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- Guideline: Neurological and psychiatric disorders in HIV-positive children and adolescents
- Management of diarrhoea in HIV-positive adults
- HIV and the placenta
- Closing the gaps on PMTCT

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SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

MESSAGE
From the Editor

This edition of the Journal, released to coincide with the Southern African HIV Clinicians Society's biannual conference, showcases local clinical research in keeping with the conference theme, 'Excelling in Clinical Care'.

In their forum article, Geffen *et al.*[1] open the issue with a call for two potentially significant adaptations to the 'one size fits all' policies that characterise many public sector services, to deliver antiretroviral therapy across southern Africa. Paediatric neurological and psychiatric complications are an area of particular complexity in HIV management, and to help primary care providers investigate, diagnose and manage children, Nassen *et al.*[2] have produced simple yet comprehensive guidelines.

Two submissions explore the prevention of mother-to-child transmission of HIV from very different perspectives. First, Pillay *et al.*[3] investigate the potential role of DC-SIGN and related molecules in the vertical transmission of HIV. Shifting from molecular methods to health systems perspectives, Ibeto *et al.*[4] explore the patient- and service-level factors that may contribute to HIV transmission at a population level.

Two articles showcase strong examples of local clinical research. Working in KwaZulu-Natal, Kudsk-Iversen *et al.*[5] describe the challenges in diagnosing and managing patients presenting with diarrhoea in a district hospital, pointing to the need for clearer guidelines – a possible future focus of the Society. Sogbanmu *et al.*[6] document the challenges in implementing guidelines for the management of cryptococcal meningitis in the Eastern Cape. These two articles demonstrate the importance of locally appropriate guidelines to support clinical care.

I hope that you enjoy this issue of the Journal and the conference. For those of you who cannot attend the sessions in Cape Town, we will run the best abstracts from the meeting in the December edition.

Happy reading.

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References

1. Geffen N, Robinson R, Venter F, Low M. One size doesn't fit all: Tailoring adult antiretroviral treatment. Southern African Journal of HIV Medicine 2014;15(3):77-78. [http://dx.doi.org/10.7196/SAJHIVMED.1095]
2. Nassen R, Donald K, Walker K, et al. Management of mental health disorders and central nervous system sequelae in HIV-positive children and adolescents. Southern African Journal of HIV Medicine 2014;15(3):81-96. [http://dx.doi.org/10.7196/SAJHIVMED.1091]
3. Pillay K, Cloete M, McLeod H. Expression of DC-SIGN and DC-SIGNR in placentas of HIV-positive patients. Southern African Journal of HIV Medicine 2014;15(3):97-101. [http://dx.doi.org/10.7196/SAJHIVMED.1094]
4. Ibeto M, Giddy J, Cox V. Closing the gaps: Steps towards elimination of mother-to-child transmission of HIV. Southern African Journal of HIV Medicine 2014;15(3):108-109. [http://dx.doi.org/10.7196/SAJHIVMED.1047]
5. Kudsk-Iversen S, Gilbert JP, Azarath A. Management of patients presenting with diarrhoea to a regional emergency department in KwaZulu-Natal: Call for clearer, more relevant guidance. Southern African Journal of HIV Medicine 2014;15(3):102-103. [http://dx.doi.org/10.7196/SAJHIVMED.1082]
6. Sogbanmu OO, John MA, Lalloo U. Management of cryptococcal meningitis in adults at Mthatha Hospital Complex, Eastern Cape, South Africa. Southern African Journal of HIV Medicine 2014;15(3):104-107. [http://dx.doi.org/10.7196/SAJHIVMED.991]

MESSAGE
From the Executive

While I was attending the Melbourne International AIDS Society (IAS) conference in July, I must admit that I was surprised at the announcement by the Minister of Health on the change in our eligibility criteria for antiretrovirals (ARVs). He announced that, to be in line with the World Health Organization, all HIV-infected individuals with a $CD4^+$ count <500 cells/µl should be started on antiretroviral therapy (ART), and that all HIV-infected pregnant women should initiate lifelong therapy, namely Option B+. The Society congratulates the National Department of Health on their willingness to amend South African ARV policy in order to treat as many individuals as possible.

In terms of raising the $CD4^+$ entry level to 500 cells/µl, it must be noted that while randomised, clinical trial data on the clinical benefit of ART in patients with $CD4^+$ counts >350 cells/µl are not yet available, we do recognise that there are advantages to having more people on medication. There is a clear transmission-prevention benefit in discordant couples and there are accumulating data in the community setting.

So, as clinicians, we need to up our counselling game. The task of taking lifelong medication is an onerous one. Our current first line is not forgiving of missed doses. We, as healthcare workers, should have a thorough discussion with patients about the potential benefits, uncertainties and side-effects of medication. If patients are motivated to stick to their treatment, they should be prescribed ART; if they do not yet feel ready, they should be given time to work through the issues needed to adhere to therapy. Obviously, this would be done with close monitoring of their $CD4^+$ counts.

On another note, September 2014 brings our next conference. It promises to be packed with interesting debates, excellent plenaries and top-notch speakers. For those of you who are attending, enjoy the opportunity to network and connect with other HIV clinicians. For those of you who cannot make it, follow our Facebook page (http://www.facebook.com/SAHIVSoc), Twitter account (@SAHIVSoc) and the media.

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FORUM

One size doesn't fit all: Tailoring adult antiretroviral treatment

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Advances in antiretroviral treatment mean that patients in the public health system can be given more options in the management of their treatment. Although public health programmes tend to offer one-size-fits-all approaches, patients might benefit from a more flexible approach. In particular, we propose that people with HIV should be given more choice with regard to when to start treatment, and patients who experience efavirenz side-effects should be encouraged to switch to other medications, which will be facilitated by faster registration and lower prices of newer antiretrovirals.

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In the past decade, the standard of care for HIV treatment in the public sector has improved considerably. Our increased knowledge of antiretroviral (ARV) medicines and the additional drugs in our treatment arsenal are an opportunity to give patients a greater number of options and improve the tolerability of treatment.

When the state's antiretroviral therapy (ART) roll-out began in 2004, the CD4$^+$ initiation threshold for adults was 200 cells/µl and the first-line regimen included stavudine, a drug associated with severe side-effects. A decade later, the CD4$^+$ threshold is 350 cells/µl,[1] and will be increased soon to 500 cells/µl.[2] Additionally, stavudine has been replaced with a safer alternative, tenofovir. While 10 years ago, adults on their first regimen had to take varied-dose combinations twice daily, today most patients are being prescribed one pill once daily. This progress has resulted in ART that is easier to manage and maintain.

Public health programmes need to standardise the care offered to patients. But a one-size-fits-all approach can be too restrictive, resulting in some patients receiving suboptimal care. There is scope to offer more options to patients with HIV, at least in some facilities, with the prospect of improving their quality of life. This increased individualisation of treatment is unlikely to overburden the public health system. While there are a number of factors that affect individualising treatment, here we focus on two that we believe can be adapted in public-sector ART programmes in South Africa (SA): (*i*) efavirenz tolerability; and (*ii*) treatment initiation.

Efavirenz tolerability

In 2014, ART options are relatively plentiful, but several important ones are, for the most part, beyond the public sector. Besides nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, integrase inhibitors are now also available in the private sector, but access is limited to specific research and clinical scenarios in public facilities.

The current first-line regimen includes efavirenz, which is tolerated well by most patients. Given that over 2.5 million patients are receiving treatment in the public sector, about 2 million are likely to be receiving efavirenz. But some patients endure debilitating neurocognitive side-effects from this drug; recent data suggest a doubling of the suicide rate in people treated with efavirenz over other regimens.[3] Patients should have the opportunity to modify their regimen by switching efavirenz for a protease or integrase inhibitor.

The concern is the price and availability of alternative drugs. The standard first-line efavirenz-containing regimen costs the state less than R100 per patient per month. Protease inhibitors cost more, but have become increasingly affordable. Raltegravir, however, is not readily available in the public sector, is on the state tender at R533 per patient per month,[4] and is currently dosed twice daily. New integrase inhibitors like the daily-dosed dolutegravir are not yet available in SA, and the local price is as yet unknown.

The lag times between ARVs being approved by the US Food and Drug Administration, European Medicines Agency v. the Medicines Control Council (MCC) are extraordinarily long, especially considering that there is much greater need in SA and other sub-Saharan African countries than in North America or Europe. To improve treatment options for patients, clinicians, researchers and activists need to put pressure on pharmaceutical companies and the MCC to prioritise registration here (and in other African countries). Campaigning for lower prices of new ARV drugs must continue.

Treatment initiation

The HPTN 052[5] and PARTNER[6] studies show that HIV-positive people with suppressed viral loads and who are receiving

treatment will not transmit the virus to HIV-negative sexual partners. Also, clinical trial evidence shows that it is clinically beneficial to initiate treatment at a CD4+ count of 350 v. 250 cells/μl.[7] But the optimal CD4+ threshold to initiate patients to maximise clinical benefit remains unknown. It is possible that the benefits of starting above 350 cells/μl may be undone by interrupted drug supplies or if poor adherence results in the emergence of drug resistance. Within the next 3 years, the START[8] and TEMPRANO[9] clinical trials are likely to provide a clearer answer on the clinical benefits and risks of initiating treatment above 350 cells/μl.

But without clear evidence that the clinical benefit of earlier treatment outweighs harm due to side-effects, patients should be given the opportunity to make an informed choice. Their pathophysiology, preferences and circumstances should be taken into account to determine when it is appropriate to initiate treatment. The question of when to start treatment has become contentious, and many experts differ on this issue. This is understandable, given the current lack of evidence about the clinical and the public health benefits of suppressing viral load in sexually active people with HIV.

There is increasing pressure on people with HIV to start treatment earlier, e.g. at 500 cells/μl. The World Health Organization raised the CD4+ threshold for initiating ART to 500 cells/μl in its 2013 treatment guidelines.[10] The SA Minister of Health has announced that this threshold will also be used in SA from January 2015.[2] In response to the Minister's announcement, the Southern African HIV Clinicians Society correctly wrote: 'We … support an individualised approach in patients with a CD4+ count 350 - 500 [cells/μl]: after a discussion about the potential benefits, uncertainties, side-effects and need for impecable [sic] adherence patients should only be prescribed ART in this CD4+ range if they are motivated for lifelong ART with the required adherence. If they do not feel ready yet, ART should be deferred until their CD4+ count is below 350 [cells/μl] with a plan in place for ongoing follow-up and CD4+ monitoring.'[11]

Furthermore, the threshold of 500 cells/μl is arbitrary and not based on clinical trial findings. We therefore propose the following approach: ART should be offered to all people with HIV. As part of discussions between patients and providers, patients need to be given an informed choice.

Patients with CD4+ counts >350 cells/μl should be informed that the clinical benefits and risks of starting ART at high CD4+ counts are, as yet, unknown, and that taking treatment daily is likely to be a life-long commitment. Patients should also be informed that within a few years, more will be known about this.

Patients who are sexually active and want to minimise their risk of transmission to sexual partners should be informed that treatment can reduce the risk of transmitting HIV considerably, at least once viral load becomes undetectable.

Based on this information, patients who wish to start at a high CD4+ count should be allowed to do so. There are caveats: Early ART is not a reasonable option in facilities still using stavudine or zidovudine as first-line treatment, nor in facilities prone to stock-outs. In resource-stretched facilities with high patient loads, patients with CD4+ counts <350 cells/μl must be prioritised. Ultimately, an approach that gives patients the opportunity to make informed choices respects the principle of patient autonomy. This could lead to increased adherence, and better outcomes for individual patient's and the public's health.

Conflict of interest. N Geffen is on the INSIGHT Community Advisory Board and receives a *per diem* for travel to INSIGHT meetings and an honorarium. INSIGHT is running the START trial. F Venter is on the Data Safety Monitoring Board for the START trial.

References

1. South African National Department of Health. The South African National Antiretroviral Treatment Guidelines 2013. http://www.sahivsoc.org/upload/documents/2013%20ART%20Guidelines-Short%20Combined%20FINAL%20draft%20guidelines%2014%20March%202013.pdf (accessed 25 August 2014).
2. Green A, Skosana I. Motsoaledi reveals 'progressive' HIV treatment plans. Mail & Guardian, 24 July 2014.
3. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: An analysis of trial data. Ann Intern Med 2014;161(1):1-10. [http://dx.doi.org/10.7326/m14-0293]
4. Department of Health. Contract number HP13-2013ARV. http://www.health.gov.za/docs/contructs/hp13_2o13arv.pdf (accessed 24 July 2014).
5. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365(6):493-505. [http://dx.doi.org/10.1056/NEJMoa1105243]
6. Rodger A, Bruun T, Cambiano V, et al. HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. Conference on Retroviruses and Opportunistic Infections (CROI 2014). Boston, March 3 - 6, 2014. Abstract 153LB.
7. When To Start Consortium, Sterne JAC, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: A collaborative analysis of 18 HIV cohort studies. Lancet 2009;373(9672):1352-1363. [http://dx.doi.org/10.1016/S0140-6736(09)60612-7]
8. Babiker AG, Emery S, Fatkenheuer G, et al. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. Clin Trials 2013;10(10):S5-S36. [http://dx.doi.org/10.1177/1740774512440342]
9. Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (ANRS 12136 TEMPRANO) http://clinicaltrials.gov/ct2/show/NCT00495651 (accessed 1 June 2014)
10. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach June 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/ (accessed 27 August 2014).
11. Southern African HIV Clinicians Society. Position: Initiation of ART at a CD4 threshold above 350. http://www.sahivsoc.org/upload/documents/14%2007%2023%20Position%20ART%20initiation%20greater%20than%20350.pdf (accessed 13 August 2014).

GUIDELINE

Management of mental health disorders and central nervous system sequelae in HIV-positive children and adolescents

By the Southern African HIV Clinicians Society

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Disclaimer. Specific recommendations provided here are intended as only a guide to clinical therapy, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

HIV-positive children and adolescents are at increased risk of both central nervous system (CNS) sequelae and mental disorders owing to a number of factors, including the impact of HIV infection on the brain, social determinants of health (e.g. poverty and orphanhood) and psychosocial stressors related to living with HIV. Every effort should be made to identify perinatally HIV-infected children and initiate them on antiretroviral therapy early in life. HIV clinicians should ideally screen for mental health and neurocognitive problems, as part of the routine monitoring of children attending antiretroviral clinics. This guideline is intended as a reference tool for HIV clinicians to support the early identification, screening and management of mental health disorders and/or CNS impairment in children and adolescents. This guideline covers mental disorders (section 1) and HIV-associated neurocognitive disorders (section 2) among children and adolescents.

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Untreated perinatally HIV-infected (PHIV) children are at increased risk of central nervous system (CNS) sequelae compared with HIV-infected children who begin antiretroviral therapy (ART) in infancy. HIV invades the developing CNS earlier and with greater severity than observed in adults and with a more rapid progression to death. In addition, patients receiving ART may remain vulnerable to the effects of HIV on the brain because the CNS may be a reservoir for persistent viral replication. Initiation of ART, therefore, does not fully reverse CNS insults, particularly if treatment is not initiated during infancy.[1] Psychosocial stressors, such as poverty, orphanhood and parental illness (physical and mental), experienced by HIV-positive children living in disadvantaged communities place them at further risk of poor educational and mental health outcomes. Furthermore, the onset of adolescence presents new challenges related to adherence issues, the provision of adolescent-friendly clinical environments, academic problems, mental health problems, and sexual and other risk behaviours.[2]

1. Mental disorders among HIV-infected children and adolescents

PHIV children present with high rates of mental disorders that exceed population norms and rates in other chronically ill children.[3]

1.1 Overview of mental disorders in children and adolescents

Prevalence:

- In HIV-positive children, prevalence rates of 25 - 50%
- Most common: attention deficit hyperactivity disorder (ADHD), mood disorders, anxiety disorders, substance use disorders (SUDs) (adolescents)
- Less common: psychotic disorders, bipolar mood disorder

Risk factors:

- Previous AIDS-defining diagnosis, lower intelligence quotient, caregiver psychiatric disorder, parental loss, limit-setting problems

Effects:

- Untreated psychiatric illness may affect ART adherence, and educational and medical outcomes
- Adolescents vulnerable to depression, non-disclosure, school failure/dropout, sexual risk behaviours and SUDs

1.2 Screening for mental disorders

- Accurate diagnosis requires a thorough history, and assessment of the mental state of the child and of the family.
- Collateral information from the educator and/or extended family provides essential additional information.
- The objective is to detect and refer suspected cases of children presenting with mental health disorders for a more comprehensive assessment. The detection of psychosocial

dysfunction is important as it may contribute to non-adherence and later treatment failure.[4]
- When screening for mental health problems, remember multiple interacting factors such as those within the child, home, school and external environment, all of which influence emotions/behaviour.
- No brief screening tool has been validated worldwide specifically for the detection of mental health disorders among HIV-positive children and adolescents. Table 1 presents some well-validated screening tools that may be utilised in primary care settings.
- A rapid screen of the commonly occurring mental disorders should be performed at the ART clinic and patients should be referred for a mental health assessment (Tables 2 and 3).

1.2.1 Referral criteria based on mental health screen

Refer or discuss the child with a mental health professional (mental health nurse, psychologist, child psychiatrist, psychiatrist) if the child presents with the following:
- Symptoms of ADHD
- Frequent or daily symptoms of anxiety that have affected functioning at home and at school
- Frequent or daily symptoms of depression/low mood, which have affected functioning at home and at school
- Suicidal ideas, intentions, plans or previous attempts
- Misuse of cannabis, methamphetamine, alcohol or any other illicit substance
- Confusion or change in behaviour/functioning from baseline

Refer or discuss with a social worker if additional information reveals the following:
- Maltreatment of the child (e.g. physical or sexual abuse)
- Adverse socioeconomic circumstances requiring assistance
- Limited or no parental care (child-headed household)
- Substance abuse

1.3 Assessment and diagnosis of mental disorders

Tables 4 and 5 outline the assessment and diagnosis of ADHD and major depressive episodes, respectively.

1.4 Assessment and diagnosis of anxiety disorders

- Anxiety may present in children in a variety of ways (Table 6):
  - General symptoms include withdrawal, worries, fears, anticipation of threat and anxiety-themed dreams. These may be associated with vigilance/caution in anticipation of threat and avoidant behaviour.
  - Common physical symptoms include nausea and vomiting, headaches and abdominal cramps. Cardiovascular symptoms such as palpitations and dizziness are less common in children.
- Anxieties may be related to worries about the child's illness, the parent/caregiver, school, placement insecurity or the general environment.
- Anxiety disorders that occur more commonly in childhood include separation anxiety disorder, selective mutism and specific phobias.
- Adolescents may additionally present with social anxiety (social phobia) and panic disorder. The clinical presentation may more closely resemble that of adults. Generalised anxiety disorder may occur across the lifespan.[5]

1.5 Assessment and diagnosis of psychotic disorders

Neuropsychiatric symptoms in an HIV-positive child or adolescent include psychosis, severe mood disturbance, delirium or encephalopathy. Psychotic symptoms (hallucinations, delusions, formal thought disorder) and mania are less common among HIV-positive children and adolescents compared with adults, and therefore have a high index of suspicion of a comorbid medical condition such as a CNS disorder.
- Consider a psychotic disorder if there is a positive family history of mental illness, particularly schizophrenia or bipolar mood disorder.
- Suspect delirium if a patient presents with an acute onset of psychotic symptoms associated with confusion and clouding of consciousness that tends to fluctuate. Exclude general medical conditions (GMCs) such as seizures, meningitis, encephalitis, brain tumour or stroke. Failure to recognise delirium may delay the diagnosis of an underlying medical condition and may lead to an adverse outcome and even death.[5]

Table 1. Validated screening tools for mental disorders in children and adolescents*

Screening instrument	Clinical condition	Source
SDQ (available in English, Afrikaans, Xhosa and Zulu)	Psychosocial functioning	http://www.sdqinfo.org/py/sdqinfo/b0.py
Conner's scales (parent, teacher)	ADHD	http://www.doctorrudy.com/files/teacher_add_adhd_short.pdf http://www.doctorrudy.com/files/add_adhd_parent_long.pdf
SNAP-IV rating scale	ADHD	http://www.adhd.net/snap-iv-form.pdf
Subscale of SDQ	Depression	www.sdqinfo.org/py/sdqinfo/b0.py
Paediatric symptom checklist	Psychosocial function	http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf
SCARED	Anxiety	http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Child.pdf http://www.psychiatry.pitt.edu/sites/default/files/Documents/assessments/SCARED%20Parent.pdf

SDQ = Strengths and Difficulties Questionnaire; ADHD = attention deficit hyperactivity disorder; SNAP-IV = Swanson, Nolan and Pelham, 4th revision; SCARED = Screen for Child Anxiety Related Disorders.

* Consult the relevant International Academy of Child and Adolescent Psychiatry and Allied Professions (IACAPAP) book chapter, which provides an overview of clinical assessment of a child: http://iacapap.org/wp-content/uploads/A.5-CLINICAL-EXAMINATION-072012.pdf

1.5.1 Delirium

- Delirium is a nonspecific neuropsychiatric disorder that occurs in medically ill patients, signifying global encephalopathic dysfunction. It commonly occurs across the age extremes (the very young and geriatric patients). However, it can occur in all ages, particularly in seriously ill patients with limited cognitive reserves and/or CNS conditions. It is well recognised in the elderly but underdiagnosed in children.
- Onset confers a poorer prognosis for an underlying medical condition.
- The core features comprise an altered level of consciousness, attention disturbances and diffuse cognitive deficits. Symptoms fluctuate and may present with behavioural disturbances (e.g. aggression) and perceptual disturbances, commonly visual hallucinations.

