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Southern African Journal of HIV Medicine

- Guideline: cryptococcal meningitis in HIV-infected persons
- ART adherence clubs – long-term retention strategy
- Towards 'men who have sex with men-appropriate' health services in SA
- Challenges to delivering quality care in a PMTCT programme in Soweto
- Parental presence in households and impact of ART in Khayelitsha

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MESSAGE
From the Editor

This June edition of *SAJHIVMED* is being released to coincide with the 6th South African AIDS Conference, held in Durban. The conference programme is filled with renowned speakers from a range of backgrounds, and the focus of the meeting – integration of policies and systems in response to HIV – is particularly critical at this stage of our response to the epidemic.

Paralleling the broad focus of this meeting, the diversity of articles in this issue of the Journal emphasises the range of clinical, psychosocial and health systems challenges raised by the HIV epidemic and our responses to it. On the topic of the prevention of mother-to-child transmission (PMTCT) of HIV, Mnyani and McIntyre[1] document the challenges to providing high quality services in Soweto; while their research was conducted around previous PMTCT guidelines, the results showing the difficulties in delivering PMTCT interventions in primary care are especially noteworthy in light of recently revised national policies. In the area of mental health, Govender and Schlebusch[2] present a potentially useful screening tool for identifying patients at risk of suicidality following HIV diagnosis – a critically important but widely neglected concern. Rebe and colleagues[3] discuss the health service needs of men who have sex with men and suggest a range of approaches to the design and delivery of services. On the topic of the social impact of the epidemic, Jury and Nattrass[4] present unique insights into how the household circumstances of patients initiating ART may change over time, suggesting decreased reliance on family members for individuals stable on treatment. Meanwhile, there has been great interest in innovative strategies for managing large numbers of stable, relatively healthy ART patients in primary care. Wilkinson[5] reports on the development of 'adherence clubs' in Cape Town, which have the potential to reduce the patient load within clinical services – an approach that certainly warrants greater consideration.

This issue also features a rich array of interesting clinical case reports. Haeri Mazanderani and Ebrahim[6] discuss a case of HIV/HTLV-1 co-infection, and the seemingly paradoxical finding of progressive HIV disease with lymphocyte proliferation. There is widespread concern around the incidence of new HIV infections in pregnant women, and Kalk and colleagues[7] present two cases of mother-to-child HIV transmission that show the risks associated with acute HIV infection in pregnant and breastfeeding women. Meanwhile, Barnardt[8] presents an unusual case of Kaposi's sarcoma in pregnancy, with complexities in managing concomitant infection, malignancy and pregnancy.

Complementing these traditional case reports, we present here a new feature of the Journal, a critical case review that incorporates perspectives from local and international clinicians. This first instalment from Venter and colleagues[9] presents a common picture of acute liver failure with multiple potential causes; a special thanks to our discussants, Sarah Fidler and Sarah Stacey, for outlining their clinical thinking. Ideas for future cases to approach in this format will be most welcome – please send in your suggestions.

Happy reading.

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MESSAGE
From the Executive

Mid-year and the cold is settling in. The hype about the introduction of fixed-dose combinations (FDCs) has passed. We have started giving these combinations to the first priority group; so newly diagnosed HIV-infected patients and pregnant women are starting on one tablet once a day. While this is very exciting and without a doubt the way forward, there are still reports of stock-outs of other medications.

The Southern African HIV Clinicians Society is actively engaging and forming links with other Southern African countries. I spent a very fruitful weekend in Harare for the inaugural meeting of the reconstituted Zimbabwean branch. Over 70 keen healthcare workers attended a full-day meeting packed with lots of teaching and discussion. What I personally love about travelling and meeting other HIV clinicians is seeing the same drive and passion to find solutions. We are all part of a massive movement of healthcare workers who simply want solutions to the health crisis. Formal barriers have been broken down as we share what we have done and learn what others are doing.

The ultimate vision of the Society is to engage with all the Ministries of Health in the region and come up with one unified response to HIV and TB.

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FORUM

ART adherence clubs: A long-term retention strategy for clinically stable patients receiving antiretroviral therapy

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The ART-adherence club model described here provides patient-friendly access to antiretroviral therapy (ART) for clinically stable patients. It reduces the burden that stable patients place on healthcare facilities, increasing clinical human resources for new patients, and those clinically unstable and at risk of failing treatment. In the model, 30 patients are allocated to an ART club. The group meets either at a facility or community venue for less than an hour every 2 months. Group meetings are facilitated by a lay club facilitator who provides a quick clinical assessment, referral where necessary, and dispenses pre-packed ART. From January 2011 to December 2012, after adoption for phased rollout by the Western Cape Government, more than 600 ART clubs were established in Cape Town, providing ART care to over 16 000 patients. This extensive, rapid rollout demonstrates active buy-in from patients and facility staff. South Africa should consider a similar model for national rollout.

S Afr J HIV Med 2013;14(2):48-50. DOI:10.7196/SAJHIVMED.924

South Africa (SA)'s National Strategic Plan 2012 - 2016 aims to ensure that 80% of all HIV-positive patients who are eligible for antiretroviral therapy (ART), estimated at more than 3 million, are initiated on such treatment by 2016. It further aims to retain 70% of these patients in care 5 years after treatment initiation. By early 2013, 1.9 million people in SA were initiated on ART, with studies estimating retention to be <70% after 3 years of commencing treatment.[1,2]

The growing numbers of patients attending healthcare facilities place increasing pressure on already stretched human-resource capacity, impacting the time taken to deliver services and the quality of care provided. In turn, the cost to patients of having to return to facilities regularly, the long waiting times at facilities, competing demands on time, including work and family responsibilities, and dissatisfaction with the quality of care, all affect long-term retention.[3]

Effective long-term retention models of care are needed that offer quick, inexpensive and patient-friendly access to treatment and care for stable ART patients.[4] Such models should also aim to decrease the burden that stable patients place on healthcare facilities, thereby increasing human resources for new patients and those who are clinically unstable and at risk of failing treatment. The ART-adherence clubs piloted by Médecins Sans Frontières (MSF) in Khayelitsha, SA, represent one such model.

ART-adherence clubs

ART-adherence clubs are an option for rapid service delivery; 30 patients are allocated to a group and meet either at a facility or community venue for less than an hour every 2 months. These group meetings are facilitated by a lay club facilitator who provides a quick clinical assessment, with referral to a clinician, where necessary, and dispenses pre-packed ART. Club members establish a positive group dynamic over time, which renders much-needed peer support for adherence to lifelong treatment.

Club facilitators refer any patient reporting symptoms or ill health, or who recorded weight loss since their last club visitation. The club is supported by a facility nurse who is available to see patients referred by the facilitator, immediately after a club session. All club patients receive annual blood tests, with scheduling aligned and blood samples taken at the same session. Two months later, all members are seen by the club nurse for their annual clinical consultation and repeat prescriptions of ART.

Patients qualify for ART club membership if they have been on the same ART regimen for longer than 12 months, have two consecutive undetectable viral loads, and do not have any clinical conditions that require regular follow-up. While in the clinic waiting room, patients are encouraged to request their clinician to assess them for club recruitment.

Club patients are entitled to send a 'buddy' to collect their treatment from their ART club. However, patients themselves must attend every second club session, including the annual blood investigation and annual clinical consultation sessions. Patients can be removed from club care and returned to mainstream care when more intensive clinical or adherence follow-up is required. A patient exits the club when he/she misses a mandatory club session and fails to attend the clinic within 5 days. Patients determined by the club nurse to require more regular follow-up and those with elevated viral loads are also returned to mainstream care.

Club patients are monitored by completion of a simple register by the facilitator. Attendance is then captured as club

Fig. 2. Patients at an ART adherence club meeting.

plus clinic attendance in the clinic's electronic database by the clinic data capturer. ART clubs are considered part of the ART service at a facility and are managed by a facility-based nurse (called the 'clubs manager') who is responsible for the scheduling of club dates, the smooth running of clubs, clinical governance and club reporting requirements.

Pilot: Experience from Khayelitsha

MSF began with a pilot project of 20 clubs at the Ubuntu clinic, Site B, Khayelitsha in 2007. A retrospective observational evaluation found that retention in clinic care after 40 months was 97% for club patients compared with 85% among those who qualified for clubs but continued to be managed outside of the club model. Club participants were also 67% less likely to experience virological rebound, indicating better adherence in clubs than in mainstream care.[5]

The club model was adapted both during and after the completion of the initial pilot. At first, clubs allowed membership in excess of 50 patients, but this was later limited to 30 patients after lay club facilitators struggled to manage club sessions and it was felt that smaller groups would improve peer support among members. Eligibility criteria were also amended from >18 months on ART to >12 months on ART, at the time when routine viral load testing changed from every 6 months to annually after the first year of ART.

To obtain buy-in upfront from the facility manager and improve staff participation in the club model, a formalised ART club staff organogram was introduced, with clearly defined roles and responsibilities for each team member. Most importantly, the clubs manager required the requisite delegated authority from the facility manager to ensure the effective implementation and smooth running of the clubs. While the clubs manager has, in the past, also taken on the role of the full-time club nurse, placing the responsibility entirely on a single clinician, this led to a parallel service with limited capacity to expand. Daily rotation of the club nurse function within a facility ensures collective responsibility for the management of club patients.

The implementation of clubs and their expansion within a facility is dependent on the clinic pharmacist, as the club model relies on the pre-packing of ART. While supplying club patients with pre-packed ART adds no additional burden to supplying the same patients as facility patients, the club model does not alleviate overall pharmacy burden. Furthermore, the benefits of not seeing each individual patient at the pharmacy window can be overlooked.

Space limitations can create an obstacle to club implementation or expansion beyond one club a day within a facility. While full decentralisation into the community is the goal, community venues close to the clinic can be utilised without requiring additional logistical support. The Ubuntu clinic utilises a room at the local library, approximately 500 metres from the facility, where half of its day clubs meet. It has also started evening clubs at 18h00, utilising extended hours. This has allowed for 3 club meetings a day. Allocating patients to a club designated for a specific feeder area makes it easier to move clubs into the community at a later stage.

Overall, there has been widespread buy-in and participation by clinic staff and patients in the ART clubs in Khayelitsha. There is a continued, high demand for more ART clubs in facilities where club rollout has slowed or stopped.

Further detail on how to establish clubs, the ART club staff organogram, lessons learnt through the Khayelitsha implementation experience and tools utilised in the ART club model, are available online (http://www.msf.org.za/publication/art-club-toolkit).

