opportunistic infections or other features of systemic immunocompromise which may cause or confound the clinical picture.

## A CLINICAL CASE

A 30-year-old woman presented to a rural district hospital in the Eastern Cape. She was unable to give any history. Her family said she had recently returned from Cape Town. She had seemed normal on the day she arrived home but since then had become increasingly confused but with no specific complaints. Her patient records confirmed that she had recently completed 6 months of TB treatment and had started antiretrovirals (ARVs), comprising stavudine (D4T), lamivudine (3TC) and efavirenz, 2 months previously. Her CD4 nadir was 180 cells/µl.

On examination she was apyrexial, with a pulse rate of 120/min and a blood glucose level of 8.0 mmol/l. There was no meningism or clear focal neurological deficit, so lumbar puncture was not performed. On mental state examination she was found to be agitated and aggressive, with loud and incoherent speech; it was not possible to elicit delusions, but she appeared to be hallucinating. She gave appropriate answers to some simple questions and was orientated to month and year but not to day or date. A working diagnosis of psychosis secondary to HIV was made.

### CLINICAL PRESENTATION

- Where history from the patient is limited, a collateral history is essential.
- There are potentially multiple contributing causes, such as HIV itself, drugs including ARVs, opportunistic infections including tuberculosis or a primary psychotic disorder.
- It is critical to exclude delirium through careful clinical evaluation and targeted special investigations.

The patient was sedated with haloperidol and diazepam and admitted for further investigation. The following day she remained aggressive and confused. Efavirenz was stopped but D4T and 3TC were continued. Over the next week there was gradual improvement in her mental state. She became oriented to day and place, but complained of seeing people who were coming to steal her medication. Collateral history from her mother was that she had no known previous psychiatric history and that the hallucinations had started during her father's funeral a week before admission.

The results of basic blood tests were normal other than C-reactive protein (CRP) 63.4 mg/l and platelets 67 x $10^9$/l.

### INVESTIGATION

- In a case where severe behavioural disturbance is present in a setting of severe immunocompromise, investigations should include basic blood work-up, as well as lumbar puncture and a computed tomography scan of the brain.
- If confusion is prominent and/or the patient has a headache and/or fever, it is prudent to request polymerase chain reaction (PCR) testing of the cerebrospinal fluid for cytomegalovirus, herpes simplex virus, Epstein-Barr virus and JC virus.

After 1 week, the diagnosis of psychosis secondary to HIV was confirmed by a doctor at a tertiary level psychiatric unit. The recommendation was to wean the patient off haloperidol and replace it with risperidone. Risperidone is not available at level 1 district hospitals, so haloperidol 2.5 mg 3 times daily was continued. Nevirapine was introduced after 10 days. She was discharged a week later.

Two weeks later, having defaulted her follow-up appointment, she presented with what the admitting doctor described as 'aggressive and psychotic behaviour'. He increased the haloperidol dose to 5 mg twice

a day plus diazepam 5 mg at night. She claimed that her family were trying to kill her. She was prescribed fluphenazine 12.5 mg as an intramuscular injection and over the next week she settled and regained orientation to time, person and place. Five days later, after much discussion with her family, she was discharged with a review date in 1 month.

One month later, the clinical presentation recurred. She was sedated with haloperidol and lorazepam and after consultation with an HIV psychiatrist valproate 200 mg bd was added. It had emerged that prominent mood symptoms were present, namely irritability and expansiveness. The persecutory delusions were paired with grandiosity. Over the next week she gradually improved and regained her orientation to time and place. Valproate was increased to 400 mg bd and nevirapine was changed back to efavirenz on the basis that stopping the efavirenz had had no impact on her mental state and there is a potential drug-drug interaction between valproate and nevirapine.

A week later, the patient was feeling well with no psychotic symptoms and was fully orientated. She was discharged with a prescription for valproate 400 mg bd. She has now been followed up regularly for 4 months. She remains completely well and is adherent to both her valproate and ARVs.

**PSYCHOTROPICS**

- Haloperidol is safe to use in this setting with the drawback of a high potential for extrapyramidal side-effects; atypical antipsychotics, such as risperidone 0.5 - 2 mg 2 × daily or quetiapine 50 - 200 mg 2 × daily, if available, may be better.
- In the short term, lorazepam 2 - 4 mg 8-hourly (or oxazepam if liver impairment is present) may be used for sedation.
- If manic symptoms are a prominent feature, consider using valproate 300 mg 2 × daily, increasing to 600 mg 2 × daily; use lower doses and monitor liver function tests if liver impairment is present.