Children who have not been initiated on ART due to adequate $CD4^+$ counts and who have psychiatric symptoms that are poorly responsive to antipsychotics may have detectible/high CNS viral loads despite undetectable serum viral loads (due to differing mutations in cerebrospinal fluid (CSF) and serum). These children should be initiated on ART, which may contribute to the resolution of psychotic symptoms.

Children already on ART who have psychotic symptoms poorly responsive to antipsychotics should be assessed for a comorbid CNS disorder and/or have their ART regimen reviewed and a CNS penetrating regimen considered.[6] The Montreal Cognitive Assessment may be a useful screening instrument to detect cognitive impairment in adolescents.

- https://pdbp.ninds.nih.gov/assets/crfs/Montreal Cognitive Assessment (MoCA)7_1.pdf
- https://pdbp.ninds.nih.gov/assets/crfs/Montreal%20Cognitive%20Assessment%20Scoring%20and%20Instructions.pdf

1.6 Differential diagnoses to consider

- Schizophreniform disorder
- Schizophrenia
- Bipolar mood disorder: usually a history of a previous episode of elevated mood resulting in abnormal behaviour, e.g. decreased sleep, euphoria, hypersexuality, grandiosity and increased energy
- Mood or psychotic disorder secondary to GMC: HIV encephalopathy, seizures, tumours (frontal lobe), side-effect of efavirenz
- Substance-induced psychotic or mood disorder: cannabis, meth-amphetamine

1.7 Mental status examination of the child or adolescent

The mental status examination of a child comprises observation of play, quality of caregiver-child interactions, verbalisations and also interpretation of drawings. The mental state of an adolescent more closely resembles that of an adult patient.

1.7.1 Recording the mental state examination (MSE)

The MSE is an essential part of the psychiatric evaluation. The objective is to describe the child or adolescent's appearance, behaviour, symptoms and cognitive functioning during the examination.

- Physical appearance: age, grooming, clothes, cleanliness, dysmorphic features, bruising, scars
- Behaviour and manner of relating to caregivers and interviewer: eye contact, ability to co-operate, quality of play, interaction with caregiver
- Mood and affect: range, type and appropriateness of affect (objectively euthymic, depressed, elevated)
- Anxiety: fears, separation difficulties, phobias
- Psychomotor behaviour: activity level, tics, co-ordination
- Content and form of thinking: delusions, preoccupations, ruminations, violence, anxiety themes, thought disorder
- Speech and language: fluency, language skills, volume, rate
- Perceptual abnormalities: evidence of hallucinations (e.g. visual, auditory, olfactory)
- Overall cognitive ability: developmentally appropriate behaviour and drawings, general knowledge, vocabulary
- Attention, concentration and memory: attention and concentration, short- and long-term recall
- Level of consciousness: fluctuation, orientation for time, person and place
- Insight and judgement into own condition: acknowledgement of problem, attitude to receiving help, willingness to adhere to treatment, ability to judge hypothetical situations

The child should ideally be interviewed in his/her first language.

1.8 Management of HIV-positive children and adolescents presenting with mental disorders

See Fig. 1, which summarises the assessment and management of HIV-positive children presenting to primary care services.

1.8.1 Risk assessment

- Risk assessment includes evaluation of the following:
  - Risk to self: suicidal thoughts or intent or self-harming behaviour; a patient may require hospitalisation in cases of a serious suicide attempt or intent
  - Risk to others: thoughts or intention to harm others
  - Risk-taking behaviour such as reckless driving, violence, disinhibited sexual behaviour, antisocial behaviour (engaging in unlawful acts) and unprotected sex
- Additional risk to children is related to adverse child care, e.g. minimal parental/family or social support, neglect, physical, emotional or sexual abuse, abandonment.

1.8.2 Referral

- Be aware of referral pathways in your own facility and local district. Communicate with colleagues providing mental health services at primary and district levels, such as a dedicated mental health nurse practitioner, psychiatric registrar, psychologist, occupational therapist and district psychiatrist.
- Have a high index of suspicion for new-onset psychiatric symptoms that may present as a result of an acute or subacute infection or general medical condition, such as AIDS-defining infections, intracranial viral or bacterial infections, and delirious states due to substance abuse/withdrawal/infection or medication.
- Referral for any suspected mental health problems at primary level care should be to a mental health nurse practitioner (or psychiatric registrar, if available). Less severe or uncomplicated cases may be

managed at primary level in discussion with the district psychiatrist and mental health team at specialist level.
- Complex cases (e.g. comorbid psychiatric and medical illness such as seizures, other CNS conditions, comorbid substance misuse and psychotic symptoms, catatonia and severe depression) should be referred to the district psychiatrist or specialist child and adolescent mental health (CAMH) services within the catchment area for assessment and possible hospitalisation.
  - Refer suspected cases of child abuse to the facility social worker, who may refer to an external social worker for statutory intervention.
  - Refer to an occupational therapist at community level, who may do group-based interventions, or adherence groups and functional assessments.
  - Refer to the district psychologist for a psychological evaluation of the child and family.

1.8.3 Liaison

- Communicate with the educator and school psychologist (with the family's consent) to obtain accurate information.
- Liaise with relevant adult services if you suspect parent or caregiver mental health problems.

1.8.4 Attitude to family

- Be sensitive and non-judgemental in your attitude.
- Be aware of and attend to issues about stigma.
- Comply with the rules of confidentiality at all times.

Table 2. Detecting commonly occurring mental disorders among HIV-infected children

Interviewee	Questions	
Parent/ caregiver	ADHD	Ask about level of activity, attention and impulsivity, e.g.: • Does the child struggle to sit still, move around constantly, fidget? • Is he/she able to concentrate on a task, focus on homework? • Does he/she wait his/her turn or act without thinking? Example answer: *When he watches TV, he rocks and moves all the time and then gets up and walks/runs around. He looks around and interrupts conversations while he is doing his homework. He runs over the road without looking.*
	Depression/ mood symptoms	• Is the child tearful, irritable, withdrawn from peers, disinterested in play most of the time? • Does the child talk about death or say he/she wants to die? Example answer: *She is moody and gets angry and cries quickly. She doesn't want to play with her friends anymore. She used to like to play with her doll but now doesn't want to. She sometimes says she wants to die.*
	Anxiety symptoms	• Does the child worry excessively, or feel fearful/scared? Example answer: *She is quiet and is scared of the dark and thunder. She worries that she will fail at school and worries about me (that I will get sick and die) and that there is no money. She talks about it all the time and it makes her not want to play or go to school.*
Child	School	Tell me about school: • What do you like? What don't you like about school? • Have you been in trouble at school? What for? Example answer: *I like my teacher and playing outside. I don't like schoolwork (sums, reading out loud in class) and when the other children tease me or hit me. I was in trouble because I didn't do my homework.*
	Mood	• What makes you happy or laugh a lot? • What makes you sad or want to cry? Example answer: *I am happy when I play with my friend and when I go out with my mommy to the shop. I cry when they argue or fight in the house. I feel sad when I stay long in hospital.*
	Anxiety	• Do you have a lot of worries? Example answer: *Yes, I worry that I am sick and that I have to go to hospital and may die. I worry about my mommy because she is sick too. I worry that she won't be able to work anymore. I worry when it rains hard as the water may flood our house, and then we have nowhere to go.* • Pick a feeling that you feel almost every day, e.g. happy, sad, scared, worried. (You may present the child with pictures of different faces.) Example answer: *I feel worried a lot, like every day.*
Caregiver: academic enquiry		• Ask to see the latest school report • Send the teacher Conner's scale (ADHD screening tool) • Send a written request for information about the child

ADHD = attention deficit hyperactivity disorder.

Table 3. Detecting commonly occurring mental disorders among HIV-infected adolescents

Interviewee	Questions
Parent/ caregiver	• Is your adolescent very moody, tearful, sad and withdrawn? • Does your child ever say he/she wants to die or talk about attempted suicide? • Is he/she worried, fearful/scared or complaining of nightmares? • Do you know if your adolescent has taken drugs or had unprotected sex? Example answers: *She locks herself in her room, is irritable, ignores us/doesn't talk to us. I hear her crying in her room a lot. She worries that she will fail, says she can't sleep and that she is having bad dreams. She sometimes says she wants to die/will kill herself.* *He smokes 'weed'/'ganja' with his friends. He has a girlfriend but I don't know if they use condoms.*
Adolescent	• Do you feel sad or worried, or feel like crying very often (every day or most days)? • Do you think about death or wanting to die? • Have you experimented with alcohol/drugs or had unprotected sex? Example answers: *I feel bad, like low/down, so that I don't feel like getting out of bed. I think all the time of bad stuff, like I'm going to die or be alone.* *Yea, I worry about a lot of stuff, that my boyfriend will leave me if he finds out I'm positive, that I'm going to fail or that I'm going to get sick as I keep forgetting to take the medicine for HIV.* *I smoke 'weed'/'ganja' with my friends and we drink brandy over the weekend. My girlfriend is on the injection so we don't use condoms.*
Caregiver/adolescent: academic enquiry	Ask to see the latest school report. Ask the adolescent to report on his/her academic function and school, e.g.: • Tell me about school, e.g. your likes and dislikes? Are you ever in trouble at school? What for? Ask the adolescent to report on his/her academic functioning and school, e.g.: • Tell me about school, e.g. likes and dislikes? Are you ever in trouble at school? What for? Send the teacher a copy of Conner's scale or SNAP-IV to complete and a written request for information about the adolescent.

SNAP-IV = Swanson, Nolan and Pelham, 4th revision.

Table 4. Assessment and diagnosis of ADHD[5]

DSM-V criteria	Presentation in children	Presentation in adolescents
Persistent inattention and/or hyperactivity/impulsivity		
Inattention symptoms (six or more of following): • Poor attention to details, careless mistakes • Difficulty sustaining attention • Does not listen • Does not follow instructions • Struggles to organise activities and tasks • Task avoidant or dislikes tasks • Loses things • Easily distracted by external stimuli • Forgetfulness	As per *DSM-V* criteria	As per *DSM-V* criteria
Hyperactivity/impulsivity symptoms (six or more of following): • Fidgety • Leaves seat • Runs or climbs when not appropriate • Unable to play or engage in leisure activities • Often 'on the go', acts 'like a motor' • Talks excessively • Blurts out answers • Struggles to wait turn • Interrupts or intrudes on others	As per *DSM-V* criteria	Hyperactivity symptoms may wane but impulsivity persists in some cases to adulthood

ADHD = attention deficit hyperactivity disorder; *DSM-V = Diagnostic and Statistical Manual of Mental Disorders* (5th edition).

Table 5. Assessment and diagnosis of major depressive episode[5]

DSM-V criteria	Presentation in children	Presentation in adolescents
• Depressed mood almost all day, every day OR • Loss of interest or enjoyment of usually pleasurable activities for most of the day	• Irritable mood, tearfulness • Loss of interest in play, toys or friends • Decline in academic performance	• Similar to adults • Irritability • Social withdrawal from peer group
AND • Diminished pleasure or interest in most activities, most of the day • Significant weight loss (i.e. >5 kg) • Insomnia or hypersomnia (inability to sleep/ excessive sleep) • Psychomotor agitation or retardation • Loss of energy or fatigue • Feelings of worthlessness or inappropriate, excessive guilt • Decreased ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others) • Thoughts of death that are recurrent, or recurrent suicidal ideation without a specific plan, or a specific plan for committing suicide or a suicide attempt	• Somatic complaints such as abdominal pain and/or headache	• Suicide risk may increase

DSM-V = Diagnostic and Statistical Manual of Mental Disorders (5th edition).

1.8.5 Management of depression and anxiety in HIV-positive children and adolescents

- Conduct a thorough history and clinical assessment. This includes information about functioning at school.
- Interview the child/adolescent alone and with the caregiver.
- Initiate first-line psychosocial intervention, i.e. address precipitating or perpetuating stressors, e.g. bullying, stigma. Refer the child for play/individual/group therapy if resources are available and according to the child's intellectual ability; alternatively, refer to the school counsellor. Refer parents to local parenting groups and/or for their own psychological or psychiatric interventions as necessary.
- For moderate to severe symptoms, initiate selective serotonin re-uptake inhibitor (SSRI) in addition to psychosocial management.
  - Initiate with a low dose and titrate slowly, preferably with citalopram 5 mg or 10 mg daily, or fluoxetine 5 mg or 10 mg daily if citalopram is not available. (Administer by opening a capsule into 20 ml of orange juice to create a 1 mg/ml solution. Use a 5 ml or 10 ml syringe to measure out the daily dose. Keep the remainder refrigerated.)

Fluoxetine or citalopram may be prescribed for moderate to severe depression and anxiety disorders. Citalopram is preferable because of potential drug-drug interactions between fluoxetine and certain antiretroviral medications. Fluoxetine can increase agitation and impulsivity, so monitor closely.

  - Titrate up to the therapeutic dose (as per EDL).
  - Monitor adolescents or older children closely for suicidal ideation and SSRI side-effects, e.g. behavioural disinhibition or activation.
  - Review in 1 month. Titrate up to 10 - 20 mg (or beyond up to a maximum of 30 - 40 mg) if indicated and if there are no adverse side-effects.
  - Reassure the patient and parent that most side-effects are transient and dose related.
- Refer a child with moderate to severe symptoms and with poor response to treatment to a local child psychiatric service if available, or discuss with a psychiatrist (or child psychiatrist if available).
- Treatment for depression should ideally be for 6 - 12 months after symptom resolution, after which the patient may be weaned off medication. Discuss with a mental health professional or child psychiatrist.
- Treatment duration for anxiety disorders is usually 6 - 12 months after symptom resolution. However, treatment duration and discontinuation of medication management should be individualised according to the specific anxiety disorder, severity, recurrence and treatment response. Discuss with a mental health professional or child psychiatrist.

1.8.6 Management of ADHD in HIV-positive children and adolescents

- Conduct a thorough history and clinical assessment. It is important to include all spheres of the child's environment (including home, school and peers).
- Ask the parent and teacher to complete a Connor's or SNAP report.
- Establish baseline weight and height, and calculate and plot body mass index (BMI).
- Initiate psychosocial intervention, including support for parents and teachers, input on positive reinforcement, and establishing structure and routine in the child's day. Refer parents to a local parenting group if available.
- If indicated, initiate stimulant medication. The dosage should be based on the child's age and weight, i.e 1 mg/kg body weight/day.
  - In children 6 years and older, start with 5 mg short-acting methylphenidate 2 - 3 times daily (5 mg every 3 - 3.5 hours), e.g. initiate 5 mg at 07h30, 5 mg at 11h00 and 5 mg at 14h30. Increase weekly by 5 - 10 mg, but do not exceed 30 mg daily.
  - Alternatively, in older children or adolescents, initiate long-acting methylphenidate 20 mg daily at 07h30, if available.
  - Medication should be initiated only after confirmation of the diagnosis by a psychiatry registrar, medical officer or district psychiatrist.

Table 6. Overview of anxiety disorders in children and adolescents

Anxiety disorder	*DSM-V* criteria	Clinical presentation in children
Separation anxiety disorder	• Excessive fear of separation from attachment figure that is inappropriate for developmental stage	• Stays close to parent and refusal to be away from home. Could lead to school refusal • Becomes very distressed when separated • Worries that attachment figure will not come home, or will become ill, become a victim of an accident, or will die
Selective mutism	• Failure to speak in situations or environments where there is an expectation for speaking, e.g. school. Interferes with normal functioning • Not associated with language problem. No associated communication disorder	• The child fails to speak or reciprocate with speech when spoken to • The child speaks freely at home or when alone with familiar family figures • Child is anxious in social situations • May lead to academic problems and social difficulties
Specific phobia	• Marked anxiety or fear about a specific situation or object e.g. animals, injections, heights, blood • Fear is out of proportion to the danger posed by the object or situation • Persistent and lasts 6 months or longer • Causes significant distress and impairment	• The object of phobia evokes an immediate and extreme reaction • The fear is expressed by tantrums, crying, clinging or freezing
Social anxiety disorder (social phobia)	• Social situations evoke fear or anxiety, when the individual is exposed to scrutiny by others (conversations, being observed, meeting unfamiliar people, delivering a talk in front of class or large group) • The person fears humiliation or embarrassment • The social situation is endured with extreme discomfort or avoided	• Occurs among peers • The anxiety may be expressed by freezing, tantrums, clingy behaviour, crying or failure to speak
Panic disorder	• Feelings of intense discomfort and fear associated with physical symptoms such as sweating, palpitations, shaking, chest pain, nausea, chills or feeling hot, and numbness/tingling sensations	• Abrupt onset and peaks within minutes • Onset may be from a calm or anxious state • Intense fears of losing control or death
Generalised anxiety disorder	• Excessive uncontrollable worry and anxiety occurring most days for longer than 6 months • Requires three of six accompanying symptoms: poor sleep, fatigue, muscle tension, poor concentration, restlessness and irritability • Causes distress and significant impairment in functioning	• Asks constant questions and seeks reassurance • Complains of headaches and abdominal cramps • Anxiety dreams, e.g. of being chased, storms, wild animals • Requires only one of six accompanying symptoms: poor sleep, fatigue, muscle tension, poor concentration, restlessness and irritability

DSM-V = Diagnostic and Statistical Manual of Mental Disorders (5th edition).

- Use the lowest effective dosage.
- Educate parents about effects and possible side-effects.

There are no known drug-drug interactions between methylphenidate and antiretroviral medications.

- Review the child in one month. Check pulse and blood pressure. If abnormal, do an electrocardiogram (ECG), lower the dosage and continue to monitor. Medication should be discontinued if an ECG abnormality is detected and/or cardiovascular disease is observed. Refer to a cardiologist if a cardiovascular abnormality is detected.
- Assess response to methylphenidate through direct observation and feedback from teachers and parents.
- Assess weight and height and plot BMI at each visit. If there is loss of appetite, encourage the parent to provide additional calories and snacks such as a peanut butter sandwich at night for extra protein. Stop treatment if growth curve flattens or there is significant weight loss >5 kg.

1.8.7 Management of children presenting with psychotic symptoms and/or mania

- Complex cases should ideally be referred for neuropsychiatric assessment and further investigation (including CNS investigation and neurocognitive testing) at a tertiary-level service.
- Behaviourally disturbed psychotic adolescents should be referred for admission.
- Exclude delirium before considering a primary psychotic illness. Investigations such as chest X-ray, full blood count, temperature, pulse and urine dipsticks can be used to screen for delirium before referring to secondary level for further investigations such as lumbar punctures and/or neuroimaging.

- Antipsychotics may be initiated at low doses, but with caution and after discussion with a psychiatrist. Initiate risperidone 0.5 - 1 mg daily and increase the dose by 0.25 - 0.5 mg daily every 1 - 2 weeks, depending on tolerance and age of the child. Refer for admission to tertiary CAMH or psychiatric unit if doses in excess of 3 mg are required.

1.8.8 Medication management

- Do not prescribe psychotropic medication to children or adolescents if there is diagnostic uncertainty and/or there has not been a thorough psychiatric assessment and consultation with a specialist.
- It is important to be cautious about the use of psychotropic medications in the management of behaviour disorders in the context of HIV because of high pill burden and potential drug interactions. If medications are not seen to be working, they should be discontinued and polypharmacy should be avoided.
- Initiate at lower doses and increase slowly. Monitor for untoward side-effects.
- Be aware of drug-drug interactions between certain antiretroviral and psychotropic medications (particularly SSRIs) (Table 7).
- Be aware of neurological and psychological side-effects of some antiretroviral medications.

1.8.9 Other diagnoses or symptomatology to consider as part of the assessment and management of HIV-positive children and adolescents

1.8.9.1 Suicide

- Definition: deliberate self-harm where the intention is to die.
- A suicide risk assessment is essential in the assessment of all patients with HIV presenting with psychiatric symptoms such as depression, anxiety, psychosis or self-harming behaviour.
- Suicide attempts in children and adolescents may be impulsive and often related to an intercurrent stressor, which may not always be severe. However, the outcome may be fatal.

Suicide risk assessment

High suicide risk is indicated by any one or more of the factors below:

- Previous suicide attempt
- Pre-existing mental illness
- Family history of suicide
- Substance abuse
- Gender (adolescent males are at increased risk of completed suicide; adolescent females make more suicide attempts)

The following may further contribute to risk:

- Stressful life events
- Physical and sexual abuse
- Poor parent-child communication

Management of suicidal ideation

- Assess suicide risk severity.
- Screen for and treat underlying mental illness, especially depression.
- Develop a safety plan in collaboration with the patient and family.
- Consider hospitalisation if assessment indicates high risk.
- Do not discharge without an adequate psychiatric evaluation if high risk.[7]

1.8.9.2 Management of trauma-related disorders in children and adolescents with HIV

- Psychosocial counselling and support strategies include compassionate early debriefing, family support and psychoeducation.
- Psychotherapy: cognitive behaviour therapy is useful.

Table 7. Commonly used psychotropic medications and their interactions*

Class	Drug	Possible side-effects	Possible drug interactions
SSRIs	Fluoxetine	Headache, nausea/vomiting, behavioural activation	Potential increase in efavirenz levels
	Citalopram	Headache, nausea/vomiting	-
Antipsychotics			
FGAs	Haloperidol	EPSEs (dystonia, tremor, akathisia, cogwheeling, bradykinesia), neuroleptic malignant syndrome	-
SGAs	Risperidone	EPSEs at higher doses, sedation, weight gain, metabolic syndrome	Possible interactions with protease inhibitors
	Olanzapine	Sedation, metabolic syndrome, CVS side-effects	Probable interactions with protease inhibitors
	Clozapine	Best to avoid without specialist support	Probable interactions with protease inhibitors
Mood stabilisers	Lithium carbonate	Toxicity, which may be life threatening	Avoid with tenofovir
	Sodium valproate	Sedation, thrombocytopenia, toxicity	-
	Lamotrigine	Stevens-Johnson syndrome	Possible interactions with protease inhibitors

SSRIs = selective serotonin re-uptake inhibitors; FGAs = first-generation antipsychotics; EPSEs = extrapyramidal side-effects; SGAs = second-generation antipsychotics; CVS = cardiovascular.