Implementation beyond the pilot

In early 2011, the ART club model was adopted by the Western Cape Government (WCG) Department of Health (DoH) for phased rollout initially in the Cape Town Metro. A partnership was formed between the WCG DoH, City Health (City of Cape Town), MSF and the Institute for Health Improvement (IHI), to support implementation.[6]

Fig. 1 illustrates the implementation strategy adopted by the partnership. First, a steering committee with representatives from each partner was formed and HIV/AIDS, sexually transmitted infections (STIs) and tuberculosis (TB) (HAST) managers or facility-based doctors were identified to become club mentors. The club mentors were trained on the ART club model and were tasked with supporting the implementation of ART clubs in 1 - 3 pilot facilities. Facilities with the highest patient load were prioritised. The next phase was to invite 10 - 12 facility club teams (including the clubs manager, club nurse, club facilitator(s), clinic pharmacist and clinic data capturer) to attend a learning session where they were trained by the steering committee and club mentors and supported in making an implementation plan. The facility club mentor supported the team at the facility intensively at first and with routine support visits thereafter. Six months later, the same facility club teams attended a second learning session where they reported back on progress. Any challenges experienced were discussed with other facilities and the steering committee allowed for the sharing of possible solutions. Where club implementation at these pilot facilities continued to face obstacles, a third learning session could be convened. In general, for this process to be successful, it is important to have buy-in and active support from facility management and sub-district management throughout the implementation process.

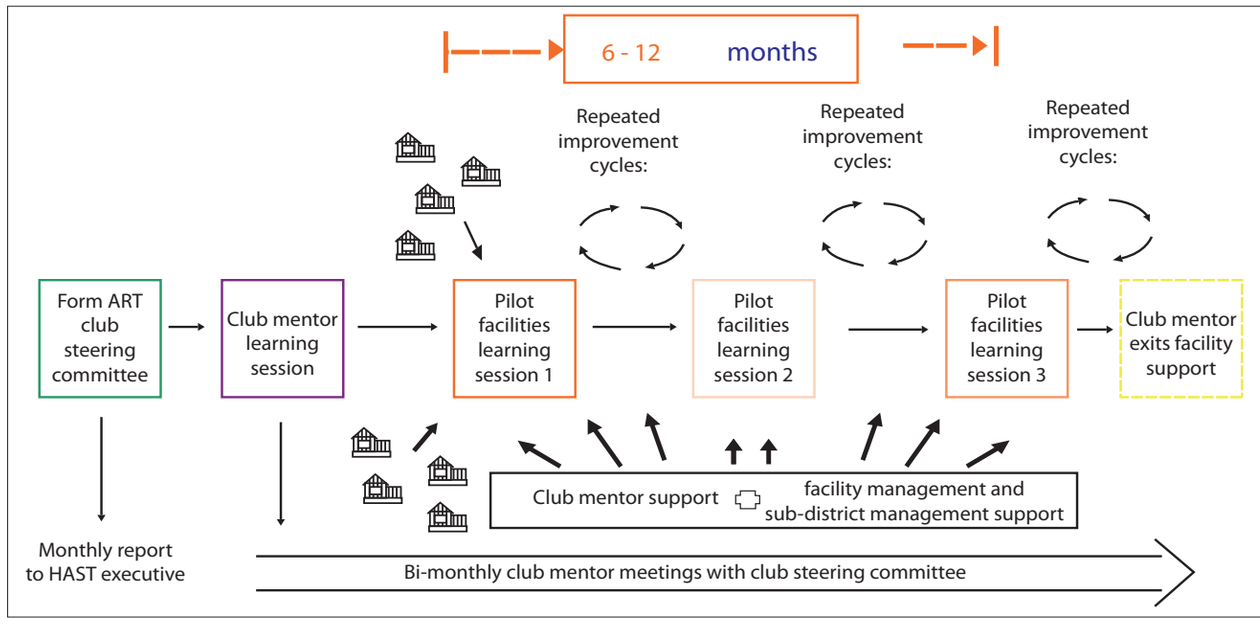

Fig. 1. Schema for the implementation of ART adherence clubs. HAST = HIV/AIDS, sexually transmitted infections (STIs) and tuberculosis (TB).

By 31 December 2012, the Cape Town Metro had implemented over 600 clubs with more than 16 000 stable ART patients accessing care and treatment accordingly. This amounts to approximately 15% of ART patients in care in Cape Town. The partnership won a 2012 Platinum Award from the prestigious Impumelelo Social Innovations Centre for adopting and implementing this innovative approach to managing large numbers of patients receiving ART.

Resources to operate adherence clubs

Each facility running ART clubs requires a club team. The role of the clubs manager is part time, but does require sufficient time to carry out club-management responsibilities. At least one full-time lay club facilitator is required per 40 ART clubs. In addition, a facility nurse needs to be allocated as the club nurse on the clinic roster for each day on which a club session takes places. The nurse can usually continue to see clinic patients as he/she is infrequently required to see a club patient after a club session, other than the annual blood investigation and annual clinical consultation sessions.

In the Cape Town Metro, club facilitation has been included in the job profile of facility counsellors. Additional counsellor posts have been allocated to facilities – one for facilities with more than 15 clubs and two for facilities with more than 40 clubs. Where clubs are run in the community, community-care workers could serve as club facilitators. In addition, resources may be spared by adapting the ART club-visit schedule and associated ART supply from 2- to 3-monthly.

Pharmacy-related bottlenecks to club rollout can be pre-empted by allocating an additional pharmacy assistant where the number of facility clubs exceeds 15, or alternatively, by utilising a central dispensing service for pre-packing ART as demonstrated in the Cape Town Metro. Access to fixed-dose combinations (FDCs) is imperative to support accelerated ART club rollout. In addition to supporting long-term adherence, FDCs reduce the pre-packing burden on pharmacy staff and make it logistically simpler to transport pre-packed ART drugs to ART club locations.

Conclusion

The ART-adherence club model improves adherence and long-term retention in care among clinically stable ART patients, while optimising health resources to manage new ART patients and patients at risk of failing treatment. The impressively extensive and quick rollout in the Cape Town Metro demonstrates active buy-in from patients and facility staff by addressing the obvious need for quick, patient-friendly access to care and treatment for clinically stable ART patients. It is imperative that SA considers a similar model for national rollout.

Conflict of interest. The author contributed to the development of the club model and is the MSF representative on the WCG DoH ART club steering committee.

Acknowledgements. ART club steering committee: J Mouton (WCG DoH), K Jennings (City Health), M Youngleson (IHI), B Harley (City Health), C Cragg (WCG DoH), S Jacobs (WCG DoH), E Kriel (WCG DoH); and the Ubuntu, MSF and Treatment Action Campaign (TAC) Khayelitsha staff who contributed to the development of, and continue to support ART clubs.

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FORUM
Towards 'men who have sex with men-appropriate' health services in South Africa

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Health programming for men who have sex with men (MSM) in South Africa has been ignored or absent until fairly recently, despite this population being at high risk for HIV acquisition and transmission. Anova Health Institute, with support from the US President's Emergency Plan for AIDS Relief (PEPFAR)/United States Agency for International Development (USAID) and in collaboration with the South African National Department of Health, launched the first state sector MSM-targeted sexual health clinic in 2010. The clinic has been successful in attracting and retaining MSM in care, and lessons learned are described in this article. Components contributing to the creation of MSM-appropriate healthcare services are discussed.

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Until fairly recently, the healthcare needs of men who have sex with men (MSM) have been under-researched and under-resourced in South Africa (SA).[1] This has occurred despite emerging local evidence confirming high rates of HIV among this key population. Notwithstanding inclusion in the country's previous National Strategic Plan for HIV and AIDS, STIs and TB (2007 - 2011), services for MSM were not scaled up nationally, although impressive strides have been made in some provinces such as the Western Cape and Gauteng. Evidence from modelling studies shows that in settings where concentrated HIV epidemics exist among key populations in countries with generalised heterosexual epidemics, failure to provide targeted and tailored HIV prevention and treatment programmes to key populations negatively affects HIV rates among the general population.[2]

MSM in SA comprise of a diverse group of men who share only one behavioural commonality: they have sex with other men.[3] Many MSM in SA do not identify with gay culture, which may be viewed as a Eurocentric cultural construct often considered foreign and 'un-African'.[4] The behaviour of MSM has, however, occurred across all cultures and all times, including in SA, and is therefore well described in African oral histories. Colonial oppressors were largely responsible for the criminalisation of sodomy on the continent.[5] Homosexual activity in SA therefore often remains clandestine, with MSM identifying as heterosexual and dismissive of Westernised gay culture.[3] This has implications for health messaging as non-gay-identifying MSM are not targeted in either mainstream heterosexual or gay media platforms and remain invisible in healthcare settings.

For multi-factorial reasons, MSM are at particular risk for HIV acquisition and transmission.[6] Biologically, unprotected receptive anal sexual intercourse is about 16 times more likely to transmit HIV than unprotected vaginal sexual intercourse.[7] This is due to the friable nature of the rectal mucosa, which does not contain mucous-producing cells like the thicker, self-lubricating lining of the vagina.

The vulnerability of MSM is further increased by structural factors such as a lack of funding for MSM-appropriate services, lack of specific skills training of health providers, and institutionalised stigma within the public healthcare sector. MSM patients generally avoid being identified as MSM, culminating in their elevated risk of HIV acquisition, transmission being overlooked, and a lack of counselling about the risks associated with unprotected anal sex.[8]

Organisations such as the Anova Health Institute, through it's innovative Health4Men project, and the Desmond Tutu HIV Foundation have been active in addressing these concerns in SA. In 2009 the Anova Health Institute, with support from the US President's Emergency Plan for AIDS Relief (PEPFAR)/ United States Agency for International Development (USAID), launched the first state sector clinic dedicated to MSM in the country. A further 6 sites have subsequently become operational across multiple provinces. Invaluable lessons have been learned through this process, which will undoubtedly serve as a template for the ongoing expansion of such services.[4,9-11]

MSM experience mainstream state sector healthcare services as unfriendly and prejudiced, which creates a barrier to accessing such services.[12] Many local healthcare centres have become friendly to women at the exclusion of men. Women are a captive audience in these clinics, which

they attend for antenatal care, childhood vaccinations, completion of children's road-to-health growth charts and other services. Clinics respond by improving their female-specific skills and services. It is not unusual to find most of the educational materials in HIV clinics focusing on issues such as breastfeeding and female contraception, thereby alienating HIV-positive men. Other barriers to MSM healthcare access include fears about confidentiality related to their HIV status and sexual behaviour. The local catchment area of primary healthcare services is also often problematic; MSM who experience community-based stigma are unlikely to attend a clinic where they are known to other patients or staff members.

For a health provision site to be considered MSM-appropriate, a number of criteria need to be met. Firstly, most MSM require more than a friendly service (often incorrectly referred to as an MSM-*sensitised* service); they expect *competence* regarding their specific sexual healthcare needs. Services therefore need to be both sensitive and competent if they are to attract and retain MSM in care.[4]

The Ivan Toms Centre for Men's Health (ITCMH), a clinic of the Anova Health Institute in partnership with the Western Cape Department of Health (DoH) and funded by PEPFAR through USAID, was inaugurated in February 2010 in Cape Town. It has since provided care to over 3 800 MSM. There are a few features which have contributed to the success of this clinic. There is buy-in and commitment by the provincial and National DoH.[13] The service is marketed as a sexual health clinic for men. It is neither an HIV nor an antiretroviral therapy (ART) clinic, which means that patients in the waiting room cannot be identified as HIV-positive. Approximately half of the clients in the cohort are HIV-positive and half of those are receiving ART. Other MSM attend for HIV and sexually transmitted infection (STI) screening, syndromic STI management, counselling and other mental healthcare services, harm-reduction services for MSM who use drugs, or for research and information purposes. This model assists in providing an enabling space that promotes feelings of anonymity regarding the reason for attendance, and allays fears of being identified as gay or HIV-infected when attending the clinic.