## DISCUSSION

Neuropsychiatric presentations in late-stage HIV require clinicians to carefully exclude a range of possible contributory causes. One case series reported a 2% incidence of new-onset psychosis in patients presenting with an AIDS-defining diagnosis. Of these, 50% had an underlying infective or metabolic cause while 50% were thought to have an HIV-related psychosis.[3]

Infectious causes may be due to bacteria, mycobacteria, viruses, fungi or spirochaetes and may form part of an immune reconstitution inflammatory syndrome (IRIS) if occurring after the onset of ARV medication. In the above case, the absence of fever and headache weighed against this possibility.

Medication-related causes of psychosis also occur. These include ARVs,[4] antituberculosis drugs and prednisone. Efavirenz is often implicated. A stepwise approach to removing potential drug causes is advised – treat the psychosis or mania appropriately, and if no response is seen, remove the most likely offending agent. Once the effect (or not) of this move has been appraised, an informed decision to make additional changes or switches can be made.

Primary psychiatric disorders are frequently seen in the setting of HIV infection. While bipolar disorder, mania and major depressive disorder with psychosis must all be considered, so too must the effects of psychosocial stressors such as bereavement, loss, unemployment and disability. Psychotropic treatments need to be used alongside psychosocial measures, which include educating families, addressing needs for disability grants and counselling.

The management of behaviourally disturbed patients with HIV in a remote rural hospital presents many challenges. One such problem is that once the diagnosis of HIV infection is made there is a tendency to attribute multiple symptoms to the HIV itself without a full consideration of other possibilities. While the initial probability of HIV-related psychosis may be fairly high in the presence of suggestive features, a definitive diagnosis requires the exclusion of a number of other possibilities.

A similar problem is related to the treatment of all patients with psychiatric illness in this setting, namely that they are labelled a 'psych patient' without consideration of which of many underlying conditions may be responsible for their symptoms. This situation is exacerbated by lack of resources. Under these conditions the standard of care for patients with features of psychosis is monthly injectable antipsychotics with reliance on the patient and relatives to ensure adherence. Patients with features of depression are similarly prescribed low-dose amitriptyline, often without a full explanation of time course or dose of treatment required. With more complex interventions being beyond the scope of the service, it is perhaps understandable that little attention is paid to the exact diagnosis. However, despite these drawbacks it is important that all patients are seen by a doctor at the district hospital and that complex cases be referred to the tertiary centre for an opinion and a follow-up plan before being referred back to peripheral clinics.

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ORIGINAL ARTICLE

# USEFULNESS OF THE HIV DEMENTIA SCALE IN NIGERIAN PATIENTS WITH HIV/AIDS

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**Objective.** Information on the cognitive complications of HIV/AIDS from sub-Saharan Africa, where statistics on HIV are alarming, is sparse because of lack of validated cognitive tools. This study assessed the usefulness and predictive validity of the HIV Dementia Scale (HDS) as a screening tool in HIV-positive Nigerians.

**Design.** HIV-positive patients were randomly selected over a period of 2 months.

**Setting.** The HIV/AIDS outpatient clinic at the University of Benin Teaching Hospital, Benin City, Nigeria.

**Subjects.** Asymptomatic and symptomatic HIV-positive patients were compared with controls matched with regard to age, gender and level of education.

**Outcome measures.** Cognitive performances on the modified HDS.

**Results.** Performances on the HDS of 160 HIV-positive subjects (80 asymptomatic and 80 symptomatic) were compared with those of 80 HIV-negative controls. The mean HDS scores (maximum 12) were 10.78 (significant deviation (SD) 1.18) (HIV-negative subjects), 8.85 (SD 1.38) (HIV, asymptomatic) and 5.2 (SD 1.13) (HIV, symptomatic); $p<0.01$. The HDS was found to have sensitivity of 97.3%, specificity of 80.4%, accuracy of 91.9% and a positive predictive value of 91.4% and a negative predictive value of 93.2%.

**Conclusion.** The HDS was shown to be a sensitive screening tool for patients with HIV/AIDS in sub-Saharan Africa, but it was insensitive to memory impairment in asymptomatic HIV-positive patients.