* Source: http://www.druginteractions.org

- Medication such as SSRIs may be indicated if there is a poor response to treatment or severe symptoms.
- Check for alcohol and substance abuse in older adolescents.
- Refer to specialist care if there is a poor response to treatment.[8,9]

Post-traumatic stress disorder

- Post-traumatic stress disorder (PTSD) can occur when a person has experienced, witnessed or been confronted with an event that involves actual or threatened death, harm or injury, to themselves or to others, with resultant shock, fear, helplessness or horror.
- The prevalence of PTSD in adolescents living with HIV is not known, but studies report a prevalence range of 15 - 64% in adult samples, suggesting that PTSD may also be common in adolescents.[9]
- Children may have significant symptoms of PTSD but may not meet full *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) (*DSM-V*) criteria (Table 8), as they may have difficulty verbalising their emotions.

1.8.9.3 Adjustment disorders

- An adjustment disorder is the development of a behavioural or emotional response to an identifiable stressor within 3 months of the stressor, resolving within 6 months of termination of the stressor.
- Patients may present with depressive, anxiety and/or behavioural symptoms but do not meet criteria for depression, anxiety or disruptive behaviour disorders.[4]
- Treatment for adjustment disorders includes supportive psychotherapy and improving coping mechanisms. Short-term medication may be considered.
- Children and adolescents with HIV in Africa often have multiple psychosocial challenges/stressful life events that make them more emotionally vulnerable and isolated.[10]
- The effect of the virus is thus compounded by negative life events that further negatively affect neurocognitive development.

Common stressful life events for HIV-positive children

- Ill caregiver who cannot cope with parenting
- Death of caregiver

Table 8. PTSD criteria in children and adolescents

DSM-V criteria	Presentation: preschooler	Presentation: child	Presentation: adolescent
• Onset after experiencing or witnessing a serious traumatic event (e.g. rape, assault, accidents) • Symptoms may occur soon after the event or with delayed onset • Symptoms: intrusive memories (reliving, flashbacks, nightmares), hyperarousal (increased startle response, anxiety symptoms), avoidance (avoiding situations that remind of the traumatic event, numbing, feeling of foreshortened future)	Nightmares, inconsolable crying, repetitive play of traumatic content, regression, e.g. bedwetting	Fearful, repetitive play, traumatic content in drawings, hyperarousal and avoidance of painful stimuli, poor concentration, temper tantrums	Similar to adults

PTSD = posttraumatic stress disorder; *DSM-V* = *Diagnostic and Statistical Manual of Mental Disorders* (5th edition).

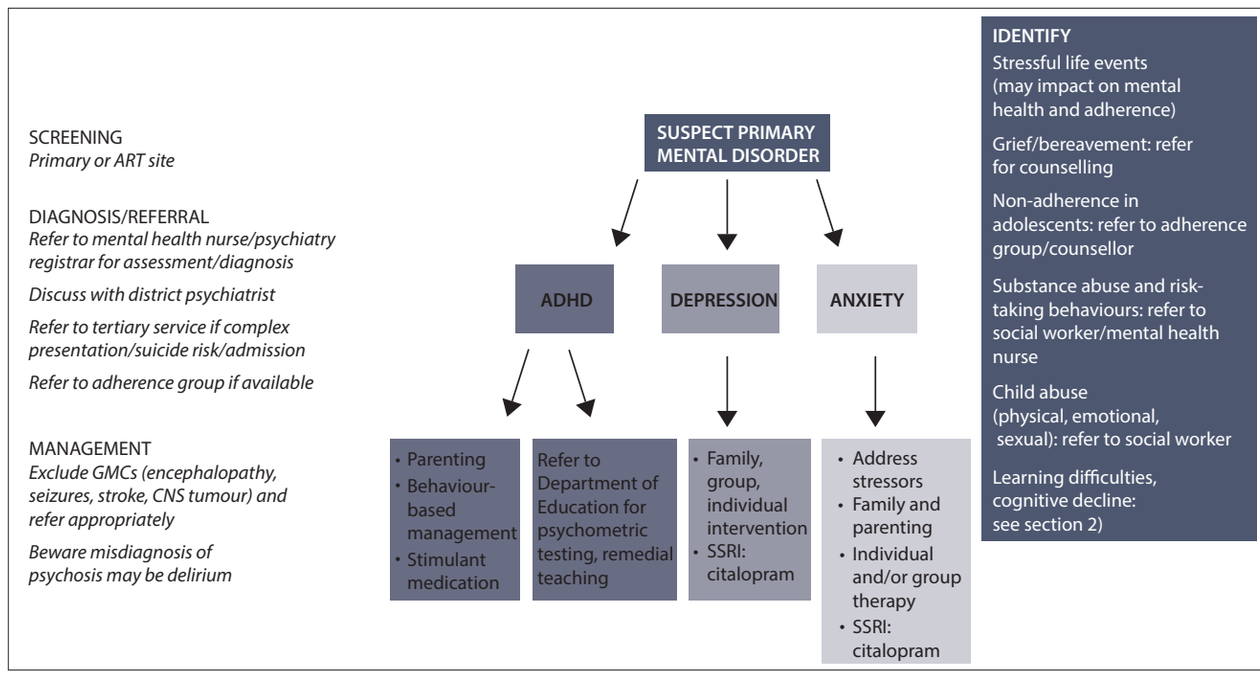

Fig. 1. Recognising primary mental disorders in HIV-positive children and adolescents. (ART = antiretroviral therapy; ADHD = attention deficit hyperactivity disorder; GMCs = general medical conditions; CNS = central nervous system; SSRI = selective serotonin re-uptake inhibitor.)

- Multiple caregivers or child-headed households
- Sick siblings
- Poverty
- Multiple hospital visits
- Disrupted schooling
- Disclosure issues
- Stigma

Grief and bereavement

- Children may lose one or both parents to AIDS and are then often separated from siblings and moved about in an attempt to continue to provide for their basic physical needs.
- These children are often left fearful and anxious or confused.
- In addition, HIV-positive children may have fears about their own mortality.
- It is important that children be allowed to express their grief. Grief reactions are influenced by the child's developmental age and coping mechanisms (Table 9).
- Very young bereaved children may experience regression such as thumb sucking, have nightmares or become clingy. They may also present with acting-out behaviours.
- Bereavement in older children may present with aggressive or impulsive behaviour, poor performance at school, and/or poor concentration or emotional outbursts.[11]
- Supportive therapy/counselling at a developmentally appropriate level of the child and family is the mainstay of treatment.

Table 9. Children's developmental stages of grief[12]

Age (years)	View of death
0 - 2	Very limited but realises person not there
3 - 5	Thinks loved one will return; no concept of finality of death
6 - 8	Curiosity about death; magical thinking
9 - 12	Understands finality and irreversibility of death
13 - 18	Understands finality of death

1.8.9.4 The disruptive and aggressive child and adolescent

- A high prevalence of challenging or disruptive behaviours exist in HIV-positive children and adolescents, including ADHD, ADHD-like impulsivity and hyperactivity, aggression, oppositionality and conduct disturbances.[2]
- However, aggression and disruptive behaviours may arise from medical problems in the child or adolescent, or may be a manifestation of a mood or anxiety-related problem.
- Adolescents in particular struggle with mood and behavioural regulation.
- There is no direct link between HIV itself and disruptive behaviour. Factors such as poverty, prenatal alcohol and drug exposure, malnutrition, family disruption, social chaos and educational deprivation may play a role.

Table 10. Conduct disorder in children and adolescents

DSM-V criteria	Presentation: child	Presentation: adolescent
Aggression towards people and animals • Frequent threats, bullying or intimidation of others • Frequently initiating physical fights • Use of a weapon that can cause serious physical harm to others • Physically cruel to people • Physically cruel to animals • While confronting a victim, has stolen from him/her (e.g. mugging) • Has coerced someone into sexual activity Destruction of property • Deliberate engagement in fire setting with the intention of causing serious damage • Deliberate destruction of others' property Deceitfulness or theft • Housebreaking or breaking into a car or building • Frequently lying to obtain favours or goods to avoid obligations • Theft of items of non-trivial value without confronting a victim Serious violations of rules • Frequently staying out at night despite parental prohibitions, beginning before the age of 13 years • Has more than once run away from home overnight while living in a parental or parental surrogate home, or once without returning for a lengthy period • Frequently truant from school	• Aggression • Difficulties adhering to rules and age-appropriate expectations • Reluctance to engage positively with authority figures; senseless resistance and/or open hostility and defiance • Bullying • Conflict with peers • Truanting; educational failure	• Serious violation of societal rules; significant risk-taking behaviour • Promiscuity; early sexual debut • Substance misuse • Mood instability • Serious aggression • Self-destructive (self-harming) behaviour • Move into delinquent and/or criminal behaviour • Negative peer associations • Truanting; educational failure

DSM-V = Diagnostic and Statistical Manual of Mental Disorders (5th edition).

- There is a further association between behaviour disorders and high rates of neurocognitive and neurodevelopmental delay in HIV-positive children.
- Two disorders that require specific consideration are conduct disorder and oppositional defiant disorder.

Conduct disorder

Definition: a repetitive and persistent pattern of behaviour that violates the basic rights of others or where major age-appropriate societal norms or rules are transgressed (Table 10).[5]

Oppositional defiant disorder

- Definition: a pattern of argumentative/defiant behaviour and angry/irritable mood or vindictiveness lasting at least 6 months.
- Classification requires exhibition of at least four symptoms from any of the categories in Table 11 during an interaction with at least one individual who is not a sibling.[5]

Common co-occurring disorders in children with disruptive or aggressive behaviour

Aggressive and disruptive behaviour may present with co-occurring difficulties such as:

- ADHD
- Learning disorders and language difficulties
- Intellectual disability
- Anxiety and depressive disorders
- Adjustment disorders
- Substance use disorders
- Trauma-related disorders
- Disruptive mood dysregulation disorder
- Bereavement
- Epilepsy
- Sensory integration difficulties
- Delirium (may be secondary to opportunistic infection or a medication)
- Psychotic disorders

Management of behaviour problems in children and adolescents with HIV

- Explore the family's circumstances, particularly parenting practices and harsh discipline.
- Obtain information from the school and/or recent report cards and any other structures that might be involved with the child or the family (e.g. social services, justice).
- Establish an alliance with the child and his/her parent/caregiver; try not to get drawn into the anger and power struggle that often arises out of the child's behaviour.
- Optimise the management of HIV; ensure adherence to antiretroviral medication, establish extent of health and viral suppression and ensure that no intercurrent opportunistic infections have arisen.
- Manage co-occurring problems. These may be more responsive to treatment and addressing them may improve the behavioural 'dyscontrol', i.e. aggression, impulsivity and risk-taking behaviours.
- Address learning and educational problems. This may necessitate more formal psycho-educational assessment and/or referral to local educational authorities, and may be as simple as establishing contact with the school and its support structures.
- Refer to social services if there are concerns of neglect or maltreatment, child-headed households, poverty, household instability or parental illness.
- Encourage participation in prosocial activities and environments in the local community (e.g. sports and cultural activities).
- Psychotropic medication may prove useful, but is seldom the only solution in addressing behaviour disorders in HIV-positive children. Medications are often more successful in treating comorbid problems, e.g. methylphenidate for ADHD, anticonvulsants (sodium valproate, lamotrigine and carbamazepine) for epilepsy, SSRIs for anxiety and depression.
- Seek supervision and get support from your colleagues; working with these children and their families can be demoralising and frustrating.

Management of conduct disorder and oppositional defiant disorder in HIV-positive children and adolescents

- Assess family functioning and parenting, and establish that the child not been maltreated (physical, emotional or sexual abuse or neglect).
- Refer family to a parenting support group or parenting skills training.
- Refer for individual and/or group psychological intervention, depending on the intellectual capacity of the child or adolescent, his/her capacity to engage in relationship and motivation to participate.
- Risperidone may be useful in reducing aggression and impulsivity, but will need to be carefully monitored for the occurrence of EPSE. A dose of 0.5 - 1 mg/day, with a maximum dose of 1 - 2 mg daily, is recommended. Discuss with a mental health professional if there is a poor response to the maximum dosage.
- Mood stabilisers may be used to aid behavioural management and affective dysregulation associated with behaviour disorders. These should ideally be prescribed by a specialist and monitored carefully.

Table 11. Overview of oppositional defiant disorder

DSM-V criteria	Clinical presentation
• Angry/irritable mood • Frequently loses temper • Easily annoyed or touchy • Often resentful and angry • Argumentative/defiant behaviour • Frequently argues with adults and authority figures • Frequently refuses to comply with requests from authority figures or with rules • Frequently deliberately annoys others • Mistakes or misbehaviour frequently blamed on others • Vindictiveness • Spiteful or vindictive at least twice within the last 6 months	• Temper outbursts (sometimes referred to as rage attacks in younger children) • Persistent stubbornness; resistance to directions • Unwillingness to compromise, give in or negotiate with adults or peers • No need to please • Deliberate or persistent testing of limits • Verbal (and minor physical) aggression • Low self-esteem • Mood lability and low frustration tolerance

DSM-V = Diagnostic and Statistical Manual of Mental Disorders (5th edition).

1.8.10 Psychological interventions

1.8.10.1 Psychosocial support for children

- Psychosocial support can be understood as any type of initiative that seeks to protect or promote the well-being of a child or adolescent, and prevent or treat mental health problems.
- It should form part of a broad framework of care that includes the family, parents, school and community, and that encompasses a range of interventions combined to achieve the best possible outcomes. The provision of psychosocial support involves a range of stakeholders: caregivers, family members, teachers, and healthcare providers including psychological and social services.
- Psychosocial support includes the provision of individual counselling, the availability of facility- and community-based support groups, parenting programmes and peer support initiatives, and information and education workshops.[12]
- To be effective, psychosocial intervention should be tailored to the context and take into account the child's age and stage of development. It is essential that there is focus on enabling an HIV-positive child to establish their identity, manage their care, live positively, cope with challenges and work towards a healthy future.
- HIV-positive children are particularly vulnerable to psychological and social stressors that can affect their development and well-being. Psychosocial support can foster resilience, enabling children and adolescents to bounce back from adverse experiences and to cope better with the multiple stressors related to HIV. Their unique psychosocial needs include assistance to deal with their illness, help to cope with loss and changes of caregiver, and support to overcome isolation associated with stigma and discrimination.[12-14]

1.8.10.2 Therapeutic support

Psychosocial intervention can take various forms including referral to support groups, psychotherapy or counselling (Table 12).[15]

1.8.10.3 Psychosocial support for adolescents

- Interventions for adolescents fall into three categories: therapeutic support, youth-centred interventions and those aimed at fostering independence.
- In the case of the former, support groups, counselling and psychotherapy provide support across a broad range of issues (Table 13).[15]
- Group-based interventions are attractive to the adolescent and are a time- and cost-effective method of delivery.[15]

1.8.10.4 Benefits of group interventions for adolescents

- Enhance self-knowledge and self-acceptance.
- Empower individuals to make change.
- Help individuals to develop coping skills.
- Build communication skills and help in relationships outside of the group.
- Give individuals freedom to express negative feelings in a safe, non-judgemental environment.
- Provide positive reinforcement and emotional support.
- Provide a platform for education, e.g. adherence to treatment.
- Foster a sense of belonging to counter feelings of isolation and inadequate social support.

1.8.11 Youth-centred interventions

- An important aspect of adolescent service provision is ensuring that it is youth friendly.
- Adolescent and Youth-friendly Service (AYFS) provision has been identified as an important aspect of service delivery in South Africa, and has a strong focus on attracting and retaining young people for ongoing care.
- Adolescents are particularly vulnerable to the harmful outcomes of risk behaviours, e.g. unprotected sex and substance abuse, but tend not to seek early treatment. There are a number of reasons for this, such as worry about stigma or fear of harsh treatment at the clinic.

Table 12. Psychosocial interventions for children

Support groups	Psychotherapy	Counselling

• Groups need to be tailored to the child's age and stage of development, e.g. with younger children play can be combined with opportunities to learn about healthy living
• Older children can benefit from experiential activities across a range of health-related topics
• Useful to allow parents and caregivers to talk about their own fears, frustrations and challenges
• Can address difficulties with disclosure. Secrecy can affect the mental health of both child and parent/caregiver
• Provides a forum for education, correction of misconceptions and skills building
• Useful for building parenting skills that can help caregivers to develop effective communication skills, set limits and discipline appropriately
	• Different types of psychotherapy are available to address a wide range of issues ranging from separation anxiety and learning or school problems to excessive shyness and low self-esteem. The choice of therapy will depend on the age and stage of the child's development
	• In particular, younger children may benefit from play therapy where the use of play materials such as toys and puppets encourage children to talk about their feelings in order to better understand and cope with their difficulties
		• The participation of children is an important aspect of counselling but is easily overlooked. Children may also be shut out of conversations because they have not been told their status
		• Providing the opportunity to talk about matters that concern them with someone who is empathic, supportive and non-judgemental is important
		• The following counselling approaches may be useful:[16]
		  • Get down to the child's eye level
		  • Speak softly and directly to the child
		  • Smile and play
		  • Be honest and patient
		  • Allow and respect normal emotions
		  • Start with the least invasive activities
		  • Give the child choices, e.g. would s/he like juice or water with medication
		  • Engage the child, e.g. talk about hobbies, friends and so on
		  • Support the parent-child relationship.
		  • Sit close to the child

Table 13. Psychosocial interventions for adolescents

Support groups	Psychotherapy	Counselling

• Three main types of groups
  • Educational
  • Social and emotional support
  • Peer-led
• Cost- and time-effective in a busy clinic
• Provide a safe space for young people to talk about personal issues, share similar challenges, discuss aspects of treatment (e.g. adherence), explore coping strategies and build a social network
• Can involve novel and interesting ways to achieve a specific goal, e.g. music, dance, drama, art or storytelling groups
• Important to understand developmental stage to ensure that groups meet the particular concerns of different age bands, e.g. discussions about puberty (young adolescents), or sexual and reproductive health issues (older adolescents)
• Support groups conducted for parents and caregivers are important and provide emotional support for carers, opportunities for discussing parenting challenges and fostering communication skills to build positive family relationships
	• The most common types of psychotherapy are cognitive behavioural therapy, and interpersonal and psychodynamic psychotherapy[17,18]
	• Cognitive behavioural therapy uses techniques to correct distortions of thinking that are seen in emotional disorders
	• Interpersonal psychotherapy is a brief, time-limited treatment based on the premise that depression occurs in the context of relationships. It covers four general areas of difficulty: grief, conflict in significant relationships, difficulties adapting to changes in relationships or life circumstances, and problems stemming from social isolation
	• Psychodynamic psychotherapy is a 'talk therapy' for adolescents based on understanding issues that are behind a young person's behaviour, thoughts and feelings. Not all young people benefit from this form of therapy and assessment for suitability is required
	• Other types of psychotherapy include family therapy, which aims to explore patterns of communication in families and to support and educate, and dialectical behaviour therapy, which is useful with older adolescents with chronic suicidal feelings or thoughts
		• May involve obtaining advice or exploring a personal or social problem
		• Positive change more likely in a relationship of trust where confidentiality is maintained. Building trust takes time and is greatly facilitated when the adolescent is able to see the same person at each visit
		• Different types of counselling include grief, substance abuse and adherence counselling
		• Adherence counselling is a form of psychosocial support that is concerned with the identification of effective strategies to promote adherence to antiretroviral treatment. Its aim is to enhance the ability of young people to take their treatment as prescribed. It is a process that includes preparation, treatment initiation, consolidation and maintenance

- Paying attention to the health needs of adolescents is crucial. As young people become more independent, they are expected to take more responsibility for their own health. Knowing where and when to get help and feeling confident that they can rely on a service that they trust and feel is there for them is fundamental to a positive outcome.[16]
- A package of services should be available to meet the diverse needs of young people.
- It is important to address obstacles that commonly inhibit the use of healthcare services by adolescents.

1.8.11.1 Overcoming obstacles to providing AFYS

- Providers should be trained to work competently and respectfully with adolescents.
- Services must be confidential, non-judgemental and private.
- Clinic hours should be convenient for young people, e.g. after school.
- Services should be accessible to all adolescents and young people, irrespective of their age, sexual orientation or marital status.
- An effective referral system should be in place.
- Opportunities should be made available for young people to be involved in the design, implementation and evaluation of the programme.
- Services should seek to involve and gain the support of those important in the lives of young people and in their communities, e.g. partners, parents, school.[16]

1.8.12 Adherence in adolescents

- Helping adolescents to achieve independence is important particularly for those transitioning to adult services.
- Part of taking increased responsibility for their healthcare involves adhering to the prescribed treatment regimen.