Clinic staff have received extensive sensitivity and competency training and are accepting of the diversity of MSM. They have become accustomed to providing service to MSM with either a feminine or masculine gender-identity, as well as to transgendered individuals. All staff are accustomed to referring to clients by their preferred name and pronoun (as opposed to their legal name).

Table 1. Recommended service package for addressing the sexual health of MSM: HIV/AIDS

Primary care prevention (HIV/AIDS)	Primary care treatment (HIV/AIDS)	Optimal specialised care

• HCT with MSM-appropriate counselling yearly or more frequently if possible exposures
• Condoms and water-based sexual lubricant
• Female condoms for anal sexual intercourse
• Access to early ART if HIV-positive to prevent transmission to sexual partners ('treatment as prevention')
• Accessible PEP according to PEP protocols
• Targeted PrEP when available (local guidelines available in a previous issue of *SAJHIVMED**)
• Counselling for behaviour change
• Reduce numbers of sexual partners
• Increase condom use, especially for the highest risk sexual behaviours (e.g. anal sex)
• Sero-sorting (choosing sexual partners on the basis of HIV status)
• Sero-positioning (choosing to be receptive in anal sex if HIV-positive and penetrative if HIV-negative)
• Address alcohol, recreational drug and tobacco use
• Screen and address mental health issues (e.g. depression)
• Screen and treat for STIs yearly or more frequently if high risk
	• $CD4^+$ count monitoring 6-monthly (point of care or laboratory)
	• Commence ART when:
	  • $CD4^+$ ≤350 cells/μl
	  • WHO stage IV
	  • Malignancies
	  (i.e. according to standard in-country guidelines on when to initiate ART)
	• Use ART according to local guidelines
	  • TDF/FTC/EFV fixed-dose combination
	  • AZT/3TC/Aluvia second-line
	• Monitor for side-effects and efficacy according to local guidelines
	  • $CD4^+$ measurement
	  • VL at 6 and 12 months, then yearly
	  • FBC, if receiving AZT
	  • ALT, if receiving NVP
	  • Creatinine clearance at ART initiation and yearly if receiving TDF
	  • Cholesterol, triglyceride and glucose
	• Monitor adherence
	  • Self-reported
	  • Pill counts
	  • Pharmacy script refills
	  • Knowledge of ART drugs
		• $CD4^+$ and VL monitoring 3 - 6-monthly
		• Consider earlier ART initiation at high $CD4^+$ count; patient will benefit directly and there is less chance of HIV transmission to sexual partners (i.e. less transmission within the MSM community) ('ART as prevention')
		• Consider early ART initiation for all hepatitis B/C and HIV co-infections
		• Expanded ART choice including ABC and ritonavir-boosted ATV to improve regimen tolerability if side-effects (also consider new classes of ART)
		• Extended monitoring
		  • $CD4^+$ and VL 3 - 6-monthly
		  • Creatine clearance at 1, 3 and 6 months and then 6-monthly
		  • Cholesterol, triglyceride and glucose
		  • DEXA scan for osteopaenia if receiving long-term TDF and other risk factors for bone disease
		  • HLA typing if planning to use abacavir
		• Extended adherence monitoring using devices such as pill bottles which register when they are opened
		• Consider PrEP for HIV-negative MSM with known high possible exposure rates to HIV
		  • Discordant couples
		  • Ongoing high-risk sexual behaviours
		  • Commercial sex workers
		  • Drug users

MSM = men who have sex with men; HCT = HIV counselling and testing; ART = antiretroviral therapy; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection; WHO = World Health Organization; SA = South Africa; TDF = tenofovir; FTC = emtricitabine; 3TC = lamivudine; EFV = efavirenz; NVP = nevirapine; AZT = zidovudine; VL = viral load; FBC = full blood count; ALT = alanine transaminase; ABC = abacavir; ATV = atazanavir; HLA = human leukocyte antigen; DEXA = dual energy X-ray absorptiometry.

* Southern African HIV Clinicians Society Consensus Committee. Southern African guidelines for the safe use of pre-exposure prophylaxis in men who have sex with men who are at risk for HIV infection. *Southern African Journal of HIV Medicine* 2012;13(2):40-55. [http://dx.doi.org/10.7196/SAJHIVMED.832]

Table 2. Recommended service package for addressing the sexual health of MSM: STIs

Disease	Primary care prevention (STIs)	Primary care treatment (STIs)	Optimal specialised care
Gonorrhoea	• Regular screening for symptoms • Condoms and water-based lubricant • Risk-reduction counselling as for HIV	• Syndromic treatment according to SA guidelines • Partner(s) notification and treatment • Be aware that gonorrhoea can occur in the urethra, pharynx or anus of MSM • Consider drug-resistant gonorrhoea in cases of treatment failure	• Confirm diagnosis with swab- and laboratory-based testing, including NAATs where available • Treat confirmed cases as for primary care • Consider screening for asymptomatic disease at urethral and non-urethral sites
Chlamydia	• Regular screening for symptoms • Condoms and water-based lubricant • Risk-reduction counselling as for HIV	• Syndromic treatment according to SA guidelines • Partner(s) notification and treatment • Be aware that chlamydial infections occur in the urethra, pharynx or anus of MSM	• Confirm diagnosis with swab- and laboratory-based testing, including NAATs where available. • Consider screening for asymptomatic disease (most cases of anal chlamydial infection will be asymptomatic)
Syphilis	• Regular assessment of risk • Condoms and water-based lubricant • Risk-reduction counselling about transmission	• Confirm syphilis with laboratory-based RPR and TPHA tests or rapid point-of-care test • Treat at point of care • Partner(s) notification and treatment	• Treat as for primary care • Consider lumbar puncture for HIV-positive MSM with positive blood syphilis serology and any neurological symptoms
Lympho-granuloma venereum	• Risk assessment • Regular screening for symptoms • Condoms and water-based lubricant	• Treat empirically if STI present and prominent inguinal lymphadenopathy • Partner(s) notification and treatment	• Confirm LGV serovar with NAATs
Human papilloma virus (warts)	• Transfers easily and not totally prevented by condom use, but condoms still useful and partly effective • Most easily transferred by contact with a visible skin wart, but the virus may transfer even without visible warts • Advise to avoid direct contact with visible warts • Cover visible warts with a plaster or condom • Gardasil vaccination will prevent some types of warts and reduce the risk of HPV-associated cancers (e.g. anal in MSM), but is very expensive	• Treat with topical preparations or cryotherapy • Partner(s) notification and treatment • Refer for surgical opinion if internal or extensive disease • Be aware that penile or anal warts can lead to embarrassment and pain, resulting in sexual dysfunction	• Can use imiquimod ointment preferentially (easier and convenient for patient) • Consider anal pap smear for MSM, especially if prior anal warts • Coagulase laser therapy to anal intra-epithelial neoplastic lesions (similar to cervical intra-epithelial neoplasia in women) • Biopsy any suspicious looking lesions and send for histological evaluation (MSM have a higher risk of anal cancers compared with heterosexual men) • Vaccinate with Gardasil (ideal to vaccinate before onset of sexual debut); might prevent warts and decrease risk of cancers; may also decrease size of existing HPV lesions
Hepatitis A	• Counselling about transmission (faecal-oral) • Risk assessment • Check hepatitis A IgG antibodies • Previous hepatitis A confers longstanding immunity • Vaccinate if susceptible • Contact trace for immunoglobulin and vaccination of known contacts	• Supportive treatment of acute hepatitis A • Refer to specialist if clinically unwell • Monitor liver function tests and limit physical activity until settled	• Hepatitis A is potentially serious if contracted in adulthood; a small percentage of patients develop severe liver dysfunction and even failure, and consequently require intensive support • Most cases recover with no permanent sequelae as hepatitis A does not have a chronic phase

continued ...

Table 2 (continued). Recommended service package for addressing the sexual health of MSM: STIs

Disease	Primary care prevention (STIs)	Primary care treatment (STIs)	Optimal specialised care
Hepatitis B	• Counselling about transmission • Risk assessment • Screen all MSM for hepatitis B surface antibodies • Vaccinate if susceptible • Contact trace for immunoglobulin and vaccination of known contacts • Screen MSM for prior hepatitis B infection using hepatitis B surface antigen • Vaccinate all regular hepatitis B-negative sexual partners of MSM known with chronic hepatitis B infections	• Acute hepatitis B requires supportive treatment • Refer if clinically unwell (encephalopathic, extreme nausea, hypoglycaemia, sepsis, etc.) • If hepatitis B and HIV co-infected, initiate TDF-based ART early to prevent disease progression. TDF/3TC should then never be stopped, even if alternative HIV drugs are required in a second-line or salvage regimen • Hepatitis B may be curable with interferon therapy, but this is very expensive with limited access	• Supportive therapy during acute disease • Perform liver function tests, hepatitis B E-antigen and hepatitis B viral load (these parameters assist hepatologists to decide who may benefit most from interferon and related therapy)
Hepatitis C	• Counselling about transmission • Screen HIV-positive MSM who use crystal methamphetamine • Harm-reduction programmes for drug users (e.g. needle exchange), condoms and water-based lubricant for anal sex • There is no vaccine available; only prevention is to avoid exposure	• Acute hepatitis C requires supportive management • Refer if clinically unwell (encephalopathic, extreme nausea, hypoglycaemia, sepsis, etc) • Antiretroviral medications such as TDF/3TC are inactive against hepatitis C, but co-infected patients should have their HIV treated early at high $CD4^+$ counts	• Perform liver function tests, hepatitis C viral load and genotyping • Refer to hepatologist for assessment for interferon therapy (lower cure rates than for hepatitis B) • Assess and manage mental health in patients taking interferon (causes potentially severe depression)

STIs = sexually transmitted infections; MSM = men who have sex with men; NAATs = nucleic acid amplification tests; RPR = rapid plasma reagin; TPHA = treponema pallidum haemaglutination assay; LGV = lymphgranuloma venereum; IgG = immunoglobulin G; HPV = human papilloma virus; TDF = tenofovir; 3TC = lamivudine.

Table 3. Examples of interventions for preventing HIV among MSM*

Psychosocial	Biomedical
Reducing number of sex partners	Increased HCT and early detection of positives
Reducing alcohol and recreational drug use	Male and female condoms
Increasing condom use for risky sexual behaviours	Condom-compatible sexual lubricant
Increasing the use of condom-compatible lubricant	Early ART
Sero-sorting	PEP
Sero-positioning	STI screening and treatment
Motivational counselling	PrEP (refer to SA guidelines)
Couples' services including targeted counselling	Microbicides (undergoing research)
Combating societal homoprejudice and increasing access to non-judgemental healthcare services	HIV vaccines (undergoing research)
Screening and management of depression and other mental health disorders	Harm-reduction programmes for drug users includes safe injection technique, clean injecting equipment (needles), treatment of soft-tissue abscesses, IEC materials, education about overdoses and linkage to rehabilitation programmes for those who want to stop drug use
Development and dissemination of appropriate healthcare and risk-reduction messages that address the specific sexual health needs of MSM	Medical male circumcision; does not provide the same risk reduction as for heterosexual men but might protect bisexual men and those who exclusively adopt the penetrative role in anal sex

MSM = men who have sex with men; HCT = HIV counselling and testing; ART = antiretroviral therapy; PEP = post-exposure prophylaxis; SA = South Africa; STI = sexually transmitted infection; PrEP = pre-exposure prophylaxic; IEC = information, education and communication.