There has been considerable interest in the neuropsychological complications of HIV/AIDS in the last two decades.[1,2] A range of HIV-related cognitive complications has been reported to include poor performance on tests of attention and concentration, movement and coordination, reaction time and mental flexibility.[1,3,4] These HIV-associated neurocognitive deficits (HAND) manifest in their mild form as minor cognitive motor disorder (MCMD) and grossly as HIV-associated dementia (HAD). The annual incidence of HAD is 7% after development of AIDS[5] and it occurs in 20% of all HIV-infected persons,[6] although prevalence rates in sub-Saharan Africa are higher, ranging between 16% and 54%.[7-9] With an HIV prevalence of 5.8% among adults there are more than 3 million people living with HIV/AIDS (PLWHA) in Nigeria, more than in any other country in the world with the exception of South Africa and India.[10-12]

HIV-associated cognitive impairment may be a factor contributing to poor medication adherence in sub-Saharan Africa. With the increasing burden of disease there is clearly a need for a simple tool for rapid screening of cognitive functioning in HIV-infected persons. Efforts to develop appropriate screening techniques include the HIV Dementia Scale (HDS),[13] a brief measure that has shown promise but lacks extensive independent evaluation. The HDS (especially the modified and international versions, which exclude a difficult-to-administer anti-saccadic task) has been shown to be simpler to administer than most cognitive tests used in HIV patients and may be useful for screening of cognitive dysfunction in clinics with no neurologist or neuropsychologist on the staff, as it does not require special training.[13,14] This attribute makes it appealing in the African setting, where it is likely to be applied by primary care providers because of the dearth of neuropsychologists in health care facilities. The present study examines the usefulness of the modified HDS in screening for cognitive deficits in a sample of HIV-positive adults in Nigeria. Dementia was diagnosed according to the universally accepted criteria in the *Diagnostic and Statistical Manual for Mental Diseases*, 4th edition (DSM-IV-TR).[15]

## PATIENTS AND METHODS

A total of 160 antiretroviral therapy-naïve subjects with positive enzyme-linked immunosorbent assays for HIV were randomly selected (using a table of random numbers) from the HIV/AIDS clinic at the University of Benin Teaching Hospital, Benin City, Nigeria, between May and June 2006. Demographic data were obtained and the HDS was used to assess the patients' cognitive status after a detailed physical examination, including a comprehensive neuropsychiatric evaluation. The HIV-positive subjects were compared with 80 healthy seronegative subjects selected randomly from hospital staff and undergraduate students. Informed consent was obtained from the patients and the controls. The patients and the controls were matched with regard to age, gender and level of education.

The HIV-positive patients were categorised into two groups, asymptomatic and symptomatic, on the basis of their CD4+ T-lymphocyte counts (< 200 cells/µl for symptomatic) and the presence of HIV/AIDS-defining symptoms (unexplained fever – core body temperature >37.2°C – for more than 4 weeks, diarrhoea for more than 4 weeks, unexplained weight loss of >10% of previous body weight, and a generalised papular rash). We did not determine HIV clades (i.e. genetic subtypes of HIV groups) owing to lack of facilities, but some earlier studies have shown that the pattern of cognitive impairments may be affected by different clades in sub-Saharan Africa.[16,17]

Clinical neuropsychological evaluation including the identification of diagnostic features of dementia based on the DSM-IV-TR was conducted on all patients by a single neurologist (OAO) who was blind to the HDS rating. Deterioration in daily functioning was determined from information provided by family members living with the patients. They were questioned on the presence of the following cognitive symptoms: (*i*) memory disturbances (forgetfulness of new events, difficulty finding words or not knowing common facts) affecting daily activities; (*ii*) inability to cope with employment, academic demands and social activities that the patient could cope with before the onset of the illness; and (*iii*) deterioration in day-to-day functioning (i.e. difficulty in driving, shopping, handling money and self-care). Patients without functional deterioration, i.e. cognitive disturbances sufficient to interfere with day-to-day functioning, were not considered to have dementia.

Exclusion criteria included age under 18 years, already being on antiretroviral therapy, co-morbidity (diabetes mellitus, hypertension, epilepsy, hepatitis, intracranial disorders such as brain tumour, and other metabolic diseases), an inconclusive diagnosis, a major axis I psychiatric illness, a history of substance abuse, presence of clinical signs of cardiac failure, alcohol intake above 120 g per week or 13 units per week, a history of previous head injury with loss of consciousness, and anticholinergic medications.

### MEASURES

The HDS was developed as a rapid screening test to assess for HAD.[13] It is a paper-and-pencil neuropsychological instrument with objective subtests measuring psychomotor processing speed, verbal memory, constructional ability and executive function (response inhibition, set shifting) (Fig. 1). The score is based on performance for each subtest. This scale also exists in a modified form (eliminating the anti-saccadic subtest, which is often difficult to administer), and both the earlier and the modified versions have been validated for determining the presence and severity of HAD.[12] The modified version was used in this study.