1.8.12.1 Improving adherence in adolescents

- Poor adherence is normal in adolescence, but the risk of drug resistance, limited treatment options, increased viral load and risks to survival mean that adherence needs to be well supported.
- Reasons for poor adherence among adolescents can be categorised into patient, treatment and socioeconomic factors.
- Stressful life events can contribute to poor adherence, as can treatment fatigue, substance abuse and mental health problems such as depression.
- Psychosocial support in the form of counselling, referrals and group participation can help young people who are finding adherence difficult. Counselling provides opportunities to develop jointly a workable treatment plan that includes treatment reminders and takes into account lifestyle issues that have the potential to interfere with adherence if not addressed.
- Ideally, adolescents should know their HIV status. Adolescents who have not been disclosed to will be unable to appreciate the importance of adherence to treatment and are less likely to understand the risks associated with engaging in unprotected sex. This makes status disclosure an important aspect of care and support.[19]

2. HIV-associated neurocognitive disorders

2.1 Neurocognitive sequelae

- In untreated children, cognitive impairment occurs early and progresses over time, with prevalence rates ranging between 8% and 60%.
- Early invasion of the developing fetal and infant brain is believed to result in the most common primary HIV-related CNS complication, HIV encephalopathy (HIVE), which refers

to the disease, damage or malfunction of the brain caused by HIV. This complication can be present before significant immunosuppression. However, its presence in a child infected with HIV constitutes an AIDS-defining illness, reflecting the severity of the condition.

2.1.1 Prevalence and impact of HIV-associated neurocognitive disorders (HANDs) in children

Prevalence:

- In untreated HIV-positive children, 8 - 60% experience cognitive impairment; disorder occurs early and progresses over time.
- Untreated HIV increases risk of CNS sequelae.[17,20,21]

Impact:

- A range of cognitive deficits occur, cognitive scores clustering in low average to borderline range for intellectual functioning.
- Although cognitive functioning improves after ART initiation, scores remain lower than population norms, with poorer academic performance and persistence of language (e.g. verbal fluency), memory, processing speed, visuospatial and attention problems or deficits. Remedial educational interventions are important.[18,22,23]
- Psychosocial stressors (poverty, orphanhood, parental physical/mental illness or loss) negatively affect adherence, educational and mental health outcomes.
- The concept of a milder form of neurocognitive disturbance in HIV-positive children, such as the adult condition of HAND is recognised but is yet to be defined in children and adolescents. This condition may have significant effects in functional terms on a child's learning potential.[24]
- Many HIV-positive children receiving ART function within normal limits compared with uninfected peers, but a subset with CNS disease follow a distinct pattern of low average cognitive functioning.
- The cognitive deficits in these children may be a result of ongoing viral replication in the brain despite virological control in the periphery or from residual effects of static HIV-1 CNS disease.
- Although HIV-positive children receiving highly active antiretroviral therapy appear to exhibit global measures of intelligence comparable with their uninfected peers, deficits may be present in specific areas such as executive functioning and working memory. Deficits in these areas can impact significantly on learning.
- Children with HAND may demonstrate few clinical signs, but an index of suspicion should be aroused when history reveals delayed motor milestones and when school reports describe school difficulties.

Centers for Disease Control and Prevention: HIV encephalopathy criteria for classification[25]

Must include at least one of the following for at least 2 months in the absence of a concurrent illness:

- Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests
- Impaired brain growth or acquired microcephaly evident by head circumference measurements or brain atrophy demonstrated by computed tomography or magnetic resonance imaging; serial imaging is required for children <2 years of age
- Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathological reflexes, ataxia or gait disturbance

2.2 Specific neuropsychological deficits

- Neuropsychological testing reveals that executive functioning deficits might be an early indicator of cognitive problems, with deficits in mental processing, sequential processing, comprehension, memory, visuospatial and time orientation tasks.
- One or more of the following must be met for diagnosis of HAND:
  - A significant drop in cognitive test scores, but generally still above the delayed range, with or without mild brain imaging abnormalities, with no loss of previously acquired skills and no apparent functional deficits (adaptive behaviour and school performance stable)
  - Cognitive test scores in the borderline range, with no significant functional deficits (and no history of significant drop or previous testing)
  - Cognitive test scores within normal limits (low average range or above) with no significant functional deficits and moderate to severe brain imaging abnormalities consistent with HIV-related changes
  - Abnormal neurological findings but not significantly affecting function.[26]
- Deficits suggestive of frontal lobe dysfunction (e.g. attention, processing speed, motor speed and visuomotor integration) are also detectible in HIV-positive children and adolescents.
- Educational interventions to address these problems are essential to improve the overall health literacy (and adherence) in infected youth as they age and assume greater treatment responsibility.
- Children infected with HIV presenting with cognitive problems may be slow to process information, slow to complete tasks or may be clumsy, and this may affect everyday living. Understanding cognition in children is compounded by the fact that developmental milestones with regard to motor function, co-ordination and the elements of cognition occur at various stages in the development of a child. Screening tools used in adults such as the International HIV Dementia Scale in their current form are thus inappropriate in children and adolescents, as each tool must accommodate the different developmental stages from childhood through to adolescence.

Cognition refers to a group of mental processes that include attention, memory, producing and understanding language, learning, reasoning, problem-solving and decision-making.

2.3 Identification and management of neurocognitive disorders

- Prevention of HIVE, HAND and AIDS-defining conditions via early ART remains the cornerstone of effective management. ART has dramatically decreased the prevalence of HIVE in the US from 35 - 50% to <2%.[27]
- Furthermore, early initiation of ART results in improved neurodevelopmental outcomes compared with deferred initiation.
- Ensuring adherence and providing treatment support are key factors in management.
- A multidisciplinary, tiered approach is recommended for the management of neurocognitive complications (Table 14).
- Referral for pure neurocognitive decline should immediately be to a paediatrician/physician, according to the age of the child.
- However, concern about contributing mental health/behavioural issues may require psychiatric review.

- If cognitive impairment develops once a child is receiving ART, check viral load and adherence.
- If a child's milestones are deteriorating or if an older child has educational or behaviour problems, and there is no obvious explanation, the child should be referred for further evaluation even if HIV infection is well suppressed.
- Treatable conditions can be diagnosed at a primary healthcare level; routine history, examination and blood tests assist in this regard (Table 15).
- Exclude indirect complications of HIV infection such as opportunistic infections (tuberculous meningitis, cytomegalic virus infection), and intrauterine exposure to alcohol and substances.

Table 14. Management of HIV-positive children at primary, secondary and tertiary care levels

Primary	• Document milestones, and measure head circumference at birth, enrolment and 6-monthly thereafter • Monitor growth and nutrition • Actively investigate and manage treatable conditions, e.g. chronic middle ear infection, epilepsy, iron deficiency anaemia • Review copies of school reports, and refer for educational support, if possible • Monitor side-effects of medication, e.g. sleep disturbances • Refer to secondary level healthcare if complicated epilepsy, positive diagnosis of HIVE, or if HAND, attention or behavioural problems are suspected
Secondary	• Paediatricians, psychiatrists, physiotherapists, occupational therapists and speech therapists at secondary level must be made available to all primary healthcare workers for up-referral as necessary • Strengthen links between educators (teacher or learning support professionals at the school) and health professionals in order to provide education goals that are realistic and that will ensure the child achieves his/her maximum potential • Refer for screening by specialists to decide if tertiary intervention is required and to manage some of the more complex general medical problems
Tertiary	• Refer for assessment by a specialist paediatrician (or developmental paediatrician) • Refer for neuroimaging • Refer to a psychologist for cognitive testing and/or neuropsychological battery (if indicated) • Refer for EEG if indicated • Refer for occupational therapy, audiology, and assessment of language and speech therapy as needed • Referral for audiometry if a language development delay is present

HIVE = HIV encephalopathy; HAND = HIV-associated neurocognitive disorder; EEG = electroencephalography.

Table 15. Medical conditions that may affect cognition[28,29]

Condition	Diagnosis	Potential effect on cognition	Management
Iron deficiency anaemia	History and full blood count	Attention problems	Iron supplements
Nasal obstruction	History, sleep studies	Learning difficulties and attention problems	Nasal spray, referral to an ENT specialist
Chronic middle ear infection	History and examination	Decreased hearing resulting in learning difficulties	Audiology, referral to an ENT specialist
Visual impairment	History and examination (e.g. use of a Snellen chart for older children and small items such as edible '100s and 1 000s' for young children)	Visuomotor problems and difficulty managing in the classroom	Refer to an optometrist/ophthalmologist as appropriate
Malnutrition	Growth charts	Specific learning difficulties and attention problems	Referral to a dietician, medical follow-up, refer to a nutrition supplementation programme
Efavirenz side-effects	Sleep history and colateral from teacher, may sleep at school, high efavirenz level	Decreased concentration and focus, poor memory	Detailed history, consider lower dose (discuss with a specialist)
Emotional problems	History and behaviour checklists	Cognitive problems, attention problems, poor scholastic performance	Refer to a psychiatric service

ENT = ear, nose and throat.

- Identify environmental and socioeconomic deprivation (orphans, poverty, malnutrition), as this may further affect cognition.
- If other factors (e.g. behavioural, acute illness, other infection) may *possibly* explain the drop in scores or low cognitive functioning, do *not* classify as HAND or encephalopathy; re-evaluate at a later stage.

2.3.1 Screening tools to detect neurocognitive impairment

- No international validated screening tools are available to test HIV-positive children for neurocognitive impairment.
- However, screening tools can be helpful in identifying children at risk for developmental problems. Examples of simple tools that can be used are available to download online (http://www.sahivsoc.org/topics?page=1&currentFilter=Mental%20Health). These include a tool for children younger than 5 years and another for schoolgoing children. These tools have not been validated, but together with the Road to Health Developmental Check List (RTHDCL) may provide local tools for use at primary and secondary level care.
- We recommend that all children be screened 6-monthly and more formally at 3 - 4 years and again at 5 - 6 years. This, together with the RTHDCL, should enable flagging of children with potential problems. Early detection of problems paves the way for interventions that would improve the quality of life of these children.
- Screening should occur in the context of general HIV clinics across all levels of healthcare.
- Screening needs to include a history, formal systemic examination and particularly a neurological examination (at least head circumference and motor examination, deep tendon reflexes and gait assessment).
- Any child with delayed developmental milestones should be referred for further assessment.
- It is important to identify contributing factors that can be managed, e.g. nutritional, emotional, poverty and deprivation factors, among others.

Conflict of interest. All expert panel members have completed and submitted conflict of interest disclosure statements. Disclosure information represents the previous 3 years (updated 3 September 2014) and includes relationships with pharmaceutical companies and medical aids: A Lachman reports receiving honoraria from Cipla Medpro and Lilly for speaking engagements; R Nassen reports receiving an honorarium from AstraZeneca for a speaking engagement. All other panel members report no conflict of interest.

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References

1. Donald K ,Walker K, Riordan G, et al. Neurological complications of HIV/AIDS in childhood. Continuing Medical Education 2011;29(4):156-159.
2. Mellins CA, Malee K. Understanding the mental health of youth living with perinatal HIV infection: Lessons learned and current challenges. J Int AIDS Soc 2013;16:18593. [http://dx.doi.org/10.7448/IAS.16.1.18593]
3. Gadow K, Angelidou K. Longitudinal study of emerging mental health concerns in youth perinatally infected with HIV and peer comparisons. J Dev Behav Pediatr 2012;33(6):456-468. [http://dx.doi.org/10.1097/DBP.0b013e31825b8482]
4. Lowenthal E, Lawlerc K, Hararic N, et al. Rapid psychosocial function screening test identified treatment failure in HIV+ African youth. AIDS Care 2012;24(6):722-727. [http://dx.doi.org/10.1080/09540121.2011.644233]
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA, USA: American Psychiatric Publishing, 2013.
6. Canestri A, Lescure F, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. Clin Infect Dis 2010:50(5):773-778. [http://dx.doi.org/10.1086/650538]
7. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children and adolescents with suicidal behaviour. J Am Acad Child Adolesc Psychiatry 2001;40(7 Suppl):24S-51S.
8. Kelly B, Raphael B, Judd F, et al. Posttraumatic stress disorder in response to HIV infection. Gen Hosp Psychiatry 1998;20(6):345-352.
9. Safren SA, Gerhung BS, Hendriksen E. Symptoms of posttraumatic stress disorder and death anxiety in persons with HIV and medication adherence difficulties. AIDS Patient Care STDS 2003;17(12):657-664. [http://dx.doi.org/10.1089/108729103771928717]
10. Sherr L. Young children with HIV/AIDS: Mapping the field. Working paper 33 in early childhood development. The Hague, Netherlands: Bernard Van Leer Foundation, 2005.
11. Sherr L, Mueller J. Where is the evidence base? Mental health issues surrounding bereavement and HIV in children. J Public Ment Health 2009;7(4):31-39.
12. Oneill JF, Selwyn PA, Schietinger H, eds. A clinical guide to supportive and palliative care for HIV/AIDS. Washington, DC: US Department of Health and Human Services, 2003.
13. Department of Health South Africa. Psychosocial Support for Children and Adolescents Infected and Affected by HIV. Pretoria: Department of Health, 2012.
14. Anesathasan A, Mcleary-Sills J, Vujovic M, et al. Foundation for the Future: Meeting the Psychosocial Needs of Children Living with HIV in Africa. Arlington, VA: USAID's AIDS Support and Technical Assistance Resources, AIDSTAR-One, Task Order 1, 2011.
15. Cheng K. Psychotherapeutic interventions. In: Cheng K, Myers KM, eds. Child and Adolescent Psychiatry: The Essentials. Philadelphia: Lippincott, 2005:439-457.
16. International Planned Parenthood Federation. Keys to Youth-friendly Services: Celebrating Diversity. London: IPPF, 2011.
17. Van Rie A, Harrington PR, Dow A, Robertson K. Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: A global perspective. Eur J Paediatr Neurol 2007;11(1):1-9. [http://dx.doi.org/10.1016/j.ejpn.2006.10.006]
18. Walker SY, Pierre RB, Christie CDC, Chang SM. Neurocognitive function in HIV-positive children in a developing country. Int J Infect Dis 2013;17(10):e862-867. [http://dx.doi.org/10.1016/j.ijid.2013.02.014]
19. Williams P, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. Pediatrics 2006;118(6):e1745-1757. [http://dx.doi.org/10.1542/peds.2006-0493]
20. Laughton B, Cornell M, Grove D, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. AIDS 2012;26(13):1685. [http://dx.doi.org/10.1097/QAD.0b013e328355d0ce]
21. Abubakar A, Van Baar A, Van de Vijver FJ, Holding P, Newton CR. Paediatric HIV and neurodevelopment in sub-Saharan Africa: A systematic review. Trop Med Int Health 2008;13(7):880-887. [http://dx.doi.org/10.1111/j.1365-3156.2008.02079.x]
22. Cooper ER, Hanson C, Diaz C, et al. Encephalopathy and progression of human immunodeficiency virus disease in a cohort of children with perinatally acquired human immunodeficiency virus infection. Women and Infants Transmission Study Group. J Pediatr 1998;132(5):808-812.
23. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: A concern for adolescence. J Int AIDS Soc 2013;16:18603. [http://dx.doi.org/10.7448/IAS.16.1.18603]
24. Donald KA, Hoare J, Eley B, Wilmshurst JM. Neurologic complications of pediatric human immunodeficiency virus: Implications for clinical practice and management challenges in the African setting. Semin Pediatr Neurol 2014;21(1):3-11. [http://dx.doi.org/10.1016/j.spen.2014.01.004]
25. Centers for Disease Control and Prevention. 1994 Revised Classification System for HIV Infection in Children Less than 13 Years of Age. Atlanta, G, USA: Centers for Disease Control and Prevention, 1994;443(RR12):1-10.
26. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis 2013;13(11):976-986. [http://dx.doi.org/10.1016/S1473-3099(13)70269-X]
27. Patel K, Ming X, Williams PL, Robertson K, Oleske J, Saege GR. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV-encephalopathy among perinatally infected children and adolescents. AIDS 2009;23(14):1893-1901. [http://dx.doi.org/10.1097/QAD.0b013e32832dc041]
28. Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: Risk and protective factors for early child development. Lancet 2011;378(9799):1325-1338. [http://dx.doi.org/10.1016/S0140-6736(11)60555-2]
29. Stein A, Desmond C, Garbarino J, et al. Predicting long-term outcomes for children affected by HIV and AIDS: Perspectives from the scientific study of children's development. AIDS 2014;28(Suppl 3):S261-S268. [http://dx.doi.org/10.1097/QAD.0000000000000328]

ORIGINAL ARTICLE

Expression of DC-SIGN and DC-SIGNRs in placentas of HIV-positive patients

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Background. Human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin (DC-SIGN) is a mannose-binding lectin that initiates interaction between dendritic cells and resting T-lymphocytes. DC-SIGN is highly expressed in placental tissue on dendritic cells and Hofbauer cells, and it is suggested that HIV may become adsorbed to DC-SIGN on Hofbauer cells as part of the mechanism of mother-to-child HIV transmission. A possible mechanism of transfer of the virus from the Hofbauer cells to the fetus is the subsequent adsorption to DC-SIGN-related molecules (DC-SIGNRs), present on immediately adjacent capillary vascular endothelium. However, data on DC-SIGN and DC-SIGNR expression in the placenta are few.

Methods. Forty term placentas from HIV-positive mothers and 21 term placentas from HIV-negative mothers underwent immunohistochemistry staining for DC-SIGN and DC-SIGNR expression. Five random sets of 10 villi were assessed, and the average number of positive cells were counted in each case. In addition, where possible, maternal and cord blood viral loads and maternal $CD4^+$ counts were performed in the HIV-positive group only.

Results. The median maternal $CD4^+$ count was 377 cells/μl and 27% of participants had undetectable viral loads; the median detectable viral load was 3.72 log. Most (97%) of the cord bloods tested in infants from HIV-positive mothers had lower than detectable viral loads. HIV-positive cases had significantly greater expression of both DC-SIGNRs (median values in HIV-positive cases, 14.5 positive cells/10 villi (pc/10villi), compared with 11 pc/10villi in HIV-negative cases, p=0.020) and DC-SIGN (median value in HIV-positive cases, 26.5 pc/10villi, compared with 23 pc/10villi in HIV-negative cases, p=0.037). DC-SIGNR expression was also noted in Hofbauer cells and decidual macrophages in addition to endothelium (reported currently). There was no difference in expression of DC-SIGN and DC-SIGNRs in patients with or without chorioamnionitis, but there was an inverse relationship between DC-SIGN and DC-SIGNR expression and maternal $CD4^+$ counts in HIV-positive cases.

Conclusion. Both DC-SIGN and DC-SIGNR expression were higher in placentas from HIV-positive mothers compared with HIV-negative cases. These lectins may be potential new therapeutic targets for preventing vertical transmission of HIV.

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The rate of vertical transmission of HIV is estimated at between 13% and 39% in non-breastfeeding women.[1] Most of these cases occur during the intrapartum period during vaginal delivery. However, a small percentage results from HIV infection across the placenta (1 - 2%). A possible mechanism for late-gestation HIV transmission may be maternal-fetal transfusions during labour, which is significantly lower in elective caesarean sections (CSs).[2]

Reverse transcriptase inhibitors (azidothymidine/zidovudine (AZT) and lamivudine) rapidly cross the placenta, and cord blood levels equal or exceed those in the maternal circulation at the time of delivery.[3] Even a single dose of nevirapine, when administered during labour and to an infant after birth, can reduce vertical transmission by 50% because it rapidly crosses the placenta.[3,4] The use of highly active antiretroviral therapy (HAART) throughout pregnancy and prophylactic CS have reduced the rate of vertical transmission in the US to <2%.[5]

Infants with a positive HIV polymerase chain reaction (PCR) test within 48 hours of birth are considered to have been infected *in utero*. However, infants who tested HIV-negative at birth but tested positive at 6 weeks or 12 weeks postnatally with PCR testing are considered to have been infected intrapartum or immediately post partum.[6] In addition, HIV has been demonstrated in second-trimester fetuses and second-trimester cord bloods with associated placental HIV infection supporting *in utero* transmission.[7-9]

Factors that may increase the risk of mother-to-infant transmission include advanced HIV-related illness, low $CD4^+$ counts, high HIV-1 viral loads (VLs), the presence of sexually transmitted diseases, viral phenotype, premature rupture of membranes, chorioamnionitis and absence of maternal autologous neutralising antibodies.[2] But even at the highest VLs, only about half of exposed infants become infected with HIV.[2,4]

It has been proposed that a breach in the trophoblast layer lining the chorionic villi may result in contact of Hofbauer cells

(specialised fetal macrophages) with maternal blood and amniotic fluid. There may also be entry of HIV into the trophoblast layer with subsequent infection of the cell, or the virus could traverse the cells intact, following release at the basolateral surface and exposure to stromal cells. The two pathways are not mutually exclusive.[2] However, trophoblast cells are reported to be only 'moderately susceptible' to HIV infection *in vitro*.[10] It has been shown that tumour necrosis factor alpha (TNFα) significantly upregulated transcytosis of HIV-1 across the trophoblast layer whereas an anti-inflammatory drug (tenidap) significantly reduced transcytosis rates.[5]

Infection of trophoblast cells remains controversial.[11] C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4) were demonstrated on placental macrophages and lymphocytes, but not in trophoblast cells.

Mattern *et al*.[12] demonstrated p24 antigen within scattered Hofbauer cells but not within trophoblast cells or vascular endothelium, in 5/19 term placentas (26%) from HIV-positive women. There was no association between p24 antigen detection and vertical transmission.[12] Another study showed positive Hofbauer cell staining for p24 in 4/9 (44%) placentas from HIV-positive mothers, but there was also decidual macrophage (*n*=1), intermediate trophoblast (*n*=1) and villous endothelium (*n*=1) positivity.[13]

Human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin (DC-SIGN) is a type II mannose-binding lectin that initiates interaction between dendritic cells and resting T-lymphocytes. It is highly expressed in dendritic cells on mucosal tissue and has also been found to be highly expressed in placental tissue on maternal decidual cells and fetal Hofbauer cells.[14] It has been proposed that HIV may become adsorbed to DC-SIGN on Hofbauer cells and/or infect Hofbauer cells. Various mechanisms have been proposed that may allow transfer of the virus from the Hofbauer cells to the fetus.