*Source: De Swardt and Rebe.[4]

Fig. 1. The Ukwazana (getting to know each other) campaign. An example of HIV risk-reduction messaging designed to reach MSM though township taverns/shebeens where MSM congregate.

Fig. 2. An example of HIV risk-reduction messaging designed to reach gay-identified MSM through gay-targeted publications (the pink press).

MSM resources

South African MSM resources

- Anova Health Institute: http://www.anovahealth.co.za | Tel: +27 (0)11 715 5800
- Health4Men: http://www.health4men.co.za | Tel: +27 (0)21 421 6127
- The Ivan Toms Centre for Men's Health | Tel: +27 (0) 21 447 2887
- Health4men Yeoville: email: yeoville@ahovahealth.co.za | Tel: +27 (0)72 654 0816
- Health4Men Connect: http://h4M/mobi
  (MSM-specific information via cellular phone technology)
- Other Health4Men sites or services: email: info@health4men.co.za | Tel: +27 (0)21 421 6127
- Durban Lesbian and Gay Community Centre: email: info@gaycentre.org.za |
  Tel: +27(0)31 301 2145
- Gay and Lesbian Network (Pietermaritzburg): email: info@gaylesbiankzn.org |
  Tel: +27(0) 33 342 6165
- OUT LGBTI Well Being (Pretoria): email: administrator@out.org.za | Tel: +27(0)12 344 5108
- The Desmond Tutu HIV Centre: http://www.desmondtutuhivcentre.org.za |
  Tel: +27(0)21 650 6966
- Triangle Project (Cape Town): email: info@triangle.org.za | Tel: +27(0)21 686 1475

International website resources for MSM health

- The Body: http://www.thebody.com
- Gay Men Fighting AIDS: http://www.gmfa.org.za
- The Global Forum on MSM and HIV (MSMGF): http://www.msmgf.org
- International Rectal Microbicides Advocates: http://www.rectalmicrobicides.org

The scope of practice encompasses holistic sexual health, including STI and HIV prevention, diagnostic and treatment services, as well as in-house access to mental healthcare services provided by staff who have specific experience in providing such care to MSM. Staff have been intensely trained in the specific features of sexual health pertaining to MSM. Medical staff have an expert understanding of how STI presentations, diagnosis and management plans differ in MSM, compared with heterosexual men. A good example is training in physical examination to detect and diagnose anal and pharyngeal presentations of STIs.

A package of care has been developed for the clinic and a clinical manual is available for guidance both in print format and online (http://www.anovahealth.co.za).[4] It is understood that clinics may not be able to provide an optimal level of MSM healthcare due to resource constraints; therefore, a package of minimal and optimal services has been developed (see Tables 1 - 3).

Some specific features of the ITCMH that have worked well include the provision of MSM-sensitive HIV screening. Counsellors are trained to ask about male and female partners, to identify specific sexual behaviours and their risks (e.g. receptive unprotected anal intercourse), and to avoid adopting a hetero-normative attitude to counselling (such as asking an MSM couple which is the man and which is the women in a relationship). MSM are also encouraged to screen for HIV together with their partners.[14]

Since MSM are at an elevated risk of acquiring and transmitting HIV, prevention technologies assume particular importance. Condoms, although generally available via the state, are mainly marketed through heterosexually-targeted campaigns that do not address the risks of unprotected anal sex. Condom-compatible lubricant required for comfortable anal sex is largely unavailable. Medical male circumcision is likely to fail to protect MSM to the same degree as heterosexual men, which leaves a deficit of effective prevention interventions.[15] Available HIV-prevention resources that are evidence-based – such as condoms, lubricants, post- and pre-exposure prophylaxis (PEP and PrEP), and early treatment for positive MSM – should be prominent at all MSM-targeted sites.

Marketing MSM-appropriate services is challenging, especially in areas where MSM do not disclose their sexual behaviours and remain hidden to the healthcare system. It has taken time for MSM groups to develop trust in the clinic and the most effective marketing has occurred by word of mouth via clients who have had a positive health-affirming experience at the clinic. Health4Men employs peer educators, and key individuals in MSM communities from specific geographical areas have been recruited as ambassadors for the programme. Marketing and information, education and communication (IEC) materials

have been developed through testing with MSM focus groups to ensure that the language is locally understood and contextually correct. Health information, referral links and interactive questions and answers are also available from the Health4Men's mHealth programme 'Health4men Connect' (h4m.mobi) and the programme's website.

The ITCMH was followed by the launch of the Simon Nkoli Centre For Men's Health in Soweto and, more recently, the Khayelitsha Male Clinic (Cape Town), the Zola and Chiawelo clinics (both in Soweto) and the Yeoville clinic (central Johannesburg). These sites have built on the evidence and experience gained from providing services at the ITCMH. Guidelines for the management of common MSM health problems have been developed and packaged into an intensive training package, which can be delivered at healthcare facility level to improve staff attitudes and skills and better allow for the provision of non-judgemental, appropriate MSM-targeted healthcare. Over time, once enough state clinics have received such training, it is hoped that MSM-specific healthcare services can be mainstreamed in standard HIV/ART/STI clinics. Many resources have been developed locally and abroad to assist healthcare providers in caring for their MSM clients in a compassionate and competent manner, even in instances where the beliefs of healthcare workers do not usually encompass an understanding of diverse male sexual identities and behaviours.

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ORIGINAL ARTICLE

A suicide risk screening scale for HIV-infected persons in the immediate post-diagnosis period

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Background. The risk of suicidal tendencies in HIV-infected persons appears high and may parallel the increasing prevalence of suicidal behaviour in South Africa.
Objective. To construct a brief suicide risk screening scale (SRSS) as a self-administered instrument to screen for suicidal ideation in recently diagnosed HIV-infected persons.
Methods. An SRSS was developed, drawing 14 items from two established screening tests, and assessed using a sample of 150 HIV-infected consenting adults identified at a voluntary counselling and testing (VCT) clinic at an academic district level hospital in Durban, South Africa. Participants returned three weeks after their initial assessment for a re-assessment.
Results. The internal consistency of the SRSS was good (Cronbach's alpha, 0.87), and its sensitivity (81%) was higher than its specificity (47%). The findings suggest that, despite certain limitations, the SRSS may be a valuable screening tool for suicidal ideation at VCT clinics.
Conclusion. Screening for suicide risk and possible suicidal behaviour in HIV-positive persons may form a routine aspect of comprehensive patient care at VCT clinics to assist with effective prevention and treatment.

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Globally, suicide and HIV/AIDS remain two of the greatest healthcare issues, particularly in low- and middle-income countries where approximately 85% of suicides occur.[1-3] The World Health Organization (WHO) predicted that global suicide mortality will increase to 1.53 million per annum by the year 2020.[2] Suicide mortality rates have changed significantly in South Africa (SA) since apartheid, with differences evident across cities, races and gender.[4] SA has a relatively high 12-month prevalence of anxiety and mood disorders compared with other countries, which adds to the burden of suicide risk.[5] In 2007 the overall rates for suicide in SA were high (0.9/100 000),[6] and there is an increasing occurrence of suicide among youth and men, consistent with the international trend.[7] At least one suicide is committed every hour in SA, and 20 more unsuccessful attempts are made in the same time-span, with one-third of non-fatal attempts recorded among youth.[6-8]

The risk factors for suicide are diverse and inter-related, and may be particularly complex in HIV-infected individuals. One systematic literature review showed a high suicidal risk in persons with HIV: 19.7% were described as generally suicidal, 26.9% as having suicidal ideation and 9.4% completed suicides.[9] There is also a high rate of lifetime suicide risk associated with depression.[10] The prevalence of depression and anxiety in people living with HIV/AIDS is almost double that of HIV-negative individuals.[11]

There is growing evidence that this is true in SA and other African countries.[12,13] The risk of suicide appears to be increasing in the context of the HIV epidemic.[14,15] Several SA studies have documented a correlation between suicidality and HIV at different points in disease progression,[12,13-18] including the high prevalence of suicidal ideation among HIV-positive pregnant mothers.[16] In a recent study conducted among HIV-positive persons in SA, suicidal ideation increased over a 6-week period and was present in 24% of the HIV-positive participants following HIV counselling and testing.[17] This correlated with results of the WHO Multisite Intervention Study on Suicidal Behaviours (SUPRE-MISS) community survey, where the highest rates of lifetime suicidal thoughts and plans were found in Durban (25.4% and 15.6%, respectively).[17,19] Despite the introduction of antiretroviral therapy (ART), the suicide rate remains more than 3 times higher among HIV-positive persons than in the general population.[20] Although the international findings on the correlation between suicide and HIV/AIDS are diverse,[10] the results show compelling evidence to screen for suicide risk and intervene as early as possible.[9,10-12] Despite this, the assessment of suicide risk is not a routine aspect of HIV patient care in SA.

The lack of consistent definitions of suicidal behaviour across studies has led to confusion in the field of suicidology. Suicidality encompasses a range of suicidal behaviours, which in turn involve degrees of self-destruction that may be fatal or non-fatal. Suicidal ideation is defined as having the intent to commit suicide, wanting to take one's own life or thoughts about suicide without actually making plans to commit suicide. To prevent suicides, healthcare professionals need to understand the reasons why people have suicidal thoughts or display suicidal behaviour. While there are a number of psychometric, clinical and biological measures to detect suicide risk,[21-23] this risk in itself is difficult to measure and predict with high degrees of accuracy[23] because of its multifactorial and multidimensional nature.

Suicide risk can be assessed by a variety of self-report and interviewer-administered measures. Selecting a self-report and/or a structured-interview format to measure suicidal symptoms is a critical decision. For example, although interviewer-administered measures may allow for greater flexibility for conducting appropriate assessments of suicidal behaviour, these measures usually require more time and expense (for administration and training) than self-report measures. In contrast, self-report questionnaires may be inadequate for measuring suicidality in cognitively impaired or highly emotional individuals with concentration difficulties, although findings in this regard are mixed.[24,25] Although self-report measures are often used as screening tools, an adequate evaluation of suicidality should include both self-report and interviewer-administered measures.