The modified scale has a maximum score of 12, i.e. psychomotor speed score of 6, verbal memory recall score of 4, and construction task score of 2. Details are outlined in Fig. 1. For the psychomotor speed and construction task, the subject is timed using a stopwatch and the appropriate score given as indicated in Fig. 1. The modified HDS was administered by one of the authors (EE), who had no prior knowledge of the functional status categorisation using the DSM-IV-TR.

### STATISTICAL ANALYSES

Statistical analysis was done using Epi Info 2000 software (Centers for Diseases Control and Prevention, Atlanta, Ga). The age, gender and level of education of the three groups were analysed for significant differences using the chi-square test. The means of the performances of the HIV-positive patients were compared with those of the controls using the two-way analysis of variance. An *F*-test was used to determine the trend of linearity between cognitive performances and CD4+ levels. The level of significance was $p<0.05$. A receiver operating curve (ROC) was used to determine the cut-off score for HDS. The strength of association between cognitive disturbance and HIV seropositivity was determined with Mantel-Haenszel matched analysis and expressed as a likelihood ratio with 95% confidence interval (CI). The predictive value model using the 2×2 contingency table yielded the sensitivity, specificity and predictive values.

## RESULTS

The demographic data for the subjects are set out in Table I. The majority were in the 21 - 40-year age range. Clinical characteristics of the HIV-positive symptomatic subjects are set out in Table II. Mean (SD) CD4+ T-lymphocyte counts for the controls, the asymptomatic HIV-positive patients and the symptomatic HIV-positive patients were 668 (SD 8.6), 286 (SD 7.4) and 102 (SD 10.8) cells/µl, respectively ($p<0.01$). Mean (SD) total

| Maximum score | Subject's score | Test |
|---|---|---|
| | | ***Memory – Registration***<br>Give 4 words to recall and 1 second to say each. Then ask the patient all 4 after you have said them. |
| 6 | | ***Psychomotor speed***<br>Ask patient to write the alphabet in uppercase letters horizontally across the page (use back of questionnaire) and record time …… seconds.<br>**≤21sec = 6; 21.1 – 24 sec = 5; 24.1 – 27 sec = 4; 27.1 – 30 sec = 3; 30.1 – 33 sec = 2; 33.1 - 36 = 1; >36 sec = 0** |
| 4 | | **Memory – Recall**<br>Ask for the 4 words from Memory – Registration test above. Give 1 point for each correct word. For words not recalled, prompt with a semantic clue. Give half a point for each correct word after prompting. |
| 2 | | **Construction**<br>Copy the cube below; record time …… seconds<br>**<25 sec = 2; 25 – 35 sec = 1; >35 sec = 0** |

*Fig. 1. Modified HIV Dementia Scale.*

HDS scores (maximum 12) for the controls, asymptomatic HIV-positive patients and symptomatic HIV-seropositive patients were 10.78 (SD 1.18), 8.85 (SD 1.38) and 5.2 (SD 1.13), respectively ($F$=522.28, $p$<0.001). Details of the performances for the three categories are set out in Table III. There was a significant difference between the total scores for the normal subjects and the HIV-positive patients, irrespective of whether the patients were symptomatic or not. The asymptomatic HIV-positive patients performed better than the symptomatic patients ($t$=20.13, $p$<0.001). Comparison of the memory scores did not reveal a significant difference between the performances of the controls and the asymptomatic HIV-positive patients, but the performance of the symptomatic HIV-positive patients was significantly poorer ($p$<0.05).

The psychomotor speed of the HIV-positive subjects was significantly prolonged compared with the controls ($p$<0.001) but the time taken to perform the construction task did not differ significantly between the controls and the asymptomatic seropositive patients ($p$>0.05), although the construction task was performed poorly by the asymptomatic HIV-positive group (Table III). Deterioration in the performance of the HIV-seropositive subjects as CD4+ T-lymphocyte counts decreased was observed. The $F$-test for linear trend showed this observation to be significant ($p$<0.05), as outlined in Table IV.