One mechanism includes subsequent adsorption to DC-SIGN-related molecules (DC-SIGNRs) present on immediately adjacent capillary vascular endothelium.[14] A DC-SIGNR is a transmembrane lectin that binds mannose residues including the glycans of ICAM3 and HIV-1 and HIV-2. It is prominently expressed on endothelial cells derived from liver sinusoids, lymph node sinuses and placenta.[15] However, the possible role of DC-SIGN and DC-SIGNRs in vertical transmission of HIV is still poorly understood.

The purpose of this study was to assess the expression of DC-SIGN and DC-SIGNRs in placentas of HIV-positive patients with the following objectives: to compare the expression of DC-SIGN and DC-SIGNRs in placentas of HIV-positive and HIV-negative patients; to correlate the expression of DC-SIGN and DC-SIGNRs with VLs, history of antiretroviral therapy and evidence of *in-utero* HIV transmission (if possible); and to assess the placentas from HIV-positive patients for pathology, including chorioamnionitis and the presence of specific infective agents.

Methods

Forty placentas from HIV-positive patients at term gestation were collected from the Department of Obstetrics and Gynaecology, Mowbray Maternity Hospital, Cape Town, South Africa. In addition, 21 placentas from HIV-negative patients were collected. Ethical approval for the study was granted by the Faculty of Health Sciences at the University of Cape Town and informed consent for research was obtained from the patients (REC REF 290/2005).

The research included histology and immunohistochemistry of the placentas, performed in the Division of Anatomical Pathology, Groote Schuur Hospital, Cape Town. The placentas were fixed in 10% buffered formalin and analysed in the postmortem laboratory. The analysis included macroscopic description (with plate weight), serial sectioning and taking of three blocks, depending on the presence of macroscopic abnormality, which included umbilical cord, membranes, cord insertion site and a peripheral section of placenta.

Haematoxylin and eosin stained sections were analysed by K Pillay and a placental histopathology report was issued. One suitable block was selected for immunohistochemistry. Two micrometre sections were cut onto poly-L-lysine coated slides and stained with DC-SIGN (purified mouse antihuman CD209 antibody, dilution 1:40, BD Biosciences, US) and DC-SIGNRs (monoclonal antihuman CD209L antibody, dilution 1:40, R&D systems, US) using the Envision kit. Diaminobenzidine (brown) was used as chromogen. Positive and negative controls were run simultaneously.

Five random sets of 10 villi were assessed and an average number of positive cells were counted in each case. Maternal and fetal VLs, with blood taken at the time of delivery, were performed for the HIV-positive group in the Department of Virology, Groote Schuur Hospital, Cape Town.

Data were analysed using Stata Version 10.0 (Stata Corporation, US). Median values of $CD4^+$ cell count, HIV VL and DC-SIGNR expression were compared using the Wilcoxon rank-sum test; proportions were compared using Fisher's exact test; and correlations were analysed using Spearman's rho.

Results

Forty term placentas from HIV-positive mothers (mean age (range) 26 (14 - 38) years) and 21 term placentas from HIV-negative mothers (28 (16 - 40) years) were assessed.

All HIV-positive mothers received antiretrovirals for the prevention of mother-to-child transmission (PMTCT). The majority started AZT monotherapy in the third trimester (85%, *n*=34), 2 were on AZT and nevirapine or lamivudine (5%) and 4 were on HAART before pregnancy (10%). Two of the 40 HIV-positive patients tested positive for syphilis (Venereal Disease Research Laboratory (VDRL)-positive) and received treatment for this, while none of the HIV-negative mothers was VDRL-positive.

Most of the deliveries were by CS in both groups (Table 1). There were 2/38 (5%) small for gestational age (SGA) babies from HIV-positive mothers, one with a history of gestational proteinuric hypertension even though the placenta was histologically normal. There were 3/21 (14%) SGA babies from the HIV-negative cases, two of whom showed ischaemic changes histologically.

Table 1. Antenatal history and delivery

HIV status	VDRL-positive	Delivery	SGA
HIV-positive (*n*=40)	2	10 NVD	2
		30 CS	
HIV-negative (*n*=21)	0	5 NVD	3
		16 CS	

VDRL = Venereal Disease Research Laboratory; NVD = normal vaginal delivery; CS = caesarean section; SGA = small for gestational age.

In the HIV-positive group, the median maternal CD4⁺ count was 324.5 cells/μl (interquartile range 246 - 522) (*n*=38) and 27% of HIV-positive participants had undetectable VLs; the median detectable VL was 3.59 log (*n*=33).

In infants from HIV-positive mothers, 97% of the cord bloods tested had lower than detectable VLs (30/31). The mother of the infant with the positive cord blood (*n*=1) had higher than median VL, lower than median CD4⁺ count, received AZT, and the placenta showed chorioamnionitis with cord-vessel vasculitis and chronic deciduitis.

In the HIV-positive group, 15 placentas showed chorioamnionitis (grade 1 *n*=7, grade 2 *n*=6, grade 3 *n*=2; stage 1 *n*=3, stage 2 *n*=9, stage 3 *n*=3). There was also plate-vessel vasculitis (*n*=9), cord-vessel vasculitis (*n*=7) and funisitis (*n*=2). In the HIV-negative group, there were three cases of chorioamnionitis (grade 2 *n*=2, grade 3 *n*=1; stage 1 *n*=1, stage 3 *n*=2) and two cases of mild cord-vessel vasculitis with no evidence of plate-vessel vasculitis or funisitis in this group.

There was no significant difference in the incidence of chorioamnionitis between placentas from HIV-positive and HIV-negative mothers (*p*=0.084). There were 9 cases of chronic deciduitis, 7 in HIV-positive placentas and 2 in HIV-negative patients (*p*=0.704). There was no evidence of villitis or intervillositis, and no opportunistic infections (e.g. cytomegalovirus inclusions, toxoplasmosis or cryptococcosis) were noted on morphology.

Additional features that were noted on histology in the HIV-positive group included evidence of meconium exposure (*n*=10), focal infarct (*n*=1), focal decidual vasculopathy (*n*=1), dysmaturity (*n*=3), fetal thrombotic vasculopathy (*n*=1), chorangiosis (*n*=1), intervillous thrombus (*n*=2) and intervillous haemorrhage (*n*=3); and in the HIV-negative group, infarcts (*n*=2), decidual vasculopathy (*n*=1) and dysmaturity (*n*=2).

DC-SIGN expression was noted in Hofbauer cells (Fig. 1) and decidual macrophages (Fig. 2) while DC-SIGNR expression was seen in endothelial cells (Fig. 3), some Hofbauer cells and decidual macrophages (Fig. 4). Decidual macrophage staining for DC-SIGNRs has not been described previously in the literature.

HIV-positive cases had significantly greater expression of both DC-SIGNRs (median values in HIV-positive cases, 14.5 positive cells/10 villi (pc/10villi), compared with 11 pc/10villi in HIV-negative cases, *p*=0.020) and DC-SIGN (median values in HIV-positive cases, 26.5 pc/10villi, compared with 23 pc/10villi in HIV-negative cases, *p*=0.037).

In addition, the expression of DC-SIGN and DC-SIGNRs was inversely associated with CD4⁺ count in HIV-positive cases ($p<0.05$ for both, Fig. 5) but the relationship with maternal VL was not statistically significant. There was no significant difference in the expression of DC-SIGN (*p*=0.833) and DC-SIGNRs (*p*=0.557) in placentas with or without placental membrane inflammation. There was also no association with mode of delivery (normal vaginal delivery v. CS).

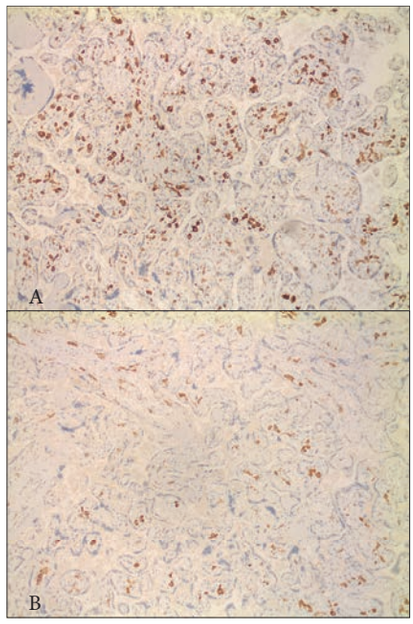

Fig. 1. A. DC-SIGN expression in Hofbauer cells in an HIV-positive case with chorioamnionitis and a CD4⁺ count of 118 cells/μl; B. DC-SIGN expression in Hofbauer cells in an HIV-negative case. (DC-SIGN = human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin.)

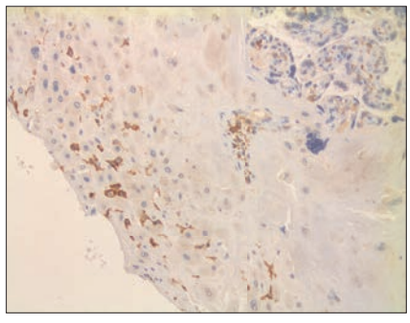

Fig. 2. DC-SIGN expression in decidual macrophages in an HIV-positive case with the only detectable viral load in the cord blood. (DC-SIGN = human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin.)

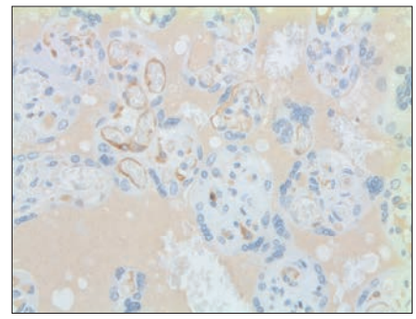

Fig. 3. DC-SIGNR expression in endothelial cells and Hofbauer cells in an HIV-positive case with maternal CD4⁺ count of 365 cells/μl and a viral load of 3.84 log. (DC-SIGNR = human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin-related molecule.)

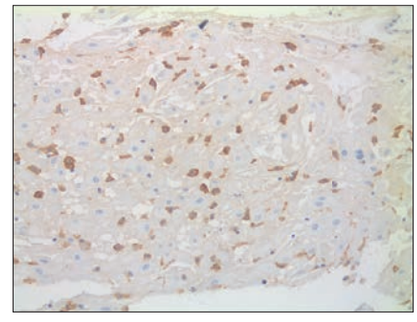

Fig. 4. DC-SIGNR expression in decidual macrophages in an HIV-positive case with maternal CD4⁺ count of 45 cells/μl. (DC-SIGNR = human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin-related molecule.)

Discussion

In the placenta, no co-expression of DC-SIGN and DC-SIGNRs was detected previously.[15] DC-SIGNR expression was detected only on capillary endothelial cells, whereas DC-SIGN was expressed only by Hofbauer cells.[15] However, Mummidi *et al.*[16] demonstrated expression of DC-SIGN on placental capillary endothelium as well. DC-SIGNRs showed a low level of expression in the endometrium.[17] In this study, we demonstrated DC-SIGNR expression on Hofbauer cells and decidual cells as well.

DC-SIGN and DC-SIGNR lectins have been shown to mediate infection in cis (cells with DC-SIGN receptors e.g. dendritic cells) and trans (e.g. T-lymphocytes) cells.[18] Currently, it is felt that DC-SIGN and DC-SIGNRs represent the best candidate molecules for mediating intrauterine transmission.[10] DC-SIGN and DC-SIGNRs appear to function

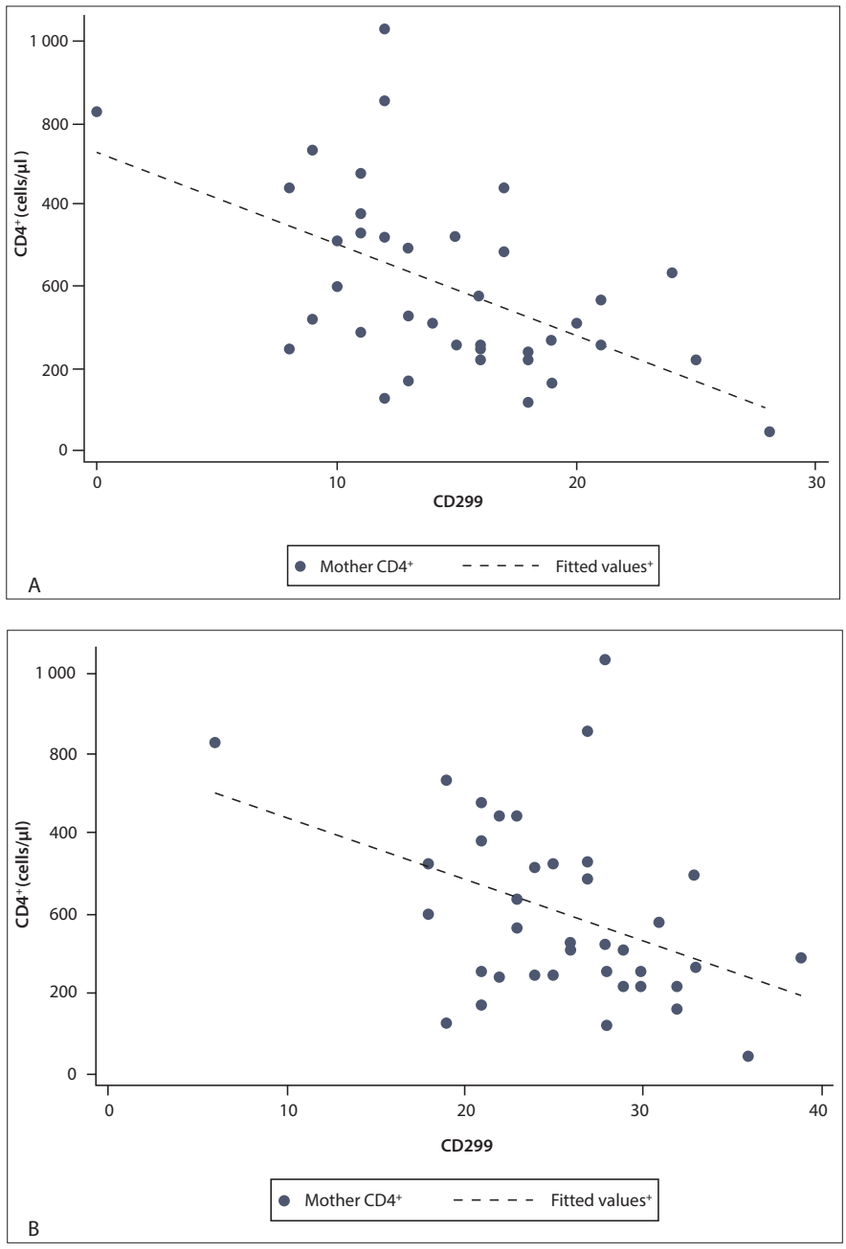

Fig. 5. A. CD4+ v. DC-SIGNRs (CD299) showing a statistically significant inverse correlation, the higher the expression, the lower the CD4+ count; B. CD4+ v. DC-SIGN (CD209) showing a statistically significant inverse correlation, the higher the expression, the lower the CD4+ count. (DC-SIGNR = human dendritic cell-specific intracellular adhesion molecule-3 (ICAM3)-grabbing non-integrin-related molecules.)

as universal attachment factors for primate lentiviruses, namely HIV-1, HIV-2 and simian immunodeficiency viruses.[19] However, research in this field is still in progress and many studies are *in vitro* in nature. One such study has shown a decrease in DC-SIGN expression following infection with HHV-6.[20,21] According to these papers, this may apply to the infection of HIV-1, or DC-SIGN expression may be up-regulated in the setting of HIV-1. Another *in-vitro* study has shown that while DC-SIGN is up-regulated by type 1 and type 2 cytokines, there is no association between DC-SIGN expression and the degree of HIV-1 transmission from macrophages to CD4+ T-cells.[21] The situation *in vi*vo may be different.

A few studies have shown that anti-DC-SIGN reactive antibodies block HIV transmission to cells mediated by DC-SIGN.[22] If studies find a significant association between DC-SIGN expression and intrauterine transmission, then transplacental transmission of HIV may be retarded by the administration of DC-SIGN- and DC-SIGNR-blocking molecules. Other lectin receptors include mannose receptor and langerin expressed on intradermal dendritic cells and Langerhans cells (DC-SIGN negative), respectively, which may have HIV-binding affinity.[23] DC-SIGN on dendritic cells has been shown to bind and transfer HIV through its interaction with HIV gp120. Disruption of this interaction represents a potential new therapeutic approach for preventing HIV transmission.[24]

Gurney *et al.*[24] found that DC-SIGN-positive dendritic cells in the submucosa may be responsible for the transfer of HIV-1 from the periphery to the draining lymph nodes during primary sexual mucosal transmission of HIV-1. DC-SIGN-positive cells appear to be immature dendritic cells in that they did not express the dendritic cell maturation molecule CD83. The Hofbauer cells have also been shown to be human leukocyte antigen (HLA) II+ , CD68+, CD14 low+, CD4+, and S100±, CD86– and CMRF-44–.[23,25]

DC-SIGN is also expressed by some decidual cells with CD14high+ and S100-negative phenotype compared with the Hofbauer cells. DC-SIGN-positive Hofbauer cells co-express CD4+ and chemokine receptors CCR-5 and CXCR4.[23] Gurney *et al.*[24] have demonstrated an increase in DC-SIGN-positive cells in the gut mucosa of HIV-positive patients (two - four-fold greater). Increased DC-SIGN expression in the gut mucosa correlated with a type 2 environment (increased interleukin (IL)-10/IL-12 ratio) and a decrease in the levels of the costimulatory molecules CD86 and CD80.

Micro-array analysis experiments have shown that IL-10-induced dendritic cells result in a DC-SIGN high-expressing subset. There is a shift in pregnancy towards the production of T-helper 2 (Th2) cytokines, including IL-4 and IL-10, promoted by progesterone.[4] The Th2 cytokines IL-4 and IL-13 play an important role in inducing DC-SIGN expression under specific conditions.[23] However, it has been shown that placentas from non-transmitting women maintain normal type 2 placental cytokines (IL-4, IL-10) whereas transmitting women have placentas that express type 1 cytokines (interferon-gamma, tumour necrosis factor beta).[11] Other cytokines (TNFα, IL-6, etc.) stimulate the HIV infection and facilitate transmission during pregnancy.[2]

In this study, we found an increase in DC-SIGN expression in placentas from HIV-positive patients, which may be due to the increased cytokine milieu.

It has been shown that an anti-DC-SIGN antibody blocked virus binding to dendritic cells by almost 90%, with low viral inocula close to those found in seminal fluid from untreated HIV-positive patients.[24] In addition, when the HIV was exposed to the total mucosal mononuclear cells, about 40-fold more viruses were bound to the DC-SIGN-positive population compared with the total gut mononuclear cell population. Therefore, more than 90% of the bound virus was associated with the DC-SIGN-positive cells, which only constitute about 1 - 5% of the total mucosal mononuclear cell population. DC-SIGN is therefore a potential target for therapeutic intervention to reduce viral transmission (after sexual transmission and during vertical transmission).[14,24] The ability of DC-SIGN to enhance infection markedly when virus levels are low may be of particular importance in the setting of prophylaxis against mother-to-child transmission and HAART.[26]

Placental membrane inflammation comprises histological evidence of chorioamnionitis and/or funisitis with or without associated vasculitis. Plasma cell (chronic) deciduitis is demonstrated by the presence of plasma cells in the maternal decidua.[27]

Jauniaux *et al*.[28] demonstrated a high incidence of chorioamnionitis (43%) in placentas from HIV-positive women, but villitis was absent. According to the study by Schwartz *et al*.,[29] no histopathological finding occurred with increased frequency in placentas of transmitting women even though there was a trend towards increased frequency of plasma cell deciduitis. Only 1/17 transmitting women had a placenta with low-grade neutrophilic inflammation. More uninfected women had villitis.[29] Chandwani *et al*.[30] demonstrated no cases of villitis and a higher incidence of chorionitis in placentas from HIV-positive women and p24 antigen within trophoblastic cells, contrary to other studies.[30]

In our study, we demonstrated no significant difference in placental membrane inflammation or chronic deciduitis between HIV-positive and HIV-negative women. There were no cases of villitis or intervillositis in any of the cases. In addition, there was no association of DC-SIGN or DC-SIGNR expression with placental membrane inflammation.

Conclusion

Both DC-SIGN and DC-SIGNR expression were higher in placentas from HIV-positive mothers compared with HIV-negative cases, and this was statistically significant. DC-SIGNR expression was also noted in Hofbauer cells and decidual macrophages in addition to endothelium (reported currently). There was no association of DC-SIGN or DC-SIGNR expression with the presence of placental membrane inflammation, but there was a statistically significant inverse relationship between DC-SIGN and DC-SIGNR expression and maternal $CD4^+$ counts in HIV-positive cases. There was possible *in utero* transmission of HIV in one of the 40 HIV-positive cases (3%).