Since its publication in 1974, Beck's Hopelessness Scale (BHS) has become an internationally-accepted and widely used measure in suicide prevention.[26] The scale has been extensively researched and validated as a measure to predict suicide and is still being used worldwide.[27,28] Although depression, hopelessness and suicide correlate closely, hopelessness was identified as one of the most important psychological, predictive and modifiable risk factors.[27,28] In this context, the aim of the present study was to construct a short, reliable and valid instrument with high screening and clinical utility with which to screen for suicide risk in recently diagnosed HIV-infected persons at a voluntary counselling and testing (VCT) clinic in Durban. This was intended to identify individuals whose suicidal ideation was severe enough to warrant treatment and suicide prevention.

Methods

Participants and setting

The sample consisted of 150 HIV-infected adults, presenting for the first time to be tested for HIV at a VCT clinic in an academic district-level hospital in Durban. All participants who tested HIV-positive following VCT were informed about the study by the resident VCT counsellor. Participants who consented voluntarily were enrolled in the study and were asked to complete the suicide risk screening scale (SRSS) and the SUPRE-MISS instrument at baseline and three weeks later. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BF202/09) and permission to conduct the study was granted by the relevant health institution.

Instruments

Two well-known and extensively used scales were utilised to assess aspects of suicidality in various population groups, *viz.* the BHS and the Beck Depression Inventory (BDI). Although these items do not directly assess suicidal behaviour, they measure hopelessness and immediate suicide risk. The BHS contains 20 true/false items (11 negatively and 9 positively phrased), with the severity of hopelessness (an indirect indicator of suicide risk) calculated by adding the scores for the 20 items. The total scores range from 0 (no hopelessness) to 20 (maximum level of hopelessness). The BDI, developed as a standardised measurement to assess the grades and severity of depression in order to monitor the change over time, contains 21 behavioural manifestations (items) of depression, which

Table 1. Suicide risk screening scale

This questionnaire consists of 14 statements (sentences). Please read the statements carefully one by one and answer them. If the statement describes your attitude for the past week, including now, write 'T' in the block provided. If the statement is false for you, write 'F' in the block.

Item	Statement	T or F
V1	I might as well give up because there's nothing I can do about making things better for myself	
V2	I can't imagine what my life would be like in 10 years	
V3	My future seems dark to me	
V4	I just don't get the breaks, and there's no reason to believe that I will in the future	
V5	All I can see ahead of me is unpleasantness rather than pleasantness	
V6	I don't expect to get what I really want	
V7	Things just won't work out the way I want them to	
V8	I never get what I want, so it's foolish to want anything	
V9	It is very unlikely that I would get any real satisfaction in the future	
V10	The future seems vague and uncertain to me	
V11	There's no use in really trying to get something I want because I probably won't get it	
V12	I have thoughts of killing myself, but I would not carry it out	
V13	I would like to kill myself	
V14	I would like to kill myself if I had the chance	

describe the symptoms from low to high. The items are scored individually from 0 to 3; these are added to obtain a total score of 0 - 63. A value <9 represents no or minimal depression, 17 - 29 moderate depression and >30 severe depression. Co-morbid conditions have been found to affect specificity of severity ratings at both the low- and high-end scores.[27] Several researchers have used items from both scales to validate the use of shorter versions in specific populations.[27,29,30]

For the present study, 14 items were selected from these scales to construct the SRSS (Table 1). The 11 BHS items selected are negatively phrased questions that reflect expectations of failure or motivational components (items V2, V9, V11, V16, V17, V20) and future uncertainty or cognitive components (items V4, V7, V12, V14, V18). Item selection was based on patient responses in the related previous studies, by choosing those with the highest and lowest scores at the two time-points using the complete BHS and BDI.[17,18] What the components measure has been addressed in other research.[29,31]

Our rationale for item selection incorporated several additional considerations. Firstly, patients with extreme pessimism would endorse the negative items selected and thus be more likely to be scored to have a higher suicide risk.[29,30] Secondly, the item-size pool is underscored by a theoretical framework that the patients' perceived hopelessness about their situation and future could be linked to suicide risk. This stems from the premise that cognitions mainly centre around an uncertain future and the loss of perspective in finding solutions to problems, which lead to hopelessness and consequently to suicidal ideation or attempt.[26] In line with the BHS scoring, the items of the SRSS were scored: true = 1; false = 0.

In the absence of a gold standard, an instrument previously tested in the general population in Durban was used as a proxy: the community survey aspect of SUPRE-MISS, based on the European Parasuicide Study Interview Schedule, which had been applied in the WHO/EURO Multicentre Study on Suicidal Behaviour.[19] The following questions were asked: (*i*) 'Have you ever seriously thought about committing suicide?'; (*ii*) 'Have you ever made a plan for committing suicide?'; (*iii*) 'Have you ever attempted suicide?'. The SUPRE-MISS instruments were pilot-tested, translated into different languages and validated. Since the SUPRE-MISS instrument was deemed reliable to predict suicidal behaviour, it was used as the reference to test the validity of the SRSS.

Statistical analysis

SPSS version 10.0 was used for data analysis. Receiver operating characteristic (ROC) analyses were used to determine the sensitivity, specificity and optimal cut-off points of the SRSS to predict suicidal ideation. Inter-item characteristics, internal consistency, reliability and validity analyses were also performed.

Results

The mean age of participants at baseline was 33.5 years (standard deviation (SD) ±9.4). The cut-off points of the SRSS scores and their corresponding sensitivity and specificity values are shown in Table 2. A cut-off score of 4.5 (≥4 being a positive result) achieved 68% sensitivity and 64% specificity in predicting suicidal ideation and is therefore the recommended cut-off for the SRSS. In establishing cut-off points on the SRSS that would optimise sensitivity and specificity via ROC analysis, it was decided that, ideally, the test should be more sensitive than specific to identify as many probable suicidal patients as possible. Sensitivity is paramount to suicide prediction and was our rationale for maximising sensitivity in the present analysis. The area under the curve (AUC) in ROC analysis was 0.730 at baseline (95% CI 0.64 - 0.81) and 0.776 at three weeks (95% CI 0.68 - 0.87) (Figs 1 and 2, respectively).

Inter-item characteristics and internal consistency

Table 3 displays the corrected item-total correlation at baseline and three weeks later. The corrected item total was >0.30 for all items except for V2 ('I can't imagine what my

Table 2. SRSS cut-off points and corresponding sensitivity and specificity to predict suicidal ideation at baseline and at three weeks

Time-point	Cut-off	Sensitivity	Specificity
Baseline	-1.0000	1.000	1.000
	0.5000	1.000	0.914
	1.5000	0.947	0.774
	2.5000	0.912	0.624
	3.5000	0.807	0.527
	4.5000	0.684	0.355
	5.5000	0.632	0.301
	6.5000	0.579	0.258
	7.5000	0.526	0.204
	8.5000	0.439	0.161
	9.5000	0.368	0.129
	10.5000	0.281	0.108
	11.5000	0.175	0.000
	12.5000	0.053	0.000
	13.5000	0.035	0.000
	15.0000	0.000	0.000
Three weeks	2.5000	0.811	0.532
	3.5000	0.757	0.455
	4.5000	0.676	0.364
	5.5000	0.676	0.273
	6.5000	0.649	0.195
	7.5000	0.622	0.182
	8.5000	0.568	0.130
	9.5000	0.568	0.104
	10.5000	0.459	0.0091
	12.0000	0.405	0.000
	13.5000	0.351	0.000
	15.0000	0.000	0.000

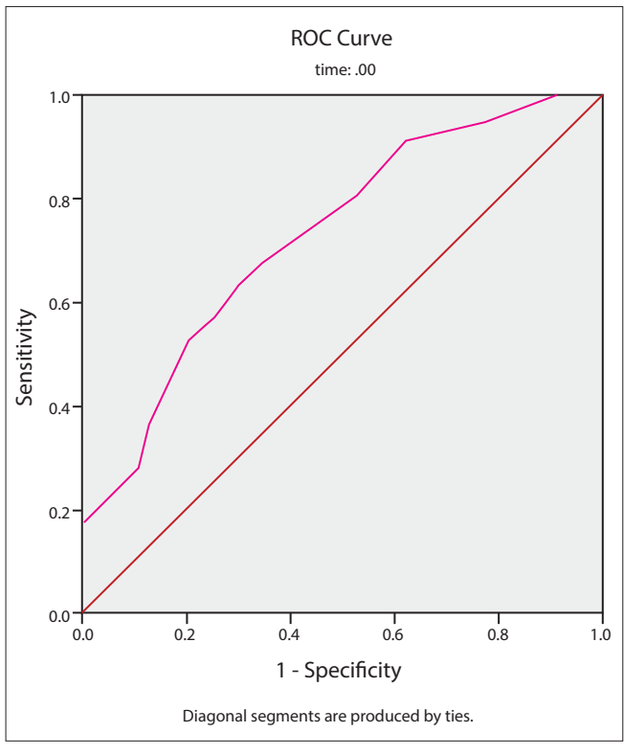

Fig. 1. ROC curve of SRSS scores for suicidal ideation immediately post-diagnosis (baseline) in HIV-infected adults.

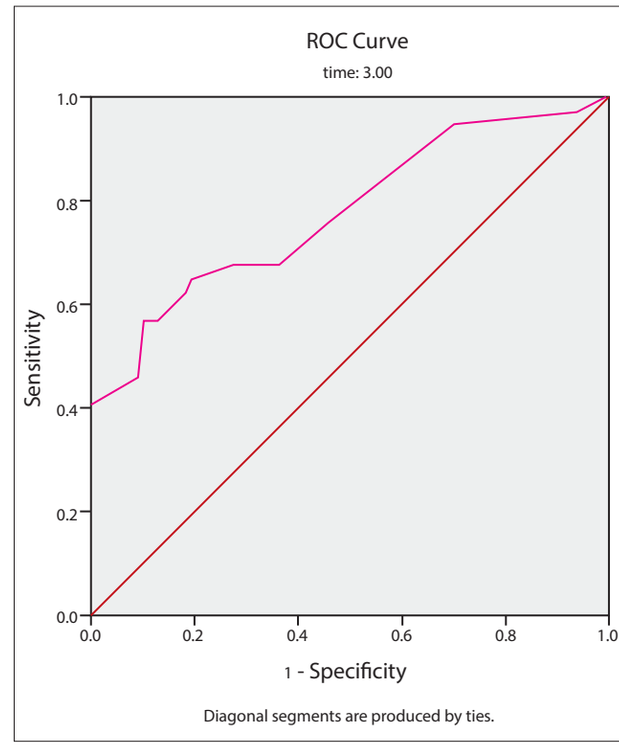

Fig. 2 ROC curve of SRSS scores for suicidal ideation three weeks post-diagnosis in HIV-infected adults.