A cut-off score of 9, obtained by ROC analysis, was used to determine the sensitivity, specificity and predictive values of the HDS. The HDS total scores were below the cut-off score of 9 in 109 HIV-seropositive patients (68.1%), but 41 (25.6%) of the patients had no features of functional deterioration and their HDS total scores were above 9. The total HDS scores were normal (i.e. above the cut-off score of 9) in 10 patients with functional deterioration, while 4 patients had no functional deterioration but had abnormal total HDS scores (Table V). This implies false-positive and false-negative rates of 8.6% and 6.8%, respectively. The likelihood ratio for cognitive disturbance in HIV-positive patients based on modified HDS scores in the presence of functional deterioration was 41 (95% CI 13 - 138). This implies that patients with clinical evidence of dementia based on cognitive symptoms sufficient to interfere with functional abilities are approximately 40 times more likely to have a score of <9 on the modified HDS. The sensitivity of the modified HDS was 97%, the specificity was 80%, the positive predictive value was 91% and the negative predictive value was 93% (overall accuracy, 92%).

## TABLE I. DEMOGRAPHIC DATA OF THE STUDY SUBJECTS

| | Controls (*N*=80) | Asymptomatic HIV positive (*N*=80) | Symptomatic HIV positive (*N*=80) |
|---|---|---|---|
| Gender | | | |
| Male | 32 | 32 | 34 |
| Female | 48 | 48 | 46 |
| $\chi^2$ | 0.104 | | |
| *p* | 0.95 | | |
| Age groups (yrs) | | | |
| ≤20 | 6 | 4 | 6 |
| 21 - 30 | 25 | 26 | 26 |
| 31 - 40 | 27 | 28 | 26 |
| 41 - 50 | 14 | 14 | 15 |
| ≥50 | 8 | 8 | 7 |
| $\chi^2$ | 0.734 | | |
| *p* | 0.99 | | |
| Age range (yrs) | 8 - 58 | 20 - 64 | 18 - 56 |
| Level of education | | | |
| Primary | 18 | 19 | 18 |
| Secondary | 37 | 38 | 38 |
| Tertiary | 25 | 23 | 24 |
| $\chi^2$ | 0.137 | | |
| *p* | 0.99 | | |

Primary education = maximum of 6 years of schooling; secondary education = more than 6 years of schooling without post-secondary education; tertiary education = more than 11 years of schooling with post-secondary education.

## TABLE II. CLINICAL CHARACTERISTICS OF THE SYMPTOMATIC HIV-POSITIVE SUBJECTS

| Symptom | Frequency (*N*) | % |
|---|---|---|
| Unexplained fever (>37.2°C for >4 wks) | 72 | 90 |
| Unexplained weight loss (>10% of previous body weight) | 76 | 95 |
| Persistent diarrhoea (>4 wks) | 62 | 78 |
| Generalised papular rash | 48 | 60 |
| Generalised herpes zoster | 18 | 23 |
| Clinical/radiological signs of pulmonary tuberculosis | 54 | 68 |
| Unexplained anaemia (haematocrit <30% or haemoglobin<9 g/dl) | 68 | 85 |

## DISCUSSION

The epidemiology of HIV-associated cognitive impairment in Africa is poorly understood. Vaguely defined criteria for cognitive impairment and assessment tools that are inadequate and lack validation, coupled with absence of normative population data, have limited proper study of cognitive impairment in HIV-positive populations in these settings. Although the clinical presentation of dementia may vary, depending on the causation, the diagnostic features are constant as set out in the DSM-IV-TR. The performance of an individual in the cognitive subtests may therefore reflect the degree of interference with performing similar tasks in daily life, although this is not invariable, as a poor cognitive score does not always infer functional incapacity. By comparing the performances of HIV-positive patients with controls, we assessed the differences in their abilities in these cognitive domains.

This study showed the usefulness and predictive validity of the modified HDS as a screening cognitive tool in Nigerian patients. The findings applied to subjects who met the DSM-IV diagnostic criteria for dementia and were also reported by family members to display functional deterioration in performance of daily activities. The modified HDS revealed deficits in all the tested cognitive domains in the symptomatic HIV-positive patients. Although the modified HDS showed impairment in cognitive abilities of the asymptomatic HIV-positive patients compared with the controls, the memory performances were similar. The predictive values, sensitivity and specificity values obtained from this study are comparable to those obtained by earlier authors, who used cut-off scores of 9 and 7.5.[18,19] The memory scores and the time taken to perform the construction task did not differ significantly between controls and asymptomatic HIV-positive patients. A similar observation was reported by Smith *et al.*[20] These findings corroborate earlier reports of a low prevalence of memory impairment among asymptomatic HIV-positive patients.[4,21,22]