References

1. Kourtis AP, Lee FK, Abrams EJ, et al. Mother-to-child transmission of HIV-1: Timing and implications for prevention. Lancet Infect Dis 2006;6(11):726-732. [http://dx.doi.org/10.1016/s1473-3099(06)70629-6]
2. Anderson V, Carneiro M, Bulterys M, et al. Perinatal infections: HIV and co-infections in the placenta and therapeutic interventions - a workshop report. Placenta 2001; 22(Suppl A):S34-37. [http://dx.doi.org/10.1053/plac.2001.0641]
3. Mirochnick M. Antiretroviral pharmacology in pregnant women and their newborns. Ann N Y Acad Sci 2000;918:287-297. [http://dx.doi.org/10.1111/j.1749-6632.2000.tb05498.x]
4. Spector SA. Mother-to-infant transmission of HIV-1: The placenta fights back. J Clin Invest 2001;107(3):267-269. [http://.dx.doi.org/10.1172/JCI12094]
5. Parry S, Zhang J, Koi H, et al. Transcytosis of human immunodeficiency virus 1 across the placenta is enhanced by treatment with tumour necrosis factor alpha. J Gen Virol 2006;87(Pt8):2269-2278. [http://dx.doi.org/10.1099/vir.0.81071-0]
6. Bryson YJ, Luzuriaga K, Sullivan JL, Wara DW. Proposed definitions for in utero versus intrapartum transmission of HIV-1. N Engl J Med 1992;327(17):1246-1247.
7. Mano H, Chermann JC. Fetal human immunodeficiency virus type 1 infection of different organs in the second trimester. AIDS Res Hum Retroviruses 1991;7(1):83-88.
8. Maury W, Potts BJ, Rabson AB. HIV-1 infection of first-trimester and term human placental tissue: a possible mode of maternal-fetal transmission. J Infect Dis 1989;160(4):583-588. [http://dx.doi.org/10.1093/infdis/160.4.583]
9. De Andreis C, Simoni G, Rossella F, et al. HIV-1 proviral DNA polymerase chain reaction detection in chorionic villi after exclusion of maternal contamination by variable number of tandem repeats analysis. AIDS 1996;10(7):711-715. [http://dx.doi.org/10.1097/00002030-199606001-00004]
10. Soilleux EJ, Coleman N. Transplacental transmission of HIV: a potential role for HIV binding lectins. Int J Biochem Cell Biol 2003;35(3):283-287. [http://dx.doi.org/10.1016/S1357-2725(02)00132-2]
11. Behbahani H, Popek E, Garcia P, et al. Up-regulation of CCR5 expression in the placenta is associated with human immunodeficiency virus-1 vertical transmission. Am J Pathol 2000;157(6):1811-1818. [http://dx.doi.org/10.1016/S0002-9440(10)64819-5]
12. Mattern CF, Murray K, Jensen A, et al. Localization of human immunodeficiency virus core antigen in term human placentas. Pediatrics 1992;89(2):207-209.
13. Martin AW, Brady K, Smith SI, et al. Immunohistochemical localization of human immunodeficiency virus p24 antigen in placental tissue. Hum Pathol 1992;23(4):411-414. [http://dx.doi.org/10.1016/0046-8177(92)90088-K]
14. Geijtenbeek TB, van Vliet SJ, van Duijnhoven GC, et al. DC-SIGN, a dentritic cell-specific HIV-1 receptor present in placenta that infects T cells in trans: A review. Placenta 2001;22(Suppl A):S19-23. [http://dx.doi.org/10.1053/plac.2001.0674]
15. Soilleux EJ, Morris LS, Rushbrook S, et al. Expression of human immunodeficiency virus (HIV)-binding lectin DC-SIGNR: Consequences for HIV infection and immunity. Hum Pathol 2002;33(6):652-659. [http://dx.doi.org/10.1053/hupa.2002.124036]
16. Mummidi S, Catano G, Lam L, et al. Extensive repertoire of membrane-bound and soluble dendritic cell-specific ICAM-3-grabbing nonintegrin 1 (DC-SIGN1) and DC-SIGN2 isoforms. Inter-individual variation in expression of DC-SIGN transcripts. J Biol Chem 2001;276(36):33196-33212. [http://dx.doi.org/10.1074/jbc.M009807200]
17. Soilleux EJ, Barten R, Trowsdale J. DC-SIGN; a related gene, DC-SIGNR; and CD23 form a cluster on 19p13. J Immunol 2000;165(6):2937-2942. [http://dx.doi.org/10.4049/jimmunol.165.6.2937]
18. Gummuluru S, KewalRamani VN, Emerman M. Dendritic cell-mediated viral transfer to T cells is required for human immunodeficiency virus type 1 persistence in the face of rapid cell turnover. J Virol 2002;76(21):10692-10701. [http://dx.doi.org/10.1128/JVI.76.21.10692-10701.2002]
19. Pohlmann S, Soilleux EJ, Baribaud F, et al. DC-SIGNR, a DC-SIGN homologue expressed in endothelial cells, binds to human and simian immunodeficiency viruses and activates infection in trans. Proc Natl Acad Sci USA 2001;98(4):2670-2675. [http://dx.doi.org/10.1073/pnas.051631398]
20. Niiya H, Azuma T, Jin L, et al. Transcriptional downregulation of DC-SIGN in human herpesvirus 6-infected dendritic cells. J Gen Virol 2004;85(Pt 9):2639-2642. [http://dx.doi.org/10.1099/vir.0.80095-0]
21. Chehimi J, Luo Q, Azzoni L, et al. HIV-1 transmission and cytokine-induced expression of DC-SIGN in human monocyte-derived macrophages. J Leukoc Biol 2003;74(5):757-763. [http://dx.doi.org/10.1189/jlb.0503231]
22. Wu L, Martin TD, Vazeux R, et al. Functional evaluation of DC-SIGN monoclonal antibodies reveals DC-SIGN interactions with ICAM-3 do not promote human immunodeficiency virus type 1 transmission. J Virol 2002;76(12):5905-5914. [http://dx.doi.org/10.1128/JVI.76.12.5905-5914.2002]
23. Soilleux EJ. DC-SIGN (dendritic cell-specific ICAM-grabbing non-integrin) and DC-SIGN-related (DC-SIGNR): Friend or foe? Clin Sci (Lond) 2003;104(4):437-446. [http://dx/doi.org/10.1042/CS20020092]
24. Gurney KB, Elliott J, Nassanian H, et al. Binding and transfer of human immunodeficiency virus by DC-SIGN+ cells in human rectal mucosa. J Virol 2005;79(9):5762-5773. [http://dx.doi.org/10.1128/JVI.79.9.5762-5773.2005]
25. Bockle BC, Solder E, Kind S, et al. DC-SIGN+ CD163+ macrophages expressing hyaluronan receptor LYVE-1 are located within chorion villi of the placenta. Placenta 2008;29(2):187-192. [http:dx.doi.org/10.1016/j.placenta.2007.11.003]
26. Soilleux EJ, Morris LS, Lee B, et al. Placental expression of DC-SIGN may mediate intrauterine vertical transmission of HIV. J Pathol 2001;195(5):586-592.[http://dx.doi.org/10.1002/path.1026]
27. Wabwire-Mangen F, Gray RH, Miro FA, et al. Placental membrane inflammation and risks of maternal-to-child transmission of HIV-1 in Uganda. J Acquir Immune Defic Syndr 1999;22:379-385. [http://dx.doi.org/10.1097/00126334-199912010-00009]
28. Jauniaux E, Nessmann C, Imbert MC, et al. Morphological aspects of the placenta in HIV pregnancies. Placenta 1988;9(6):633-642. [http://dx.doi.org/10.1016/0143-4004(88)90007-0]
29. Schwartz DA, Sungkarat S, Shaffer N, et al. Placental abnormalities associated with human immunodeficiency virus type 1 infection and perinatal transmission in Bangkok, Thailand. J Infect Dis 2000;182(6):1652-1657. [http://dx.doi.org/10.1086/317634]
30. Chandwani S, Greco MA, Mittal K, et al. Pathology and human immunodeficiency virus expression in placentas of seropositive women. J Infect Dis 1991;163(5):1134-1138. [http://dx.doi.org/10.1093/infdis/163.5.1134]

ORIGINAL ARTICLE

Management of patients presenting with diarrhoea to a regional emergency department in KwaZulu-Natal: Call for clearer, more relevant guidance

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Background. HIV is prevalent throughout South Africa, and diarrhoea is a common presentation to the emergency department (ED) among both HIV-infected and -uninfected individuals.

Method. We audited the management of diarrhoea against standard guidelines in the ED of a regional hospital in KwaZulu-Natal. Patients presenting with diarrhoea as their chief complaint were eligible and data were collected prospectively.

Results. A total of 72 patients were included: 58 (81%) of patients were HIV-positive with an average $CD4^+$ count of 180 cells/µl. A total of 34 stool samples were sent for standard microscopy and culture (M&C), among which 26 were positive (76%). Forty-three patients (60%) received antibiotics, 15 of whom had positive stool M&C. In all cases, the final diagnosis was listed as acute gastroenteritis without further specification, and antibiotic use according to guidelines appeared inconsistent.

Conclusion. Based on this audit, we suggest that current guidelines are not clear concerning management of acute diarrhoea in HIV-infected individuals, and that the lack of clear management strategies is likely to affect patient safety and increase antibiotic resistance.

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HIV and related conditions are common causes of hospital presentations across South Africa (SA), and diarrhoea is a common presentation to the emergency department (ED) in high-prevalence areas.[1,2] A differential diagnosis of any HIV-seropositive patient presenting with diarrhoea will thus need to consider a wider variety of infectious pathogens as well as non-infectious causes.[3,4]

In SA, the Department of Health's Essential Medicines List (EDL) has a list of guidelines concerning diarrhoea. It states that acute diarrhoea with blood or mucus in the stool is suggestive of acute inflammatory colitis and may have an infective cause. Stool culture is advised and a course of antibiotics is recommended. HIV/AIDS is not considered in the acute diarrhoea guidelines, only in the subsequent discussion of opportunistic infections that cause chronic diarrhoea, i.e. diarrhoea lasting >4 weeks.[5] With this background, we decided to audit the management of all types of diarrhoea against EDL guidelines in the ED of a provincial hospital in KwaZulu-Natal.

Methods

All patients presenting to the ED with diarrhoea as their chief complaint were eligible for inclusion. Data were collected prospectively, between February and April 2013, including demographic characteristics, HIV status, presenting symptoms, prescription of antibiotics, blood results, final management, and stool microscopy and culture (M&C). We performed univariate analysis of clinical predictors of positive stool M&C and admission, using Fisher's exact test to examine statistical significance.

Results

A total of 72 patients were included (Table 1). We used estimated glomerular filtration rate (eGFR) and white cell count (WCC) as proxy indicators for severity. We considered an eGFR of <60 ml/min/1.73 m^2 to indicate renal impairment and a WCC of >11 × 10^9/l to indicate leucocytosis. $CD4^+$ counts were available for 28/58 HIV-seropositive patients.

A total of 34 stool samples were sent for M&C. We considered the stool M&C positive, i.e. demonstrating an infection in the bowel, if any bacteria had grown (the laboratory tested for *Salmonella* spp, *Shigella* and *Campylobacter*) or there were white cells and/or yeasts present. No specimen grew bacteria, but 26 were positive for white cells and/or yeasts.

Forty-three patients received antibiotics; Table 2 examines the use of antibiotics in relation to investigations and management. In all cases, a final diagnosis of acute gastroenteritis was made (no matter the duration), with no differentiation to suggest reason for choice or duration of antibiotic treatment.

Discussion

The majority of the patients included in our audit presented with acute-onset diarrhoea, which had a median duration of only 3 days. Upon presentation, the initial focus should be to resuscitate the patient with particular focus on fluid status, regardless of their HIV status. However, when considering the underlying condition, it is important to acknowledge the fact that most of the patients were severely immunocompromised.[3,4]

A large proportion of patients were prescribed antibiotics, and this appears unrelated to severity of disease or possibility of being admitted. This prescribing practice, factoring in that 84%

were given only a single dose of antibiotics, puts the patient at risk of both undertreated infection and the development of a resistant organism. This is a very real possibility in a region with high HIV endemicity, as observed in other studies.[6,7] Furthermore, with HIV-positive patients being treated both prophylactically and more frequently with antimicrobial agents, the risks of resistance[8] and antimicrobial-related colitis caused by *Clostridium difficile*[2,9] are further increased.

We found no correlation between positive stool microscopy and patient-reported symptoms of blood or mucus in the stool. There could be several reasons for this, and it would be worthwhile exploring this in more depth. In our audit, we requested stool M&C from a single specimen, which is a significant limitation, as multiple investigations are more likely to find a causative organism.[10] The feasibility of carrying out multiple investigations in the ED of a public hospital in a highly endemic area needs consideration. Algorithms for definitive diagnosis have been described, but require multiple investigations over multiple visits to a hospital with relatively advanced diagnostic facilities.[11]

Table 1. Demographics of audit population (*N*=72)

Admitted following presentation, *n* (%)	32 (44)
Age (years), mean (range)	39 (12 - 81)
Gender (female), *n* (%)	41 (57)
Duration of diarrhoea (days), median (range)	3 (1 - 120)
Acute (lasting <28 days), *n*	59
Chronic (lasting ≥28 days), *n*	4
Duration unknown, *n*	9
HIV status (HIV-positive), *n* (%)	58 (81)
$CD4^+$ count (cells/μl), median (range)	137 (6 - 480)
eGFR (ml/min/1.73 m^2), mean (range)	91 (9 - 282)
<60, *n*	21
≥60, *n*	48
WCC (× 10^9/l), mean (range)	9.25 (1.54 - 26.6)
<11, *n*	53
≥11, *n*	15

eGFR = estimated glomerular filtration rate; WCC = white cell count.

Conclusion

This audit found that the population coming through the ED with diarrhoeal symptoms was predominantly HIV-positive with a low $CD4^+$ count, and the signs and symptoms largely suggested acute episodes of infective diarrhoea leading to renal dysfunction and leucocytosis. Nevertheless, we found that the management was for the most part inconsistent and could put the patient at risk of both antibiotic resistance, or (as is the case for the use of ciprofloxacin) antibiotic-related *C. difficile* colitis. Although the EDL guidelines offer guidance for antibiotic prescribing, clearer prescribing and management guidelines for acute diarrhoea in HIV-positive individuals, particularly in cases of AIDS, are needed.

References

1. Kelly P, Todd J, Sianongo S, et al. Susceptibility to intestinal infection and diarrhoea in Zambian adults in relation to HIV status and CD4 count. BMC Gastroenterol 2009;9:7. [http://dx.doi.org/10.1186/1471-230X-9-7]
2. Venkat A, Piontkowsky DM, Cooney RR, Srivastava AK, Suares GA, Heidelberger CP. Care of the HIV-positive patient in the emergency department in the era of highly active antiretroviral therapy. Ann Emerg Med 2008;52(3):274-285. [http://dx.doi.org/10.1016/j.annemergmed.2008.01.324]
3. Beeching N, Jones R, Gazzard B. Gastrointestinal opportunistic infections. HIV Med 2011;12(Suppl 2):43-54. [http://dx.doi.org/10.1111/j.1468-1293.2011.00944_5.x]
4. Vyas N, Pathan N, Aziz A. Enteric pathogens in HIV-positive patients with diarrhoea and their correlation with CD4+ T-lymphocyte counts. Trop Parasitol 2012;2(1):29-34. [http://dx.doi.org/10.4103/2229-5070.97236]
5. Department of Health South Africa. Standard Treatment Guidelines and Essential Medicines List For South Africa, Hospital Level Adults, 2012 Edition. Pretoria: Department of Health, 2012.
6. Rowe JS, Shah SS, Motlhagodi S, et al. An epidemiologic review of enteropathogens in Gaborone, Botswana: Shifting patterns of resistance in an HIV endemic region. Myer L, ed. PLoS ONE 2010;5(6):e10924. [http://dx.doi.org/10.1371/journal.pone.0010924]
7. Samie A, Mashao MB, Bessong PO, NKgau TF, Momba MNB, Obi CL. Diversity and antibiograms of bacterial organisms isolated from samples of household drinking-water consumed by HIV-positive individuals in rural settings, South Africa. J Health Popul Nutr 2012;30(3):241-249.
8. Byarugaba DK. A view on antimicrobial resistance in developing countries and responsible risk factors. Int J Antimicrob Agents 2004;24(2):105-110. [http://dx.doi.org/10.1016/j.ijantimicag.2004.02.015]
9. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and Clostridium difficile-associated diarrhea. Emerg Infect Dis 2003;9(6):730-733. [http://dx.doi.org/10.3201/eid0906.020385]
10. Oude Munnink BB, Canuti M, Deijs M, et al. Unexplained diarrhoea in HIV-1 infected individuals. BMC Infect Dis 2014;14(1):22. [http://dx.doi.org/10.1186/1471-2334-14-22]
11. Feasey NA, Healey P, Gordon MA. Review article: The aetiology, investigation and management of diarrhoea in the HIV-positive patient. Aliment Pharmacol Ther 2011;34(6):587-603. [http://dx.doi.org/10.1111/j.1365-2036.2011.04781.x]

Table 2. Use of antibiotics in all cases

	Antibiotics given (*N*=43)	Antibiotics not given (*N*=29)	*p*-value
Stool M&C, *n*			1.000
Positive	15	10	
Negative	5	3	
Final outcome, *n*			0.439
Discharged	18	14	
Admitted	21	10	
Severity, *n*			
Leucocytosis and renal impairment (*n*=5)	4	1	0.633*
Only leucocytosis (*n*=10)	5	5	0.723*
Only renal impairment (*n*=16)	11	5	0.758*
None of the above (*n*=37)	22	15	
Only stat dose given, *n* (%)	36 (84)	-	
Antibiotics prescribed, as advised by the EDL guidelines, *n* (%)	25 (58)	-	

M&C = microscopy and culture; EDL = Essential Medicines List.
*Compared with no presence of leucocytosis or renal impairment.

ORIGINAL ARTICLE

Management of cryptococcal meningitis in adults at Mthatha Hospital Complex, Eastern Cape, South Africa

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Background. Cryptoccocal meningitis (CM) remains prevalent in HIV-infected individuals across South Africa (SA). Early diagnosis and management, aided by the existing Southern African HIV Clinicians Society (SAHIVSoc) 2007 guidelines on management of CM, could reduce the mortality associated with this condition.
Objective. To review the management of adult patients with CM and adherence to the SAHIVSoc 2007 guidelines in a district hospital.
Methods. A retrospective chart review of patients admitted with CM from December 2011 to May 2012 was performed. The following key recommendations of the guidelines were evaluated: measurement of cerebrospinal fluid (CSF) opening pressure at the first lumbar puncture (LP), prescription of amphotericin B (AMB)/fluconazole therapy, intravenous prehydration preceding administration of AMB, monitoring of renal function and performance of serial LPs to manage raised intracranial pressure (ICP).
Results. A total of 57 patient charts were reviewed, of which 40 (70%) were of females. The mean age (range) of the cohort was 36 (21 - 60) years. Fifty-two (91%) patients presented with headache. Confusion was recorded in 30 (53%) and vomiting in 26 (46%). The major signs observed were fever (*n*=29 (51%)) and neck stiffness (*n*=34 (60%)). Fifty-five (96%) patients were HIV-infected at presentation, with a median (range) $CD4^+$ count of 77 (13 - 90) cells/μl. None of the patients had a CSF opening pressure measured at first LP. AMB was used as an induction agent in 51 (89%) patients, of whom 47 (92%) completed 2 weeks of AMB. Of these 51, only 20 (40%) were prehydrated and 10 (18%) had two repeat LPs performed 1 week apart. Renal function was monitored in only 27 (53%) of the patients receiving AMB. This was done at baseline and twice weekly, and was consistent with the guidelines. No abnormality in renal function was recorded in these cases during the study. The mortality rate was 30% in the first 10 days of admission.
Conclusion. This chart review showed inadequate adherence to the recommendations of the 2007 SAHIVSoc guidelines in the majority of cases except for the use of AMB as a first-line antifungal agent. Control of ICP and monitoring for drug toxicity were not done as per guidelines and may impact on clinical care and outcome. Despite this, the early 30% mortality is comparable with published reports from other regions in SA, but is higher than in developed health systems.