Table 3. Corrected item-total correlations

	Baseline					Three weeks				
Item	Corrected item-total correlation	Cronbach's alpha*	Scale mean*	Mean	SD	Corrected item-total correlation	Cronbach's alpha*	Scale mean*	Mean	SD
V1	0.475	0.870	5.1333	0.3933	±0.49013	0.7300	0.919	5.1982	0.3964	±0.49137
V2	0.333	0.875	4.6667	0.8600	±0.34815	0.277	0.931	4.7297	0.8649	±0.34342
V3	0.567	0.865	5.0333	0.4933	±0.50163	0.669	0.921	5.0991	0.4955	±0.50225
V4	0.613	0.862	5.1400	0.3867	±0.48862	0.741	0.918	5.2072	0.3874	±0.48936
V5	0.612	0.862	5.0333	0.4933	±0.50163	0.701	0.920	5.1441	0.4505	±0.49980
V6	0.602	0.863	5.0400	0.4867	±0.50150	0.618	0.923	5.0991	0.4955	±0.50225
V7	0.619	0.862	5.0000	0.5267	±0.50096	0.573	0.924	5.0811	0.5135	±0.50208
V8	0.670	0.859	5.1533	0.3733	±0.48531	0.695	0.920	5.1892	0.4054	±0.49320
V9	0.624	0.861	5.0533	0.4733	±0.50096	0.740	0.918	5.1712	0.4234	±0.49634
V10	0.675	0.858	5.0733	0.4533	±0.49949	0.715	0.919	5.2162	0.3784	±0.48718
V11	0.605	0.862	5.1467	0.3800	±0.48701	0.802	0.916	5.2613	0.3333	±0.47354
V12	0.400	0.872	5.4000	0.1267	±0.33371	0.675	0.921	5.4414	0.1532	±0.36177
V13	0.318	0.875	5.4867	0.0400	±0.19662	0.675	0.921	5.4414	0.1532	±0.36177
V14	0.318	0.875	5.4867	0.0400	±0.19662	0.650	0.922	5.4505	0.1441	±0.35283

SD = standard deviation.

* If item is deleted.

life would be like in ten years'). This item had a corrected item-total correlation of 0.333 at baseline and 0.277 three weeks later. Due to its potential for ambiguity in some non-clinical samples, it has been described as an outlier; in other studies it represented one of the highest-scoring item responses at different time intervals.[13,17,18] This apparent discrepancy can be explained partially by considering various factors. For example, for some patients, being told that they have a positive HIV status can be an extremely stressful experience that constitutes a life crisis. For many, their psychological response can include the perception of 'a death image',[7] if they assume that they have been dealt

a death sentence. This, along with the myriad of possible other misconceptions, cognitive distortions, psychiatric and life-disruption complications, a shortage of healthcare resources and the fear of not being eligible for, or having access to ART,[1] makes it difficult for HIV-positive persons to visualise a long-term future.

The item-total correlations ranged from 0.318 to 0.675. At baseline, item V10 ('The future seems vague and uncertain to me') had the best corrected item total (0.675), while item V11 ('There's no use in really trying to get something I want because I probably won't get it') had the best corrected item total (0.802) at three weeks. The Cronbach's alpha for a deleted item showed that none of the items were problematic. The level of internal consistency for the SRSS was, therefore, acceptable for clinical purposes and was consistent with the findings of other studies.[27]

Reliability and validity

The overall Cronbach's alpha for the SRSS at baseline and three weeks was 0.874 and 0.915, respectively. To determine the validity of the SRSS, it was compared with the accepted instrument for SUPRE-MISS. Using a cut-off score of 4, the sensitivity for the SRSS at baseline was 81% with a positive predictive value of 48%, a specificity of 47% and a negative predictive value of 80%. At three weeks, the sensitivity was 79%, the specificity 55%, the positive predictive value 44%, and the negative predictive value 82%.

Discussion

This study demonstrated the potential utility of a simple screening tool to detect suicidality in HIV-infected individuals newly diagnosed through a VCT programme. Although the sensitivity and specificity of the SRSS were not very high (around 68%), these compared favourably with those obtained in other research.[26,29] Unlike other studies, where item 7 or the 4 items of the BHS were not administered individually, in our study the full version of the BHS was administered and the responses to the 20 items were used to deduce final scores.[29] Notably, there was a likelihood of a high level of false-positives through the use of the SRSS. The results indicate a good sensitivity at both time-periods and a comparatively low rate of false-positives. Further research and the incorporation of additional assessment items in the questionnaire are likely to have a more successful result in suicide prevention.

Equally important for screening instruments to be effective is the prevalence of risk within the population. It is well documented that SA – especially the city of Durban, where the research was conducted – has a high prevalence of HIV/AIDS, and a recent study showed that sero-positivity, age and gender were significantly associated with suicidal ideation.[17,18] It can therefore be concluded that the SRSS can be used, in conjunction with a clinical interview, as a valid screening instrument to assess for suicide risk in this setting. The use of a clinical interview, which remains the fundamental basis of suicide risk assessment, should incorporate an understanding of the patient's suicidal crisis from both an objective/descriptive as well as an experiential perspective.[23-25] The former includes objective patient data to assess suicide risk, a clinical (psychiatric/psychological) history and identification of overt suicidal manifestations and risk factors.[23-25] The latter perspective goes beyond delineation of clinical symptoms in an attempt to understand the patient's actual feelings, personal narrative, perspective, sustaining resources and beliefs about suicide.[23-25]

The assessment of hopelessness is extremely important in clinical practice, since high levels of hopelessness can lead to isolation and the inhibition to seek help timeously. Given this, VCT offers patients an option to be counselled and tested for the presence of HIV and, at the same time, provides an opportunity to identify any underlying level of hopelessness and suicide risk related to receiving a life-altering diagnosis of HIV-positivity.[17,18] The self-administered questionnaire can be completed while patients are awaiting their HIV test results. The questionnaire is easily scored and a risk assessment is performed with relative ease. A suicide intervention to be included in the post-test counselling is presently being evaluated, including re-administering the SRSS at the next clinical visit. This may decrease the rate of false-positives obtained.

Study limitations

The construction of the SRSS involved selecting items from two sub-scales, which were grouped and analysed as a single scale. The main limitation of this study was that there was no gold standard to use as a baseline reference within the context of the population studied. Furthermore, there was no reference to the participants' views on living with HIV, which can be part of a clinical interview; this should form the focus of further research.

Conclusion

Analyses have demonstrated the importance of brief scales with high clinical validity for assessing suicidal risk in daily clinic settings.[21,22] Our research shows that the SRSS can be a valuable screening tool for suicidality as part of a standard clinical interview and good clinical assessment in HIV/AIDS VCT clinics. Suicide risk assessment in patients seen at such clinics should be a routine aspect of comprehensive patient care, to assist with effective management and the prevention of possible suicidal behaviour. The SRSS is not intended as a stand-alone diagnostic tool to assess suicidal behaviour, but may be used as a triage tool to assist in the identification of high-risk patients.

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ORIGINAL ARTICLE

Challenges to delivering quality care in a prevention of mother-to-child transmission of HIV programme in Soweto

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Background. There has been little focus on the quality of care provided in the prevention of mother-to-child transmission (PMTCT) of HIV services in South Africa (SA).
Objective. To assess the quality of care in PMTCT services in Soweto, SA, focusing on the knowledge and experiences of healthcare workers and HIV-infected pregnant women accessing the services.
Methods. A cross-sectional survey was conducted in November - December 2009. A total of 201 HIV-infected pregnant women and 80 healthcare workers from 10 antenatal clinics were interviewed using standardised questionnaires.
Results. Among the HIV-infected pregnant women, the median gestational age was 20 weeks at the first antenatal visit and 32 weeks at the time of the interview. The majority of the women interviewed (71.5%) discovered that they were HIV-infected in the index pregnancy, and 87.9% disclosed their HIV status. Overall, 97.5% received counselling and 33.5% were members of a support group. Knowledge of antenatal and intra-partum PMTCT interventions was accurate in 62.7% and 43.3% of the women, respectively. Support group membership and current use of antiretroviral prophylaxis did not impact on the quality of knowledge. Of the healthcare workers, 43.8% were professional nurses and 37.5% were lay counsellors. The majority (80.0%) felt satisfied with their knowledge of the PMTCT guidelines and 96.3% felt competent in managing HIV-infected pregnant women. Yet, there were important deficiencies in the knowledge of the guidelines.
Conclusion. In our study, the knowledge of PMTCT interventions was low in both clients and healthcare workers. This points to the need to improve quality of care in PMTCT services, especially with increasingly complex PMTCT interventions recommended by international policies.

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In the past few years, South Africa (SA) has made significant progress in the provision of prevention of mother-to-child transmission (PMTCT) of HIV services, both in the delivery of more efficacious PMTCT interventions and also an increase in the proportion of women receiving the interventions.[1] According to a UNAIDS report, ~95% of HIV-infected pregnant women in SA received some antiretroviral therapy (ART) intervention for PMTCT in 2010.[2] While progress has been made, there are still several challenges in scaling up PMTCT services in the SA public healthcare sector. These relate to coverage at different steps of the PMTCT cascade, and also to the quality of care rendered in the services. According to a qualitative study documenting women's experiences of accessing ART and PMTCT programmes in several facilities in SA, health system weaknesses impacted negatively on access.[3]

Healthcare system and patient factors are important in the scale-up and success of HIV programmes (including PMTCT)[4-7] and the availability of interventions alone is not sufficient to guarantee appropriate implementation and uptake.[4-5,8-9] Healthcare facilities need to be well-resourced with competent and motivated staff to provide the services, and there needs to be service uptake and treatment adherence by patients.[4-7] The providers' and patients' knowledge and attitudes are also important.[7,8] There is evidence to suggest that the patient-provider relationship may have an effect on decision-making during the antenatal period, and on the uptake of PMTCT interventions.[10] Yet, quality of care has not been a focus in most PMTCT services in SA; most are focused on increasing coverage in the PMTCT cascade. Several reviews have found poor performance and coverage in PMTCT programmes, despite the simplicity of some interventions; hence, the focus has been on increasing coverage.[5,11,12]

We conducted a cross-sectional survey to investigate key aspects of the quality of care in PMTCT services in antenatal clinics in Soweto, SA, focusing on the PMTCT programme knowledge and experiences of (*i*) healthcare workers and (*ii*) HIV-infected pregnant women accessing the services. This was performed against the backdrop of recently updated

PMTCT guidelines in 2008, when zidovudine (AZT) monotherapy became available for prophylaxis.[13]

Methods

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand. All participants signed written informed consent to participate.

Until March 2008, all antenatal clinics in Soweto had only intrapartum single-dose nevirapine (NVP) for PMTCT for pregnant women who were not eligible for life-long ART. AZT was rolled out in phases across the antenatal clinics in March - October 2008. Prior to implementation of the guidelines, staff at the antenatal clinics, including lay counsellors, were trained on the new guidelines. The PMTCT service at each clinic was staffed by a professional nurse – a 'PMTCT co-ordinator' in charge of PMTCT services, including supervision of lay counsellors.

The study was conducted in November - December 2009; all facilities had at least 12 months of routine services under the 2008 PMTCT guidelines. Participating clinics were a mixture of low- and high-volume clinics, with 50 - 300 pregnant women presenting to each clinic per month. The HIV prevalence was 29% in 2009, and 15 - 20% of pregnant women were eligible for ART under the guidelines in place at the time (criterion: $CD4^+$ count ≤200 cells/μl).