The total scores showed the ability of the modified HDS to demonstrate the presence of cognitive impairments in HIV/AIDS, and it is therefore likely to be especially useful for population-based studies. It clearly demonstrated the presence of psychomotor retardation in the HIV-positive subjects, as has been reported by others.[1,5,14] The 68.1% prevalence of HAD observed in this study using the modified HDS is high. This figure

## TABLE III. HIV DEMENTIA SCALE SCORES FOR THE SUBJECTS

| | Controls | Asymptomatic HIV positive | Symptomatic HIV positive |
|---|---|---|---|
| Memory (mean SD)) | 3.68 (0.15) | 3.56 (0.64) ($p$>0.05)* | 1.82 (1.84) ($p$<0.001)† |
| Construction (mean (SD)) | 1.96 (0.20) | 1.23 (0.62) ($p$<0.05) | 0.84 (0.71) ($p$<0.001 |
| Time taken for task (s) (mean (SD)) (range) | 9.84 (5.84) (2 - 28) | 10.12 (3.46) (4 - 32) ($p$>0.05) | 24.21 (6.43) (16 - 56) ($p$<0.001) |
| Psychomotor speed (mean (SD)) | 5.14 (0.77) | 4.06 (1.72) ($p$<0.01) | 2.54 (1.46) ($p$<0.001) |
| Time taken for task (s) (mean (SD)) (range) | 15.9 (4.59) (10 - 36) | 19.32 (6.72) (11 - 48) ($p$<0.001) | 39.2 (2.44) (26 - 54) ($p$<0.001) |
| Total score | 10.78 (1.18) | 8.85 (1.38) ($p$<0.001) | 5.2 (1.13) ($p$<0.001) |

*Levels of significance for comparison between mean performances of the controls and asymptomatic HIV-positive subjects.
†Levels of significance for comparison between mean performances of the controls and symptomatic HIV-positive subjects.

## TABLE IV. THE COMPARISON OF COGNITIVE PERFORMANCE WITH CD4+ LEVELS USING THE *F*-TEST FOR LINEAR TREND

| Cognitive domains | Slope ($r^2$) | *F*-values | *p*-values |
|---|---|---|---|
| Memory | -0.98 (0.33) | 120.75 | $p$<0.0001 |
| Construction | -0.41 (0.26) | 86.90 | $p$<0.0001 |
| Time taken | 7.19 (0.47) | 283.45 | $p$ <0.001 |
| Psychomotor speed | -1.15 (0.31) | 111.70 | $p$<0.001 |
| Time taken | 9.15 (0.64) | 556.76 | $p$<0.001 |
| Total | -3.62 (0.65) | 579.11 | $p$<0.001 |

## TABLE V. FUNCTIONAL AND COGNITIVE STATUS OF SUBJECTS AND HDS SCORES

| | Symptomatic HIV+ (*N*=80) | Asymptomatic HIV+ (*N*=160) | HIV+ subjects (*N*=80) | Controls HIV- (*N*=80) |
|---|---|---|---|---|
| Functional status* (*N* (%)) | | | | |
| Deterioration | 80 (100.0) | 39 (48.75) | 119 (74.38) | NA |
| Still coping | 0 (0) | 41 (51.25) | 41 (25.62) | NA |
| HDS total score (mean (SD)) (maximum 12) | 5.2 (1.13) | 8.85 (1.38) | 7.03 (1.64) | 10.78 (1.18) |
| Normal (*N* (%)) | 4 (5.0) | 47 (58.75) | 51 (31.87) | 78 (97.5) |
| Abnormal† (*N* (%)) | 76 (95.0) | 33 (41.25) | 109 (68.13) | 2 (2.5) |
| $\chi^2$ 84.94 | $p$<0.001‡ | | | |

*Based on deterioration of functional abilities of patients (as expressed by family members living with patients).
†HDS cut-off score obtained by receiver operating characteristics analysis (cut-off score of 9; abnormal score <9).
‡Mantel-Haenszel matched analysis.
NA = not applicable.

is higher than rates of 16 - 54% reported by other authors in Africa[7-9] but similar to the 64.3% prevalence of cognitive impairment in a Nigerian population with asymptomatic mild HIV infection.[23] This may be due to HIV clade diversity and the differences in the sensitivity of neurocognitive assessment tools utilised in these studies. More recently studies have demonstrated the presence and pattern of cognitive impairments in black Africans with HIV/AIDS, but most of these studies used either complex psychometric[21,24] or computerised cognitive tests,[22,25] which are difficult to administer in most rural clinical settings and cumbersome for community-based research in sub-Saharan Africa.