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Worldwide, the burden of cryptoccocal meningitis (CM) is estimated to be 0.04 - 12% per year among persons with HIV, resulting in nearly 625 000 deaths.[1] Sub-Saharan Africa has the highest yearly burden with 720 000 cases (range 144 000 - 1.3 million).[1] In sub-Saharan Africa, mortality is estimated to be 50 - 70%, compared with 12% in the USA and other developed nations.[2] *Cryptococcus neoformans* infections are very rare in healthy people, with a yearly incidence of 0.4 - 1.3 cases per 100 000 in the general population.[2] In a population-based surveillance of cryptococcosis in Gauteng, South Africa (SA), the overall incidence rate was 15.6/100 000 among both HIV-positive and -negative individuals.[3] Among HIV-positive persons, the rate was 95/100 000, and among persons living with AIDS, 14/1 000.[3]

In HIV-positive individuals, CM may present with headaches, unexplained fever, nausea, vomiting, neck stiffness, confusion, seizures, abnormal behaviour, and new onset of psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness and sometimes coma.[4] Headache is the predominant symptom and was observed in 100% of cases in a study done by Baradkar *et al.*[5] Neck stiffness may be absent in some patients with CM.[6] The presentation of CM may be acute, sub-acute (over 2 - 4 weeks), or chronic (>4 weeks).[4]

Despite the availability of highly active antiretroviral treatment (HAART), the mortality from CM has not changed from the pre-HAART era. However, CM immune reconstitution inflammatory syndrome (IRIS) is implicated in the ongoing high mortality.[7] It is also not uncommon to have other opportunistic infections together with CM that contribute to mortality.[8]

Elevated intracranial pressure (ICP) results in increased mortality and morbidity. Up to 40% of CM deaths occurring during weeks 3 - 10 of treatment were associated with elevated ICP. Visual loss was also observed as a consequence of elevated ICP.[9]

A high index of suspicion is needed for the diagnosis of CM, especially in sub-Saharan Africa, where there is a dearth of standard laboratory facilities and expertise. Therefore, the role

of a detailed history and physical examination cannot be overemphasised.[10] The definitive diagnosis involves cerebrospinal fluid (CSF) microscopy, cryptococcal antigen (CrAG) detection in CSF and/or serum, and the culture of *C. neoformans*.[11] If an Indian ink stain is negative, CrAG remains a reliable test (95% sensitivity, 95% specificity). The CrAG Latex Agglutination System (Meridien Bioscience, US) is commonly used and correlates well with the fungal burden.[11]

In a retrospective study conducted in Durban, SA, the significantly higher Indian ink positivity rate and significantly higher mean CrAG titre reflected the greater fungal load in HIV-positive patients.[12] Culture of *C. neoformans* in CSF is also beneficial in the diagnosis of subsequent episodes of CM where both CrAG and Indian ink tests are not useful.[13]

The only guideline for the management of CM in our setting, prior to 2012 when this study was conducted, was published by the SAHIVSoc in 2007.[6] This guideline was updated in 2013. The initial guideline highlighted the role of amphotericin B (AMB) as the antifungal agent preferred during the induction phase of treatment. Treatment with AMB (1 mg/kg body weight (BW)/day) for 2 weeks, followed by fluconazole (400 mg/day) as a consolidation agent for 8 weeks was recommended. A dose of 200 mg fluconazole daily is indicated for secondary prophylaxis until the $CD4^+$ T-lymphocyte count is >200 cells/μl for at least 6 months and the most recent HIV-1 viral load is suppressed; this applies to patients with a first episode of CM.[6] Patients with relapse are treated with 1 mg/kg BW AMB for 2 - 4 weeks or until the CSF is sterile. Consolidation and maintenance options in relapse depend on the fluconazole minimum inhibitory concentration and include high-dose fluconazole with or without weekly AMB infusions, or voriconazole.[6]

AMB is often unavailable in our centres, hence high-dose fluconazole (800 - 1 200 mg) is often used. The latter is suboptimal at these doses.[14] For resource-limited settings where AMB is unavailable, high-dose fluconazole (1 200 mg) is recommended as an induction agent by the World Health Organization (WHO).[15]

Similar to the SAHIVSoc guidelines, Tronconso *et al.*[16] highlighted the role of monitoring renal function while patients are undergoing the induction phase with AMB. If creatinine increases by twofold, the AMB dose is omitted and prehydration with 0.9% normal saline, 1 l 8-hourly, is recommended. AMB should be stopped if the creatinine fails to decrease after this intervention.[6]

Table 1. Presenting symptoms and signs of patients admitted with cryptococcal meningitis (*N*=57)

Presenting complaints	*n*	%
Headache	52	91
Confusion	30	53
Psychotic features	11	19
Seizures	13	23
Vomiting	26	46
Signs		
Fever	29	51
Neck stiffness	34	60
Kernig's and Brudzinski's signs	34	60
Focal signs (hemiparesis)	1	2
Cranial nerve deficit	1	2

In June 2013, the SAHIVSoc updated the guideline for the prevention, diagnosis and management of CM in HIV-positive persons to be compatible with WHO guidelines. A major change from the 2007 version is the role of both AMB and fluconazole during the induction phase. The revision also highlighted timing of HAART initiation.[13]

Methods

The study was a descriptive, retrospective chart review conducted at the Mthatha General Hospital in the Eastern Cape (EC), SA, between December 2011 and May 2012. The majority of patients with CM in the OR Tambo district of the EC are managed as inpatients in this facility. The hospital serves as a referral centre and has 100 medical beds.

The inclusion criteria were adult patients >18 years of age with a first episode of CM diagnosed on lumbar puncture (LP) as part of routine care of patients with clinical features of meningitis. Patients were managed by a team of doctors that included an intern, medical officer/registrar and a family physician. The researcher did not interact with the patients.

For data collection, a researcher searched the ward register daily for cases diagnosed as CM and admitted to any of the medical wards. Data were collected from respective patient case note files. The medical records of all patients identified with CM from the ward register were available for data collection and were verified by positive laboratory results.

The data of interest were: measurements of CSF opening pressure at the first LP; whether AMB/fluconazole therapy was used; whether prehydration was administered before the receipt of AMB; and whether monitoring of renal function (rising urea and creatinine only) and ICP were done according to the recommendations of the SAHIVSoc 2007 CM guidelines.

The time of commencement of AMB was documented in the prescription/drug chart of each patient and the time of admission was recorded on the admission chart and the nurses' charts. The renal function of each patient was determined from the laboratory report in the case notes.

Data were analysed using SPSS version 18.0 (IBM, South Africa). Descriptive data were presented using frequency tables. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (number BE058/12).

Results

A total of 57 charts were reviewed over the 6-month study period, representing all patients who were admitted to the medical wards with CM in this time period. However, some patients may have died in casualty before ward admission and hence would not have been captured in the ward admission charts. The mean age (range) of the patients was 36 (21 - 60) years, and 40 were women (70%). Table 1 shows the presenting complaints, signs and their frequency of occurrence. Of the 57 patients, 52 (91%) presented with headache. Confusion was recorded in 30 (53%) and vomiting in 26 (46%) of subjects. The major signs observed were fever in 29 (51%), and meningeal signs in 34 (60%).

All patients had an initial LP for CSF laboratory analysis that included biochemistry, Indian ink stain, CrAG assay and fungal culture. A computerised tomography (CT) scan was done in only two patients with

Table 2. Concurrent opportunistic infections and comorbidities in patients with cryptococcal meningitis (*N*=57)

Opportunistic infections	*n*	%
Pulmonary tuberculosis	32	56
Oropharyngeal candidiasis	57	100
Seborrhoeic dermatitis	12	21
Oral hairy leukoplakia	8	14
Tuberculous meningitis	10	23

focal signs and cranial nerve deficits, showing a mass lesion in both cases, suggestive of cryptococcoma. There was no record of the measurement of CSF opening pressure at LP in any of the charts reviewed. The diagnosis of CM was made within 24 hours of presentation (range 3 - 8 hours) in 70% of the patients. This was calculated from the time the LP was performed to the time the microscopy result was obtained. All 57 cases were positive for microscopy and culture for *C. neoformans*, while CrAG was positive in 51 (89%) cases.

HIV infection was diagnosed for the first time in 7 (12%) of these patients. The remaining 50 (88%) were known to be HIV-positive. All had features of immunosuppression. The most frequent infections were oropharyngeal candidiasis and tuberculosis (TB) (Table 2).

The median (range) $CD4^+$ count was 77 (51 - 100) cells/μl. Twenty-two (39%) of the 57 patients were on HAART. Thirteen (23%) patients had been on ARVs for less than 6 months and the remaining 9 (16%) patients had been on ARVs for 7 - 12 months. All patients were on tenofovir, lamivudine and efavirenz and were documented to be adherent to treatment. Tenofovir was continued even when AMB was commenced.

Thirty-two (56%) of the patients had co-infection with pulmonary TB. Ten of these patients were diagnosed on sputum microscopy for acid-fast bacilli, while the remainder were diagnosed clinically and on chest radiography. Ten patients had tuberculous meningitis co-infection based on CSF lymphocytosis and raised protein.

AMB (1 mg/kg BW) was used as the induction agent for the management of CM in 51 (89%) of the patients, while the remaining 6 (11%) had intravenous fluconazole (800 mg) because AMB was out of stock. Among the 51 patients who had AMB as an induction agent, the drug was initiated in 50 (98%) cases, within 24 hours of the attending doctor writing the script. The time of commencement of AMB was documented in the prescription/drug chart by the nurse administering the dose and the time of admission was recorded on the patient chart. Only 20 (39%) patients receiving AMB had documentation of adequate prehydration. Forty-seven (92%) patients completed the 2-week course of AMB.

Renal function was monitored in 27 (53%) of the patients receiving AMB. This was done at baseline and twice weekly, and was consistent with the guideline. Results were obtained from the case files and the normal ranges for urea and creatinine were 2.1 - 7.1 mmol/l and 64 - 104 μmol/l, respectively. No abnormalities in serum urea and creatinine were recorded in these cases during the study.

Ten patients (18%) who experienced worsening headache in the ward had two repeat LPs performed for the management of raised ICP. These LPs were performed 1 week apart.

Forty patients (70%) were discharged, with the average (range) hospital stay being 21 (16 - 28) days. The in-hospital mortality rate within the first 1 - 10 days of hospital admission was 30%. Fluconazole 400 mg was dispensed on discharge for 1 week of the consolidation phase and patients were referred to a local clinic to continue treatment. Data on patients prescribed HAART were not obtained.

Discussion

There are few data on management and outcome of CM from a non-research district hospital setting in a resource-limited health system where operational challenges may have a significant impact. This study was limited by the retrospective, descriptive nature. Although all patient charts were found, documentation in the clinical notes was poor and missing data compromised this chart review.

The Mthatha complex manages 6 - 10 cases of CM in AIDS patients per month. Some cases of CM could have been missed in this review if patients died in casualty and hence were not captured in the ward admission file. This retrospective chart review of adult patients found that the management was not consistently in line with national guidelines. Unlike other studies where the incidence of CM was similar in both sexes, or higher in men,[1] we found that the disease was three times higher in women. The reason for this may be the migrant nature and different health-seeking behaviour of men in this community and warrants further investigation. All patients were HIV-positive with a median $CD4^+$ count of 77 cells/μl, consistent with the results in other studies.[1,3] An interesting observation is that 88% of patients were known to be infected with HIV prior to the diagnosis of CM. The mortality of 30% was less than that reported in a Ugandan study in a similar patient population and healthcare system, where mortality was between 40% and 50%.[7] The mortality was similar to that in other centres in SA.[17]

Many patients already diagnosed with HIV infection were not on ARVs at the time of presentation. This is of concern as it is likely that CM may have been preventable in the majority. This observation highlights the need for a more intensive rollout of ARV treatment. Our study also highlighted the occurrence of CM in the first 6 months of HAART, which may represent IRIS or reflect ongoing immunosuppression during early HAART.

Headache was the most common symptom. Vomiting, fever, confusion and psychosis were also noted. However, meningeal signs were absent in 40% of the patients. This may be owing to poor inflammatory response attributed to severe immunosuppression.

The study found that co-infections, particularly TB, were extremely high in these CM patients. This is not surprising, because of profound immunosuppression and the high prevalence of TB in our setting. Many cases of TB were diagnosed on clinical or radiological features, or suggestive CSF microscopy and biochemistry. Since these are not specific diagnostic tests, overdiagnosis of TB was possible. The CSF CrAG was found to be an extremely important test; 77% of the patients were diagnosed within 24 hours of presentation using this assay. The CrAG test should be routinely performed by the laboratory if the India ink stain is negative. The effect of early diagnosis on morbidity and mortality is well documented.[18] It was also demonstrated that patients who presented with features of neurological deficit received a CT scan as recommended by the guideline.[6] None of the patients admitted had an opening CSF pressure measured during the LP and fundoscopy was not done, which is of concern. Documentation and management of ICP was also not done. This was presumably because the hospital does not stock manometers.

Drug treatment aspects of the 2007 SAHIVSoc guidelines were followed in most

patients who received AMB as the induction agent, and all were discharged on fluconazole, 400 mg daily, as a consolidation agent.[6]

Prehydration and renal toxicity monitoring advised by the guideline were not followed, and it is surprising that more renal complications were not observed. However, documentation of fluid administration is poor in our facility. Early mortality rates may have improved if these measures had been implemented.

Conclusion

We recommend that an in-service workshop on common opportunistic infections in HIV should be provided for healthcare providers within the district hospital setting. A commitment by the Department of Health to provide necessary diagnostic tools, including manometers, and an uninterrupted drug supply would improve the management and outcome of the disease at a district level.

References

1. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 2009;23(4):525-530. [http://dx.doi.org/10.1097/QAD.0b013e328322ffac]
2. Centers for Disease Control and Prevention. C. neoformans cryptococcosis. http//:www.cdc.gov/fungal/crptococcosis-neoformans/statistics.html (accessed 27 July 2013).
3. McCarthy KM, Morgan J, Wannemuehler KA, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS 2006;20(17):2199-2206. [http://dx.doi.org/10.1097/QAD.0b013e3280106d6a]
4. Bicanic T, Harrison TS. Cryptococcal meningitis. Br Med Bull 2004;72(1):99-118. [http://dx.doi.org/10.1093/bmb/ldh043]
5. Baradkar V, Mathur M, De A, Kumar S, Rathi S. Prevalence and clinical presentation of cryptococcal meningitis among HIV seropositive patients. Indian J Sex Transm Dis 2001;30(1):19-22. [http://dx.doi.org/10.4103/0253-7184.55474]
6. McCarthy K, Meintjes G, Arthington-Skaggs B, et al. Guidelines for the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV-infected patients. S Afr J HIV Med 2008;3(25):25-35. http://sajhivmed.org.za/index.php/sajhivmed/article/view/92 (accessed 6 June 2013).
7. Kambugu A, Meya D, Rhein J, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of HAART. Clin Infect Dis 2008;46(11):1694-1701. [http://dx.doi.org/10.1086/587667]
8. Skiest DJ, Hester LJ, Hardy RD. Cryptococcal immune reconstitution inflammatory syndrome: Report of four cases in three patients and review of the literature. J Infect 2005;51(5): e289-e297. [http://dx.doi.org/10.1016/j.jinf.2005.02.031]
9. Van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med 1997;337(1):15-21.
10. Lightowler JVJ, Cooke GS, Mutevedzi P, et al. Treatment of cryptococcal meningitis in KwaZulu-Natal, South Africa. PLoS ONE 2010;5(1):e8630. [http://dx.doi.org/10.1371/journal.pone.0008630]
11. Tanner DC, Weinstein MP, Fedorciw B, Joho KL, Thorpe JJ, Reller L. Comparison of commercial kits for detection of cryptococcal antigen. J Clin Microbiol 1994;32(7):1680-1684.
12. Moosa MYS, Coovadia YM. Cryptococcal meningitis in Durban, South Africa: A comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients. Clin Infect Dis 1997;24(2):131-134.
13. Southern African HIV Clinicians Society. The Guideline for the Prevention, Diagnosis and Management of Cryptococcal Meningitis among HIV-infected Persons: 2013 Update. S Afr J HIV Med 2013;2(4):76-86. [http://dx.doi.org/10.7196/sajhivmed.930]
14. Pukkila-Worley R, Mylonakis E. Epidemiology and management of cryptococcal meningitis: Developments and challenges. Expert Opin on Pharmacother 2008;9(4):551-560. [http://dx.doi.org/10.1517/14656566.9.4.551]
15. World Health Organization. Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization, 2011:4-44. http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf (accessed 2 January 2014).
16. Troncoso A, Fumagalli J, Shinzato R, Gulotta H, Toller M, Bava J. CNS cryptococcoma in an HIV-positive patient. J Int Assoc Physicians AIDS Care (Chic) 2002;1(4):131-133.
17. Lessells RJ, Mutevedzi PC, Heller T, Newell ML. Poor long-term outcomes for cryptococcal meningitis in rural South Africa. S Afr Med J 2011;101(4):251-252.
18. Dhana A. Diagnosis of cryptococcosis and prevention of cryptococcal meningitis using a novel point-of-care lateral flow assay. Case Reports in Medicine 2013;2013(Article ID 640216):4 pp. [http://dx.doi.org/10.1155/2013/640216]

ORIGINAL ARTICLE

Closing the gaps: Steps towards elimination of mother-to-child transmission of HIV

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Background. With significant reductions in the rate of HIV mother-to-child transmission (MTCT) in South Africa, each case of failed prevention of MTCT (PMTCT) should be investigated.
Objective. To establish the cause(s) of MTCT at Khayelitsha's Community Health Centre (CHC) in order to identify obstacles to MTCT elimination.
Methods. Routinely collected data were reviewed for all HIV-infected infants identified at Khayelitsha Site B CHC from January 2012 to April 2013.
Results. A total of 926/1 158 (80%) of exposed infants had polymerase chain reaction (PCR) results, with 15/926 (1.6%) PCR-positive. Median (interquartile range (IQR)) values for the maternal indicators were as follows: maternal age, 27 (23 - 31) years; parity, 2 (1 - 3); gestational age at antenatal presentation, 21.5 (17.5 - 30.5) weeks; $CD4^+$, 377 (219 - 446) cells/μl. Of the 15 PCR-positive infants, five received ART, five received AZT and five received no prophylaxis. Viral loads were not monitored for any of the women receiving antenatal ART. Nine of the 15 (60%) delivered in hospital, with 6/9 requiring caesarean section. The median (IQR) infant birth weight was 3.0 (2.6 - 3.5) kg. All received prophylactic nevirapine post exposure. Two of the 15 were clinically unwell at birth, and 14 (86.7%) were breastfed, with 10 (66.7%) recorded as exclusively breastfed. Median (IQR) time between delivery and PCR results was 6.6 (6.1 - 7.3) weeks.
Discussion. PMTCT programmes must consider each PCR-positive infant as a sentinel event that can provide valuable insight into correcting ongoing clinical and programmatic reasons for HIV transmission. The main risk factors for MTCT identified in this study were late presentation for antenatal care, inadequate antenatal PMTCT prophylaxis and a lack of viral load monitoring.

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Over the last decade, South Africa (SA) has experienced dramatic improvements in its prevention of mother-to-child-transmission (PMTCT) programme. The first national-level PMTCT programme was introduced in 2002 and included single-dose nevirapine (Sd-NVP) during labour for the mother and to the baby postpartum, modified obstetric practices, infant feeding counselling, and the provision of free infant formula to HIV-positive mothers who chose not to breastfeed.[1] In 2005, pregnant women with CD4⁺ counts ≤200 cells/µl were eligible for triple-drug antiretroviral (ARV) therapy (ART) for their own health, and in 2008 pregnant women with CD4⁺ counts >200 cells/µl were offered 'dual therapy' (azidothymidine (AZT) from 28 weeks, and Sd-NVP in labour) and Sd-NVP with AZT postnatal infant prophylaxis. In 2010, there were further improvements to the PMTCT programme. These included routine HIV testing and counselling for pregnant women, dual therapy to prevent MTCT of HIV, highly active ARV therapy for pregnant women with a CD4⁺ cell count ≤350 cells/µl, postnatal infant prophylaxis with NVP for breastfeeding HIV-positive women and intensified efforts to integrate PMTCT services into routine maternal and child health (MCH) services.[2] The success of the national PMTCT programme was seen in the 2010 SA PMTCT evaluation (the first national evaluation of the PMTCT programme in SA), which demonstrated a significant reduction in MTCT to 3.5% (compared with an estimated transmission risk of 20 - 30% without any intervention).[3] The SA PMTCT evaluation study also showed high uptake of PMTCT services nationally, with more than 98% of women getting an HIV test during pregnancy and 92% of HIV-infected mothers receiving ARV treatment or prophylaxis.[3] SA's latest and arguably most controversial PMTCT improvements came in April 2013: SA followed the World Health Organization recommendations by offering ART to all HIV-positive pregnant or breastfeeding women regardless of CD4⁺ count.[4] In light of such achievements, what more is needed to 'close the gaps' in the PMTCT cascade and reach the Millennium Development Goal of elimination of MTCT by 2015?

The objective of this review was to establish possible cause(s) of transmission for HIV-infected infants in order to identify ongoing obstacles to elimination of MTCT. Antenatal and PMTCT history, delivery information and feeding options were obtained from routinely collected data held in antenatal clinic registers and clinical files.

Methods

For this case series, Médecins Sans Frontières (MSF) partnered with the Western Cape Department of Health (WC DoH) to review and document case histories of all PCR-positive infants found in the HIV-exposed infant register at Khayelitsha's Site B Community Health Centre in Cape Town from 1 January 2012 to 30 April 2013. Khayelitsha's Site B Community Health Centre is a campus that provides primary healthcare services including casualty, outpatient department for adults and children, an HIV/tuberculosis (TB)/drug-resistant TB (DR-TB) clinic, and a midwifery and obstetrics unit. Within its paediatric services, it has a baby clinic that is dedicated to the registration and care of HIV-exposed infants. It is the responsibility of this baby clinic to ensure that all HIV-exposed infants who attend receive a PCR test at around 6 weeks postpartum.

Results

A total of 1 158 HIV-exposed infants were recorded in the exposed infant register at Khayelitsha Site B Community Health Centre over the 16-month study period (from 1 January 2012 to 30 April 2013). Of these, 926 (80%) of exposed infants had HIV DNA PCR results available, and 15 (1.6%) were PCR-positive.