HIV-infected pregnant women

Using consecutive sampling, ART-eligible and -ineligible HIV-infected pregnant women presenting to the selected antenatal clinics for repeat visits were interviewed using a structured questionnaire. Their experiences of being HIV-infected and their knowledge of available PMTCT interventions were determined. Eight key-knowledge questions were selected; each was assigned a score of 1 for a correct answer and 0 for an incorrect answer (maximum score of 8).

Healthcare workers

Healthcare workers from the same clinics were interviewed using a different questionnaire assessing their opinions and experiences of working in a PMTCT programme and their knowledge of the PMTCT guidelines. Consecutive sampling was used to select participants. Similar to the knowledge score devised for patients, a scoring system based on eight key questions was formulated. All interviewers received training on the questionnaire, and all were fluent in the local vernacular languages.

Data analysis

Data were analysed using Stata version 12.0. Descriptive statistics used employed means and standard deviations (SDs) or medians and interquartile ranges (IQRs) (for continuous variables) and proportions (for categorical variables). We compared knowledge scores on subgroups using Student's *t*-tests and Fisher's exact tests. All statistical tests were two-sided (alpha=0.05).

Results

HIV-infected pregnant women

A total of 201 HIV-infected pregnant women were interviewed (Table 1). The mean age was 27.7 years (SD ±4.8); median gestational age was 20 weeks (IQR 16 - 24) at the first antenatal visit and 32 weeks (IQR 24 - 32) at the time of the interview. The majority of women (71.5%) discovered that they were HIV-infected in the index pregnancy. Of the women diagnosed in a previous pregnancy, 84.1% (37/44) had previously taken single-dose NVP for PMTCT. A baseline $CD4^+$ cell count was available for 92.0% of the participants: median 395 cells/μl (IQR 294 - 500); mean 420 cells/μl (SD ±190).

Overall, 87.5% (175/200) of the women had disclosed their HIV status; the majority (90.9%; 159/175) had done so to their partners. This finding did not differ according to timing of HIV diagnosis. Of the women who discovered that they were HIV-infected in the index pregnancy, 68.0% had disclosed their status. There were various reasons for non-disclosure to the partner, including fear that the partner would leave, be violent, or accuse the woman of being unfaithful and infecting him with HIV. Less than half (45.3%) of the women knew their partner's HIV status. There was a significant difference in the knowledge of the partner's HIV status between women who had, and those who had not disclosed their HIV status: 89 (50.9%) v. 0 (0%) knew the partner's HIV status, respectively (p<0.001). Of the partners with known HIV status, 81.3% were HIV-infected.

Of the women, 62.7% and 43.3% had accurate knowledge on antenatal and intra-partum prophylaxis, respectively. Overall, 97.5% (196/201) had received some counselling, 67.7% had received more than one counselling session, 88.6% (178/201) felt that the time spent on counselling was adequate, and 33.5% were part of a support group. There was no significant difference in knowledge between pregnant women who were members of a support group (mean score 5.29; SD ±0.98)), and those who were not (mean score 5.18; SD ±1.41) (p=0.542) (Table 2). There was a significant difference in knowledge between women who were already receiving AZT prophylaxis (mean score 5.44; SD ±1.18) and those who were not (mean score 4.94; SD ±1.34) (Table 3) (p=0.005).

Table 1. Characteristics of pregnant women (*N*=201)

Characteristics	
Age (years), mean (±SD)	27.7 (±4.8)
Parity, median (IQR)	2 (1 - 2)
Gravidity, median (IQR)	2 (1 - 3)
Gestational age at booking (weeks), median (IQR)	20 (16 - 24)
Gestational age at interview (weeks), median (IQR)	32 (24 - 32)
$CD4^+$ cell count (cells/μl), median (IQR)	395 (294 - 500)
When HIV status discovered (*N*=200)	
Current pregnancy	143 (71.5)
Previous pregnancy	44 (22.0)
Outside of pregnancy	13 (6.5)
Disclosed HIV status (*N*=199), *n* (%)	175 (87.9)
To whom disclosed, *n* (%)	
Partner	159 (90.9)
Parent	61 (34.9)
Sibling	42 (24.0)
Friend	30 (17.1)
Other	5 (2.9)

SD = standard deviation; IQR = interquartile range.

Table 2. Characteristics and knowledge of pregnant women who were members of a support group (*N*=67) v. those who were not (*N*=133)

Members of a support group	Yes *n* (%)	No *n* (%)	*p*-value
Characteristics			
Age (years)			
<25	18 (26.9)	35 (26.3)	
25 - 35	47 (70.1)	91 (68.4)	
>35	2 (3.0)	7 (5.3)	0.764
Parity			
≤2	58 (86.6)	109 (81.9)	
3 - 5	9 (13.4)	24 (18.1)	0.407
When HIV status discovered:			
Current pregnancy	44 (65.7)	98 (74.2)	
Previous pregnancy	21 (31.3)	23 (17.4)	
Outside of pregnancy	2 (3.0)	11 (8.3)	0.043
Disclosed HIV status	56 (83.6)	118 (88.7)	0.356
Correct knowledge			
AZT prophylaxis			
Indication	66 (98.5)	124 (93.2)	0.143
Timing of initiation	64 (95.5)	119 (90.2)	0.188
Duration of use	26 (38.8)	99 (74.4)	<0.001
Prophylaxis during labour	18 (26.9)	69 (51.9)	0.001
Need for infant prophylaxis	63 (94.0)	111 (83.5)	0.036
Type of infant prophylaxis	7 (10.5)	18 (13.5)	0.553
Duration of infant prophylaxis	52 (77.6)	62 (39.1)	<0.001
Duration of exclusive breastfeeding	59 (88.1)	87 (65.4)	0.001
Overall score, mean (±SD)	5.3 (±0.98)	5.2 (±1.41)	0.542

AZT = zidovudine; SD = standard deviation.

Table 3. Difference in knowledge in pregnant women who were already on zidovudine (AZT) prophylaxis (*N*=114) and those who were not (*N*=86)

AZT prophylaxis	Yes *n* (%)	No *n* (%)	*p*-value
Correct knowledge			
Indication for AZT	111 (97.4)	79 (91.9)	0.137
Timing of AZT initiation	101 (88.6)	82 (95.4)	0.125
Duration of use of AZT	79 (69.3)	47 (54.7)	0.034
Intrapartum prophylaxis	63 (55.3)	24 (27.9)	<0.001
Score, mean (±SD)	5.44 (±1.18)	4.94 (±1.34)	0.005

Healthcare workers

Of the healthcare workers interviewed, 43.8% were professional nurses and 37.5% were lay counsellors; the majority (81.3%) had been in their current position for longer than a year (Table 4). Less than a half (47.5%) were satisfied with their working conditions. The most dissatisfaction was in terms of remuneration; only 28.8% were satisfied with their salary. In terms of workload, 80.0% of the workers felt that the new PMTCT programme increased their workload, and 92.5% felt that there was a need for more staff for the programme.

Most healthcare workers were satisfied with their knowledge of the PMTCT guidelines (80.0%) and with their general knowledge of HIV/AIDS (91.3%). In managing HIV-infected pregnant women, 96.3% were satisfied with their competence. Training received on the new guidelines was perceived to be adequate by 63.6%. The mean score for the workers' knowledge of the PMTCT guidelines was 5.15 (SD ±1.85): 5.41 (SD ±1.56) for professional nurses v. 5.19 (SD ±1.89) for lay counsellors (p=0.586). There was no significant difference between the mean score of those who were satisfied with their knowledge of the guidelines (5.29; SD ±1.88) and those who were not (4.56; SD ±1.63) (p=0.157) (Table 5). There was also no difference between the mean score of healthcare workers who thought that the training they received was adequate (5.10; SD ±1.9) and those who did not (5.14; SD ±1.7) (p=0.926).

Table 4. Characteristics of healthcare workers (*N*=80)

Characteristics	*n* (%)
Gender (*N*=79)	
Female	74 (93.7)
Staff categories	
Professional nurse	35 (43.8)
Auxiliary nurse	9 (11.3)
Lay counsellor	30 (37.5)
Other	6 (7.5)
Time in current position	
<6 months	7 (8.8)
6 months - 1 year	8 (10.0)
>1 - 5 years	33 (41.3)
>5 - 10 years	22 (27.5)
>10 years	10 (12.5)

A high percentage of healthcare workers (86.3%) thought that HIV-infected pregnant women did not disclose their HIV status. There were a number of adverse opinions about HIV-infected women having children: 21.3% of healthcare workers thought that HIV-infected individuals should not have children; 53.8% thought HIV-infected individuals were having too many children; and 46.3% thought that social grants were an incentive for HIV-infected women to have children.

Discussion

In this cross-sectional survey, several challenges were identified in the Soweto PMTCT programmes. The majority of pregnant women discovered that they were HIV-infected during pregnancy, and although disclosure to partners was high, less than half knew their partner's HIV status. There were important deficiencies in the

Table 5. Characteristics and knowledge of healthcare workers who were satisfied with their knowledge of PMTCT (*N*=64) v. those who were not (*N*=16)

Satisfied with knowledge of PMTCT	Yes, *n* (%)	No *n* (%)	*p*-value
Characteristics			
Staff categories			
Midwife	14 (21.9)	6 (37.5)	
PMTCT coordinator	10 (15.6)	0 (0)	
PCR nurse	4 (6.1)	2 (12.5)	
Lay counsellor	28 (43.8)	2 (12.5)	
Other	8 (12.5)	6 (37.5)	
Time in current position			
<6 months	4 (6.3)	3 (18.8)	
6 months - 1 year	7 (10.9)	1 (6.3)	
2 - 5 years	30 (46.9)	3 (18.8)	
6 - 10 years	19 (29.7)	3 (18.8)	
>10 years	4 (6.3)	6 (37.5)	
Correct knowledge			
Single-dose NVP			
Efficacy	55 (85.9)	11 (68.8)	0.211
Repeat in same pregnancy	52 (81.3)	10 (62.5)	0.410
Use in subsequent pregnancies	51 (79.7)	12 (75.0)	0.933
ART use in pregnancy	44 (68.8)	8 (50.0)	0.191
Sero-conversion during pregnancy	42 (65.5)	10 (62.5)	0.754
Exclusive breastfeeding and risk of MTCT	26 (40.6)	9 (56.3)	0.190
Extended breastfeeding and risk of MTCT	50 (78.1)	12 (75.0)	0.704
Contraception for HIV-infected women	19 (29.7)	1 (6.3)	0.105
Overall score, mean (±SD)	5.3 (±1.88)	4.6 (±1.63)	0.157

PMTCT = prevention of mother-to-child transmission of HIV; PCR nurse = nurse responsible for HIV PCR tests in infants; NVP = nevirapine; ART = antiretroviral therapy; MTCT = mother-to-child transmission of HIV.

women's knowledge of the available PMTCT interventions, despite receiving counselling and their perception that the counselling that they received was adequate. Neither the number of counselling sessions received, nor participation in a support group, had an impact on the quality of knowledge.

Staff in the PMTCT programme felt well prepared and well informed prior to the rollout of the updated PMTCT programme. The majority thought that the training received was adequate and almost all felt confident about managing HIV-infected women; yet, there were several important gaps in the knowledge of the PMTCT guidelines. Job satisfaction was low, mostly in terms remuneration. Moreover, several staff members expressed negative opinions about HIV-infected women having children.