The prevalence data available for HIV-associated cognitive impairment in Africa represent rates in people presenting to tertiary care centres and are unlikely to reflect rates in the general population. The level of education of research subjects affects performance on the HDS (a higher level of education improving cognitive performance), but the effects of age and gender remain inconclusive.[3,19] The HDS has been validated in subcortical cognitive impairment, the pattern of impairment observed in HIV-associated neurocognitive deficits.[19] The modified HDS requires no computer. It is a pen-and-paper cognitive instrument that can easily be administered in rural clinic settings. It can be

administered by health care providers who are non-professionals but have received instruction in its application. It is therefore suitable for community-based research in low-income developing countries. It has acceptable false-negative and false-positive rates. On the basis of our findings we believe it to be a useful screening tool for determining the baseline cognitive abilities of patients with HIV/AIDS and recommend its use for monitoring the response of patients with HIV-associated cognitive impairment who are on highly active antiretroviral therapy (HAART), as an earlier study has demonstrated improvement in neurocognitive and functional performance in HIV-positive individuals on HAART in sub-Saharan Africa.[26]

In conclusion, this study suggests the usefulness of the HDS as a screening tool for the assessment of cognitive abilities of patients with HIV/AIDS in sub-Saharan Africa. The sensitivity, specificity and predictive values compared favourably with those obtained among patients in developed countries. It is, however, limited by its inability to detect significant memory impairment in asymptomatic HIV-seropositive patients.

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# BOOK REVIEW

*The Virus, Vitamins & Vegetables: The South African HIV/AIDS Mystery.* Edited by Kerry Cullinan and Anso Thorn. Johannesburg: Jacana, 2009. Pp. 232. Price R169.95. ISBN 978-1-77009-691-2.

Political power and bad science is never a good combination. *The Virus, Vitamins & Vegetables* is a collection of essays that takes a look at the baffling government response to the HIV/AIDS epidemic in post-apartheid South Africa and 'the failure of those in powerful positions to acknowledge that a crisis was unfolding ...'.

At first glance the book could be slightly deceptive (candy-coloured pulp-fiction cover, snappy alliterative title, and strap line, 'The South African HIV/AIDS mystery'). So you might be forgiven for expecting to settle down with something a bit satirical, perhaps with a few swipes at the former Health Minister's promotion of the antiretroviral properties of beetroot.

The introduction, however, delivers a better clue to its content. Here the editors – 'long-time slow progressors' of HIV journalism from Health-e – describe how impossible it is to walk away or 'unsee' '... the matchstick-bodies; the listless babies; the rasping whispers of those whose throats are raw from thrush ...', i.e. the ravages delivered by untreated HIV/AIDS.

The authors, some of South Africa's key writers, activists and doctors, take us down the bewildering pathway of AIDS denialism (normally relegated to the rantings of a lunatic fringe) placed firmly at the centre of government policy in the face of a massive epidemic.

'In the beginning there was Virodene' – the book kicks off with James Myburg's description of Mbeki and the ANC's involvement in the controversial research agenda of the industrial solvent dimethylformamide, 'Viorodene', promoted as an AIDS cure, though rejected by the scientific community.

Michael Cherry's chapter reveals how the giants of AIDS denialism were gathered together by government to make up the majority of a panel of experts, to 'explore all aspects of ... developing prevention and treatment strategies that are appropriate to the African reality' – meanwhile denying the provision of proven antiretroviral prophylaxis strategies to reduce perinatal transmission in HIV-positive women.

'Accidental activist', also known as paediatrician Ashraf Coovadia, explains how 'Becoming a doctor always felt right ... I wanted to use my medical skills to relieve pain, heal and, hopefully, make the world a better place. Never in my wildest dreams did I think that being a doctor in South Africa's state sector would turn me into an activist, mediator, negotiator and protester.' He describes the hoops he had to go through, including an application to the Constitutional Court with a group of activists and medical professionals, just in order to be able to get on with his job of doctoring.

Kerry Cullinan examines the 'strange bedfellows' that government chose as experts above internationally renowned South African researchers, clinicians and virologists, in particular the vitriolic, dissident lawyer Anthony Brink.

Anso Thom and Liz McGregor tell tales of charlatan vitamin peddler Mattias Rath and 'Lazaras programme' (liquidised vegetables, lemon juice, olive oil, ProNutro, and a mysterious magic ingredient named African Solution) chief, Tine van der Maas. These chapters reveal the tacit endorsement of quacks and their cures by the Minister of Health and the inevitable consequences.