Review of the maternal histories for the 15 positive infants (Table 1) found that the median (interquartile range (IQR)) maternal age was 27 (23 - 31) years, median parity was 2 (1 - 3), and median gestational age at antenatal presentation was 21.5 (17.5 - 30.5) weeks. Baseline CD4⁺ count was <350 cells/µl in 46.7% of women, with a median (IQR) CD4⁺ count of 377 (219 - 446) cells/µl. One-third of these mothers received ART: two started ART after 33 weeks' gestation and received no more than 5 weeks of ART prior to delivery, one started ART at 17 weeks' gestation but then defaulted treatment at month 1 on ART, and the remaining two started ART at 25 and 21 weeks' gestation, respectively, but had clinically unwell babies at birth, suggesting early *in utero* transmission. Five mothers received AZT for a median duration of 20 weeks (based on clinical records only; no record of degree of adherence to AZT dual therapy was found) and an additional five received no PMTCT prophylaxis (two defaulted on ART prior to

Table 1. Clinical and demographic features of mother-infant pairs where transmission of HIV occurred

Patient characteristics (*N*=15)	
Maternal age (years), median (IQR)	27 (23 - 31)
Parity, median (IQR)	2 (1 - 3)
Gestation at 1st ANC presentation (weeks), median (IQR)	21.5 (17.5 - 30.5)
Maternal CD4⁺ count (cells/µl), median (IQR)	377 (219 - 446)
CD4⁺ count (cells/µl), *n* (%)	
<200	3 (20.0)
200 - 349	4 (26.7)
≥350	8 (53.3)
PMTCT prophylaxis provided, *n* (%)	
ART	5 (33.3)
AZT	5 (33.3)
No prophylaxis	5 (33.3)
Mothers requiring hospital care at delivery, *n* (%)	9 (60)
Infant birth weight (kg), median (IQR)	3.0 (2.6 - 3.5)
Infants clinically unwell at birth, *n* (%)	2 (13.3)
Breastfed infants, *n* (%)	
Documented breastfeeding of any duration	14 (86.7)
Documented exclusive breastfeeding	10 (66.7)
Duration between delivery and PCR test (weeks), median (IQR)	6.6 (6.1 - 7.3)

IQR = interquartile range; ANC = antenatal clinic; PMTCT = prevention of mother-to-child transmission; ART = antiretroviral therapy; AZT = azidothymidine; PCR = polymerase chain reaction.

onset of pregnancy but verbally reported being on ART at booking, one presented in labour, one tested negative in pregnancy then positive in labour, and one did not receive prophylaxis despite booking at 6 weeks' gestation). Viral loads were not monitored for women on antenatal ART, as the national ART/PMTCT guidelines at the time required 1st viral load to be drawn at month 4 on ART and not prior. Out of 15 mothers, 9 (60%) required hospital care at delivery, with 6 requiring caesarean section.

Review of the early infant histories for the 15 positive infants revealed the following: median (IQR) infant birth weight was 3.0 (2.6 - 3.5) kg; all received nevirapine as postexposure prophylaxis (the duration and adherence to which was unclear from clinic records); and 14 (87%) were breastfed with 10 (67%) recorded as 'exclusively breastfed'. Median (IQR) time between delivery and PCR results was 6.6 (6.1 - 7.3) weeks.

Discussion

This case series points to several critical gaps in the PMTCT cascade in this setting. It was of great concern to discover that, consistently over the 16-month period, only 80% of exposed infants had documented PCR results. This finding is of particular concern when considered in the context of the SA PMTCT evaluation study reported intention to obtain infant PCR testing at 6 weeks; the study found that only 35% of HIV-positive mothers indicated that they planned to obtain early infant diagnosis for their infant during their 6-week immunisation visit. Multiple possible causes were identified for the suboptimal PCR testing rate, including poor patient education of the need to return at around 6 weeks for a PCR test, poor staff knowledge (because of staff turnover and shortages) of the need to ensure a PCR is done in infants presenting between 6 weeks and 18 months, the fragmentation of child health services within the facility, and insufficient staff motivation to follow up on missing PCR results or infants not returning for their initial PCR test. Further research is required to analyse in more detail all the causes of inadequate infant PCR testing coverage, along with intensified effort to improve the postnatal linkage to care of all HIV-exposed infants and their mothers.

Analysis of the maternal antenatal histories for infants found to be HIV-infected revealed further gaps in the PMTCT cascade. The need to intensify community awareness of the importance of early antenatal booking was highlighted in the following findings: median (IQR) gestational age at antenatal presentation was 21.5 (17.5 - 30.5) weeks, and one mother presented for the first time in labour (no antenatal care) despite this being her 3rd pregnancy and already knowing her HIV status. To address this gap, MSF and WC DoH have partnered with the Treatment Action Campaign to launch a community awareness campaign that aims to improve patient literacy particularly on the issue of early antenatal booking.

Inconsistency in the provision of antenatal prophylaxis and a lack of viral load monitoring for pregnant or breastfeeding women on ART were identified as further significant gaps. From clinical records, the median duration of AZT dual therapy was 20 weeks, but was complicated by: poor maternal understanding of the importance of adherence to AZT twice daily; pregnant women often running out of their AZT between appointments; staff not routinely checking AZT pill counts during antenatal visits; and no system for monitoring AZT provision or adherence. One mother, whose child is now HIV-infected, was not provided antenatal AZT prophylaxis despite booking at 6 weeks' gestation and presenting a further four times in her pregnancy; this woman was told she had booked too early to start prophylaxis on her first visit, and antenatal staff failed to detect that she had not been issued AZT on each subsequent visit. The absence of routine viral load monitoring for women on ART at antenatal booking and subsequently through pregnancy and breastfeeding resulted in failing to detect women who had defaulted ART prior to or during pregnancy; two mothers of HIV-infected infants in our review defaulted on ART prior to onset of pregnancy but verbally reported being on ART at their antenatal booking. Vigilance in viral load monitoring for women on ART during pregnancy is essential, and infant feeding choice should take into account a woman's actual or likely viral load at delivery. Of the 15 HIV-infected infants, 14 were breastfed, with 10 documented as being exclusively breastfed. In these cases, HIV transmission may have occurred due to breastfeeding in the presence of a high viral load. In a small number of cases, a complicated delivery was also linked with transmission.

These data come from a case series, and as such, have fundamental limitations related to absence of a comparator group of HIV-exposed but uninfected infants. Nonetheless, several key concerns emerge clearly. The main risk factors for MTCT identified in our review of the case histories of PCR-positive infants were late presentation to antenatal care, inadequate provision or duration of antenatal PMTCT prophylaxis, and a lack of viral load monitoring to determine whether a pregnant woman is virologically suppressed at delivery and during breastfeeding. Women with any of these risk factors should be urgently identified as high risk for transmission and provided additional adherence support, home visits by community care workers, an early infant PCR test, tailored infant feeding advice and dual postnatal infant prophylaxis.

Recent policy developments calling for provision of ART for all HIV-positive pregnant or breastfeeding women regardless of $CD4^+$ count is welcomed, and will undoubtedly improve PMTCT outcomes in SA. However, the elimination of MTCT will require intensified efforts to strengthen each step in the PMTCT cascade, from promotion of early antenatal booking to timely identification and appropriate management of high-risk pregnant or breastfeeding women. The introduction of routine birth PCR testing for high-risk infants would allow for early detection of infants infected with HIV; this would reduce the risk that HIV-positive infants are lost to follow-up prior to diagnosis and allow rapid initiation of ART. PMTCT programmes must consider each PCR-positive infant as a sentinel event that can provide valuable insight into correcting ongoing clinical and programmatic reasons for HIV transmission.

References

1. National Department of Health South Africa. Policy and Guidelines for the Implementation of the PMTCT Programme. Pretoria: National Department of Health South Africa, 2001.
2. National Department of Health South Africa/The South African National AIDS Council. Clinical Guidelines: PMTCT (Prevention of Mother-to-Child Transmission). Pretoria: National Department of Health South Africa and The South African National AIDS Council, 2010.
3. Goga AE, Dinh TH, Jackson DJ for the South African PMTCT Evaluation study group. Evaluation of the Effectiveness of the National Prevention of Mother-to-Child Transmission (PMTCT) Programme Measured at Six Weeks Postpartum in South Africa, 2010. South African Medical Research Council, National Department of Health of South Africa and President's Emergency Plant for AIDS Relief (PEPFAR/US) Centers for Disease Control and Prevention, 2012.
4. National Department of Health South Africa. The South African Antiretroviral Treatment Guideline 2013, PMTCT Guidelines, Revised March 2013. Pretoria: National Department of Health South Africa, 2013.

CASE REPORT

The diagnostic value of lymph node biopsy to detect Castleman's disease

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HIV is not indicated in the aetiology of Castleman's disease. However, it impacts on the prevalence and natural history of this disease and significantly on the disease progression. Castleman's disease is a uni- or multicentric disease of the lymph node with or without polyclonal proliferation of B-cells. It is a morphologically distinct form of lymph node hyperplasia and is characterised by significant architectural changes in all lymphatic compartments. Histopathologically, the disease is classified into two major subtypes: the hyaline-vascular type and the plasma-cell type. A mixed type is also identified, as there are frequent transitions between the types. The diagnosis of Castleman's disease needs to be made histologically. Treatment modalities include surgery, which is curative for unicentric disease, and systemic therapy, which is needed for multicentric disease. This case highlights the diagnostic value of lymph node excision biopsy in HIV-infected patients.

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A 49-year-old male patient presented to our emergency department with a 5-day history of a non-productive cough, fever, chills, shortness of breath and lower abdominal pain with associated nausea and vomiting. His background history was that of longstanding diabetes mellitus and hypertension, but he did not report an HIV diagnosis or antiretroviral use. Upon examination, the patient did not appear chronically ill. His vitals included a blood pressure of 163/73 mmHg, a respiratory rate of 25 breaths per minute and a temperature of 37.5°C. Generalised lymphadenopathy was also detected, especially in the cervical and right axillary areas. The lymph nodes were hard, non-tender, mobile and measured 1 - 2 cm in diameter. Examination of the heart and lungs revealed no abnormalities. Palpation of the abdomen confirmed splenomegaly, suprapubic tenderness and right renal angle tenderness.

Abnormal laboratory findings included haematuria, haemoglobin at 9.2 g/dl (normal range 14.3 - 18.3 g/dl), and microscopic examination of the urine-cultured *Klebsiella*. An HIV enzyme-linked immunosorbent assay was positive, and the initial $CD4^+$ was 233×10^6/l. Three specimens of nasogastric aspirates were negative for tuberculosis. A lymph node biopsy was done and the histological findings confirmed features that were in keeping with early human herpesvirus type 8 (HHV-8)-associated multicentric Castleman's disease. Also present was predominantly sinusoidal vascular proliferation in keeping with Kaposi's sarcoma. In addition, the surrounding lymphoid tissue showed against the background of what appeared to be preceding follicular hyperplasia features of marked folliculolysis, and increased plasmacytoid cells and plasma cells were also seen populating some of the follicles. Other features of Castleman's disease included the 'onion skin' arrangement of the surrounding lymphocyte (Fig. 1).

Discussion

Multicentric Castleman's disease (MCD) is an uncommon, aggressive lymphoproliferative disorder with an increased prevalence in people living with HIV.[1] It was first described in a case report by Castleman and Towne in 1954.[2] Classification of disease types is based on histopathological features, and two major subtypes are identified: the hyaline-vascular type and the plasma-cell type. A mixed type is also identified, as there are frequent transitions between the two types.[3] Based on clinical features, Castleman's disease can be divided into solitary and multicentric types. Common sites for the solitary type are in the mediastinum, neck, lung, mesentery, axillary lymph nodes,

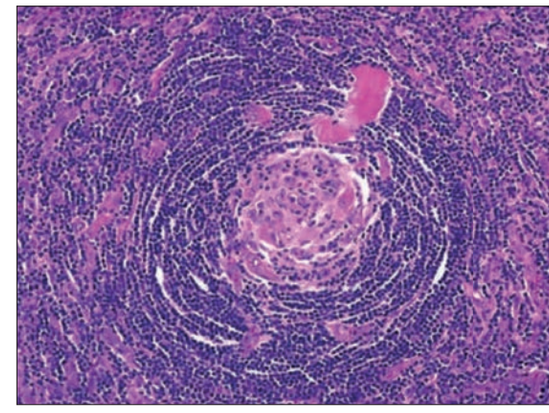

Fig. 1. Histology reveals small lymphocytes arranged in a concentric onion-skin pattern. These morphological features are characteristic of Castleman's disease.[3]

peritoneum, soft tissues and nasopharynx, where a mass forms. The dominant histopathological type, in over 90% of cases of the solitary type, is the hyaline-vascular type. The plasma-cell type is found mostly in the multicentric or systemic form of the disease. In the hyaline-vascular type, affected lymph nodes are characterised by follicular and interfollicular vascular proliferation. A wide variety of follicle sizes have been identified, and most of them contain small hyalinised blood vessels that penetrate the germinal centres in an outward concentric fashion from the perifollicular area, giving it the characteristic appearance shown in Fig. 1. Numerous capillaries and cells, especially lymphocytes, admix with some plasma cells, and in rare cases, immunoblasts fill the interfollicular areas. In contrast, in the plasma-cell type, the main features are sheets of plasma cells with large and hyperplastic follicles.[4]

In a study by O'Leary *et al*.,[5] researchers looked at 16 patients with Castleman's disease and examined the correlation between HHV-8 and Castleman's disease lymph node angiogenesis. Of the study sample, five MCD and two solitary Castleman's disease biopsies were positive for HHV-8. This represented 43% of the patients, a small proportion that may suggest a reactivation of latent HHV-8 infection in patients with Castleman's disease. Detailed analysis confirmed that HHV-8 was identified in 10% of the B-lymphocytes in the endothelial cells and in subcapsular spindle cell proliferations. A mechanism implicated in the pathogenesis of angiogenesis in Castleman's disease is via the production of HHV-8 viral interleukin 6 (IL-6).[5]

To facilitate risk stratification, prognosis and choice of treatment, staging of the disease is recommended. Three crucial aspects need to be addressed: (*i*) extent of the disease, which can be evaluated by imaging; (*ii*) the histopathological classification, as this has implications regarding therapy; and (*iii*) viral aetiology, determined by blood tests to clarify HIV status, serology to establish presence of Epstein-Barr virus, and immunostaining to detect viral IL-6.[3] Even though clinical presentation is usually nonspecific, symptoms fall into four categories: (*i*) local compression effects caused by enlarged lymph nodes; (*ii*) systemic symptoms such as fever, weight loss, night sweats, weakness and fatigue caused by B-cell involvement and related cytokine activation; (*iii*) fluid retention-associated symptoms such as oedema, ascites and pleural effusion; and (*iv*) clinical features as a result of associated complication, e.g. lymphoma.[3] As a general rule, when local compression symptoms are present, it is likely to be unicentric hyaline-vascular Castleman's disease, while when systemic symptoms are present, multicentric plasma-cell type should be considered.

Specific clinical parameters have been identified by Oksenhendler[6] to increase the rate of diagnosing Castleman's disease in HIV-positive individuals, including fever, diffuse lymphadenopathy, splenomegaly, severe cytopenia, high serum C-reactive protein levels, elevated HHV-8 DNA levels in peripheral blood mononuclear cells, extreme plasmacytosis in lymph nodes or bone marrow, nasal obstruction, respiratory symptoms, Kaposi's sarcoma lesions, a previous similar episode with spontaneous resolution, positive Coombs' test and haemophagocytic syndrome. Castleman's disease is also associated with Kaposi's sarcoma, non-Hodgkin lymphoma, paraneoplastic pemphigus and POEMS syndrome (**p**eripheral neuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal gammopathy and **s**kin signs).[3]

Modality of treatment is strongly guided by clinical classification, in particular whether a patient has unicentric or multicentric disease. Unicentric type is usually cured by surgical removal of the affected lymph nodes or local radiotherapy for sites that are unresectable; multicentric disease necessitates systemic therapy.[3] In patients who are HIV-negative, multicentric disease is often symptomatic. The treatment regimen for the HIV-negative group included: (*i*) treating underlying infection such as HHV-8 (with drugs such as ganciclovir, valganciclovir or foscarnet); (*ii*) decreasing cytokine acceleration with tocilizumab (a monoclonal antibody that blocks the IL-6 receptor) or corticosteroids (not a popular choice in view of its side-effects); (*iii*) reducing proliferation of B-cells; and (*iv*) shrinking tumour mass. Chemotherapeutic agents in combination or single agents such as cyclophosphamide, vinblastine and etoposide can be prescribed for systemic disease.[3]

A study by Mylona *et al*.[7] illustrated that life expectancy in multicentric disease appears to have improved, with the fatality rate among patients receiving antiretroviral therapy (ART) at 29% compared with the fatality rate of 75% among pre-ART patients. Another significant finding in their study was that patients on ART at the time of diagnosis of MCD had a better immunological profile and were less likely to have concurrent Kaposi's sarcoma than those commencing ART after the diagnosis of MCD was made. Despite the clinical differences between the patients receiving and those not receiving ART, their mortality rates did not vary significantly.[7] The administration of monoclonal antibodies also forms part of treatment options. Rituximab, an anti-CD20 monoclonal antibody, has been tried and a good response has been documented.[1,3,7] The safety of rituximab as a single therapeutic agent demands ongoing studies.[3]

Conclusion

Taking into consideration the high prevalence of HIV in South Africa (SA), a high clinical index of suspicion should be held when patients present with lymphadenopathy accompanied by nonspecific systemic signs, as this will increase the likelihood of diagnosing Castleman's disease. A critical aspect is careful examination so that diseases with similar clinical presentation are excluded. This case highlights the need for lymph node biopsy especially in our SA setting. As described, MCD can be associated with serious medical conditions; prompt diagnosis is thus essential. More research is needed to establish the optimal therapy for this rare disease, particularly in the context of HIV infection.

References

1. Waterston A, Bower M. Fifty years of multicentric Castleman's disease. Acta Oncol 2004;43(8):698-704. [http://dx.doi.org/10.1080/02841860410002752]
2. Castleman B, Towne VW. Case records of the Massachusetts General hospital; weekly clinicopathological exercises; found by Richard C Cabot. N Engl J Med 1954;251(10):396-400. [http://dx.doi.org/10.1056/NEJM195409022511008]
3. Schulte KM, Talat N. Castleman's disease: A two compartment model of HHV 8 infection. Nat Rev Clin Oncol 2010;7(9):533-543. [http://dx.doi.org/10.1038/nrclinonc.2010.103]
4. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 1972;29(3):670-683.
5. O'Leary J, Kennedy M, Howells D, et al. Cellular localisation of HHV-8 in Castleman's disease: Is there a link with lymph node vascularity? Mol Pathol 2000;53(2):69-76.
6. Oksenhendler E. HIV-associated multicentric Castleman disease. Curr Opin HIV AIDS 2009;4(1):16-21. [http://dx.doi.org/10.1097/COH.0b013e328319bca9]
7. Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A. Multicentric Castleman's disease in HIV infection: A systematic review of the literature. AIDS Rev 2008;10(1):25-35.

CPD QUESTIONNAIRE

September 2014 Vol. 15 No. 3

A maximum of 3 CEUs will be awarded per correctly completed test.

Effective in 2014, the CPD programme for *SAJHIVMED* will be administered by Medical Practice Consulting: CPD questionnaires must be completed online at www.mpconsulting.co.za. After submission, you can check the answers and print your certificate.

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TRUE or FALSE:

Tailoring of adult antiretroviral therapy (ART)

1. Studies show that HIV-positive people who are receiving treatment and have suppressed viral loads are unlikely to transmit the virus to HIV-negative sexual partners.
2. The optimal $CD4^+$ threshold to initiate treatment to maximise clinical benefits is widely known to be 500 cells/µl.

Management of mental health disorders and central nervous system (CNS) sequelae in HIV-positive children and adolescents

3. HIV-positive children and adolescents are at increased risk of both CNS sequelae and mental disorders.
4. HIV-positive children who begin ART in infancy are at increased risk of CNS sequelae compared with untreated perinatally HIV-infected children.
5. The most common primary HIV-related CNS complication in children is HIV encephalopathy.

Expression of DC-SIGN and DC-SIGNRs in the placentas of HIV-positive women

6. Without any form of ART or prohylaxis, most vertical transmission of HIV occurs via the virus crossing the placenta.
7. Both DC-SIGN and DC-SIGNR expression were higher in placentas from HIV-positive mothers compared with HIV-negative cases.
8. Perinatally HIV-infected children present with high rates of mental disorders that exceed population norms and rates observed in other chronically ill children.

Management of patients presenting with diarrhoea

9. In South Africa (SA), diarrhoea is a common presentation to the emergency department only among HIV-infected individuals.
10. HIV infection is not considered in the acute diarrhoea guidelines; only as an opportunistic infection that causes chronic diarrhoea.
11. Patients prescribed antibiotics for diarrhoea unrelated to severity of disease or possibility of being admitted are put at risk of both undertreated infection and the development of a resistant organism.

Management of cryptococcal meningitis (CM) in adults

12. CM is relatively uncommon among HIV-infected individuals in SA.
13. Headaches, unexplained fever, nausea, vomiting, neck stiffness, confusion, seizures, abnormal behaviour, new onset of psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness and sometimes coma are some of the ways in which CM may present in HIV-positive patients.
14. Despite the availability of highly active antiretroviral therapy (HAART), the mortality from CM has not decreased significantly from the pre-HAART era.

Steps towards elimination of mother-to-child transmission

15. There have been only minor improvements to the SA prevention of mother-to-child transmission (PMTCT) programme over the last decade.
16. An SA PMTCT evaluation study has showed a high uptake of PMTCT services nationally.
17. Routine birth polymerase chain reaction testing for high-risk infants would allow for early detection of infants infected with HIV and rapid initiation of ART.

Value of lymph node biopsy to detect Castleman's disease

18. A diagnosis of Castleman's disease can be made on clinical findings alone.
19. Multicentric Castleman's disease (MCD) is a rare, aggressive lymphoproliferative disorder with an increased prevalence in people living with HIV.
20. Modality of treatment of MCD is strongly guided by clinical classification, in particular whether a patient has uni- or multicentric disease.

INSTRUCTIONS

1. Read the journal. All the answers will be found there.
2. Go to www.mpconsulting.co.za to answer the questions.

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