Former leaders of the Treatment Action Campaign (TAC) provide the closing chapters. Zackie Achmat remembers the decade as a time of great losses and great triumphs in a personal reflection of the years struggling for health, life and dignity for people with AIDS. Sipho Mthathi looks to a post-Mbeki and Manto era, with some trepidation about Zuma's chauvinism, calling for social and economic programmes to properly address inequality and poverty.

All this and more left me with an overwhelming sense of exhaustion. In addition to stating the obvious, that too many people died unnecessarily while government questioned the link between HIV and AIDS and delayed their effective treatment, too many clever and inspiring people were distracted during this time from what would still have been a monumental task without denialism in the mix.

The editors and authors are to be applauded in that little space is wasted trying to rationalise the irrational. In the introduction the editors explain that in many ways Mbeki's official biographer, Ronald Suresh Roberts, spurred them on to put the book together, with his revisionism of a 'poor misunderstood President', who had 'never been an AIDS dissident'. More importantly the book documents an era in an attempt to try, as Justice Edwin Cameron writes, 'to understand the extent of the calamity that befell us through the mismanagement of AIDS, and how it happened, so as to forewarn us against a repetition'.

**Polly Clayden**

# CPD QUESTIONS

**Journal 35**

**Two CPD points are awarded for the correct completion and submission of the questions below.**

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1. True (A) or false (B) – click on the correct answer:
   Intrusive recollections, avoidance/numbing, and hyperarousal are significant symptoms in post-traumatic stress disorder (PTSD).

2. True (A) or false (B) – click on the correct answer:
   Benzodiazepines are important first-line agents in the management of PTSD.

3. True (A) or false (B) – click on the correct answer:
   Efavirenz is the most commonly implicated antiretroviral causing drug-induced psychosis in HIV, and this usually manifests early after drug initiation.

4. True (A) or false (B) – click on the correct answer:
   In an HIV-infected individual, a diagnosis of delirium generally does not require further work-up.

5. True (A) or false (B) – click on the correct answer:
   In an HIV-infected individual presenting with an acute psychotic episode, the possibility of an underlying primary psychiatric disorder (that is unrelated to HIV infection) warrants consideration.

6. True (A) or false (B) – click on the correct answer:
   HIV-associated psychosis always requires a lumbar puncture and computed tomography scan of the brain as part of routine work-up.

7. True (A) or false (B) – click on the correct answer:
   Haloperidol (starting dose 0.5 - 2.5 mg/day) is commonly used in the management of HIV psychosis.

8. True (A) or false (B) – click on the correct answer:
   HIV crosses the blood-brain barrier during acute infection and infects neurons only.

9. True (A) or false (B) – click on the correct answer:
   HIV-associated dementia typically involves the basal ganglia (i.e. is a subcortical dementia), and is therefore more likely to present with motor deficits compared with Alzheimer's dementia (a cortical dementia).

10. True (A) or false (B) – click on the correct answer:
    HIV may lead to subtle but measurable deficits in neurocognitive function that occur early in the course of HIV disease in otherwise asymptomatic patients.

11. True (A) or false (B) – click on the correct answer:
    Antiretroviral therapy is not an effective treatment for HIV-associated dementia.

12. True (A) or false (B) – click on the correct answer:
    The HIV dementia scale has a low sensitivity in detecting HIV-associated dementia.

13. True (A) or false (B) – click on the correct answer:
    Depression is more common in HIV-infected individuals than in those without HIV/AIDS.

14. True (A) or false (B) – click on the correct answer:
    Insomnia and wide-ranging somatic complaints in the absence of a low mood are rare presentations of depression.

15. True (A) or false (B) – click on the correct answer:
    A clinician with special psychiatric training is required to diagnose and treat depression in an HIV-infected patient at primary care level.

16. True (A) or false (B) – click on the correct answer:
    In a patient on antiretroviral therapy with poor adherence who is diagnosed with depression, effective treatment of the depression may improve treatment adherence.

17. True (A) or false (B) – click on the correct answer:
    Screening for suicidality is important in HIV primary care.

18. True (A) or false (B) – click on the correct answer:
    A 6-week course of selective serotonin reuptake inhibitors (SSRIs) should be adequate to treat most depressive episodes.

19. True (A) or false (B) – click on the correct answer:
    Fluoxetine is safe and effective for treatment of depression in HIV infection, but the potential for drug-drug interactions requires consideration.

20. True (A) or false (B) – click on the correct answer:
    Lithium is generally a better choice than valproate as a mood stabiliser for HIV-infected individuals with bipolar mood disorders as it has a safer therapeutic index.