The findings of this cross-sectional survey have important implications for PMTCT programmes in SA. Routine HIV testing for women, and men, of reproductive age needs to be encouraged, and linkages to care provided for those who test HIV-positive. This is especially important in women who are ART-eligible, as they carry a high risk of mother-to-child transmission, and ART initiated preconception decreases this risk significantly.[14] It will be important to assess the impact of the SA national HIV counselling and testing (HCT) drive on testing outside of pregnancy.[15]

Unpublished data from the Soweto PMTCT programmes indicate that the number of pregnant women presenting for antenatal care with a known HIV-positive status and already receiving ART has increased in the past 2 years (C Mnyani, unpublished data). The rate of disclosure among HIV-infected pregnant women in this survey was higher than that reported for most of sub-Saharan Africa, but similar to the findings of another study conducted in SA.[16-18] Disclosure has been shown to be important in women's uptake and adherence to PMTCT interventions.[16]

Our data on the women's knowledge of PMTCT interventions suggest that the quality of counselling given can be improved. Incorrect information, and hence incorrect practices, will be harmful in the context of PMTCT and may significantly increase the risk of mother-to-child transmission. While health knowledge is only one component of quality of care, there is evidence to suggest that poor quality of counselling, which translates to poor patient knowledge, is an important contributing factor to non-adherence to PMTCT interventions.[5,19] Poor quality of counselling has been reported even in well-functioning PMTCT sites where counsellors, some nurses, had received structured training.[20] The SA public healthcare sector depends on the services of lay counsellors who receive a stipend, and also receive variable training. Counselling services are often interrupted, and there is evidence to suggest that this has a negative effect on PMTCT services.[21]

As we scale up PMTCT programmes and introduce more complex interventions, staff preparedness, including knowledge, needs to be improved.[22,23] There needs to be a review and standardisation of training providers, and also of training content. Support using trained peers who are experts in HIV care and management has been shown to be an important intervention in building capacity.[6] Negative staff attitudes towards HIV-infected women also need to be addressed. There is evidence that HIV-infected women who fear and/or experience stigmatisation may avoid participating in PMTCT programmes.[24]

Study limitations

While our findings do have important implications, there are several limitations to this survey. Like all questionnaire-based research, the results may have been influenced by reporting biases. In this case, participants may have felt social desirability to report satisfaction with their PMTCT-related knowledge, but this potential bias was unlikely to have influenced their ability to report factual knowledge correctly. In addition, although the study was conduced under a different set of PMTCT policy guidelines, the findings are particularly noteworthy given the subsequent implementation of more complex PMTCT guidelines in SA and many other parts of Africa. The study was conducted in one urban community of high HIV prevalence and with established PMTCT services, and the results should be generalised to other settings with caution. Healthcare workers were generally reluctant to be interviewed, and this warrants further investigation. Also, we used a consecutive sampling strategy; although routine in this form of health services research, this may be more prone to bias than random sampling strategies. There are plans to perform a similar survey to assess experiences with, and knowledge of the latest SA PMTCT guidelines. Despite the limitations, there are strengths to the survey that warrant merit, including the large number of pregnant women and different categories of staff who were interviewed.

Conclusion

There are still several challenges in PMTCT services. Most importantly, knowledge of PMTCT interventions is surprisingly low in both clients and healthcare providers, and there is a need for enhanced interventions to improve the quality of care in PMTCT services. This is particularly important as PMTCT interventions become more complex during the ante- and postnatal periods.

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ORIGINAL ARTICLE

Parental presence within households and the impact of antiretroviral therapy in Khayelitsha, Cape Town

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Background. While household support is an important component of effective care and treatment in HIV/AIDS, there are few insights from Southern Africa into how household support arrangements change over time for patients starting antiretroviral therapy (ART).

Objective. We hypothesised that patients initiating ART are more likely to be living with family, especially their mothers, compared with the general population, but that over time these differences disappear.

Methods. A panel survey of ART patients was matched by age, gender and education to a comparison sample drawn from adults in Khayelitsha, Cape Town.

Results. The results show that there is a substantial potential burden of care on the families of patients starting ART, particularly mothers, and that the use of ART appears to reduce this burden over time. But, even after their health is restored, ART patients are significantly less likely to have a resident sexual partner and more likely to be living in single-person households than their counterparts in the general population.

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There is evidence that people living with HIV/AIDS (PLWHA) across sub-Saharan Africa rely on family members, especially parents, for ongoing care and support, particularly with the morbidity of advanced HIV disease. Several studies have shown that terminally ill South African (SA) adults often return to the parental home to access care and support, primarily from their mothers.[1-4] As Haour-Knipe[5] points out, this is to be expected in many settings where extended family serves as the 'primary social safety net'. A Ugandan study found that elderly parents, especially mothers, were the main caregivers for PLWHA[6] and similar dynamics have been reported in Thailand.[7] However, there are few studies exploring whether reliance on family and parental support changes after initiation of antiretroviral therapy (ART).

What sets Southern Africa – and especially SA – apart is the generally lower presence of fathers in households and the importance of 'uterine kin' (mothers, grandmothers and sisters) in providing social stability and care when necessary.[8-10] This is a consequence of SA's history of oscillating migration and apartheid, which separated families geographically, often for long periods of time. But, it is also a consequence of declining rates of marriage, to the point that it is no longer the norm.[11] Hunter argues that the rise of unemployment was the key factor behind this, as only the relatively well-off African men could afford to pay '*ilobolo*' (bridewealth) or act as reliable providers for their families.[12-14] Under these circumstances, women become incentivised to form looser connections with men (sometimes several men) and closer bonds with siblings and mothers.

The phenomenon of the 'absent father' has been well documented in SA.[15-17] What this means in terms of the supporting role of fathers, however, is unclear. According to Morrel and Richter,[15] paternal absence implies a lack of fatherly support for children's care. However, other research emphasises how fathers can and often do maintain meaningful contact with children, even when they do not reside in the household,[8] and that their role in providing care when they are in the household often goes unreported.[18,19]

We investigated aspects of living arrangements for ART patients over time, at the time of ART initiation and subsequently, and compared this with the living arrangements of people of similar age, gender and education in the general population of residents of Khayelitsha, Cape Town.

Methods

Khayelitsha is a peri-urban settlement comprising about half a million predominantly Xhosa-speaking residents. Almost half of the working-age adults are without jobs and over a quarter of pregnant women are HIV-positive.[20-22] Between 2001 (when the first ART pilot programme was established in Khayelitsha) and 2008, more than 10 000 people were successfully initiated on ART with over 93% retained in care.[23]

Table 1. Attrition analysis*

Characteristics	Loss to follow-up	In panel	Univariate probit coefficient R^2 (95% CI)	Multiple regression probit coefficient R^2 (95% CI)		
				ART start (wave 0)	ART (wave 2)	Khayelitsha (wave 2)
Age (years)	38	33	0.04† (0.02 - 0.07)	0.04‡ (0.01 - 0.07)	0.04‡ (0.01 - 0.07)	0.04‡ (0.01 0.07)
Schooling (years)	8.5	9.7	-0.07† (-0.13 - 0.01)	-0.03 (-0.10 - 0.04)	-0.01 (-0.08 - 0.06)	-0.02 (-0.09 - 0.06)
Female, %	75	80	-0.17 (-0.62 - 0.28)	-0.01 (-0.46 - 0.49)	-0.02 (-0.50 - 0.47)	-0.06 (-0.55 - 0.45)
Worst health ever at ART start, %	39	40	0.03 (-0.35 - 0.42)	-0.08 (-0.49 - 0.31)	-0.01 (-0.44 - 0.42)	-0.04 (-0.47 - 0.40)
Working, %	18	37	-0.54‡ (-0.99 - 0.09)		-0.47‡ (-0.93 - 0.00)	-0.40 (-0.90 - 0.11)
Disability grant recipient, %	83	72	0.33 (-0.13 - 0.80)		0.31 (-0.20 - 0.82)	0.241 (-0.29 - 0.77)
Per capita household income (ZAR)	487	630	-0.00 (-0.00 - 0.00)			-0.00 (-0.00 - 0.00)
Mother in household, %	19	23	-0.16 (-0.61 - 0.30)			0.16 (-0.95 - 1.27)
Father in household, %	5	5	-0.09 (-0.94 - 0.76)			0.08 (-0.93 - 1.10)
Parent-headed household, %	16	22	-0.21 (-0.69 - 0.26)			-0.18 (-1.39 - 1.04)
Partner in household, %	19	32	-0.40§ (-0.84 - 0.04)			-0.31 (-1.80 - 0.17)
Pseudo R^2				0.055	0.081	0.088
N				242	242	234
Probability > chi^2				0.018	0.007	0.064

CI = confidence interval.
*Dependent variable: 1 = loss to follow-up; 0 = in full panel study.
†$p<0.001$.
‡$p<0.05$.
§$p<0.1$.

In 2004, 242 patients receiving ART in Khayelitsha were recruited into a panel study conducted by the AIDS and Society Research Unit of the University of Cape Town. Respondents were recruited through social networks, clinic support groups and by word of mouth; hence, the sample cannot be regarded as strictly representative. However, as two-thirds of the starting ART cohort was recruited into the study, the sample can be regarded as broadly representative of the experience of the early ART patients.[24]

The first round of the survey (wave 1) was conducted in 2004 and a second wave in 2006. Retrospective questions were posed to respondents regarding their households and health at the time that they started ART, thereby allowing us to construct a retrospective 'wave 0' (i.e. at the time of ART initiation, when they were sick with AIDS) for all respondents.

The panel study allowed examination of the changes in household characteristics of ART patients over time, but we also needed to know how this compared with households in the general population. We therefore constructed a 'quasi control' dataset drawn from a survey of Khayelitsha residents (which can be regarded as representative of adult African Khayelitsha residents[29]), conducted in parallel with the ART panel study. From this dataset we drew a sub-sample of 202 respondents matched (using a probit regression) by age, gender and education to respondents in the ART sample.

Ethics approval for the studies was obtained from the Ethics Committee of the Centre for Social Science Research, in line with the ethics approval process of the University of Cape Town.

Results

Within the ART panel study, loss to follow-up was 16% (of the 242 respondents interviewed in 2004, only 202 were present for all subsequent interviews). Older respondents in wave 1 were more likely to be lost to follow-up (Table 1), but the effect was small (for each additional year of age, the probability of loss to follow-up rose by 4%). Those without jobs were more likely to be lost to follow-up (being employed cut the probability of loss to follow-up by one-half), but once controls were implemented for household income and other household characteristics, the effect of being employed became statistically insignificant. Having a resident sexual partner reduced the probability of attrition, but this effect also became statistically insignificant once controls were implemented for other factors. In multivariate analysis, there were no systematic differences in socio-economic and demographic characteristics between those lost to follow-up and those retained in care, other than small differences in age. Furthermore, the explanatory power of the regression models remained low in all specifications.

The matching process resulted in a matched and balanced panel dataset of ART patients and Khayelitsha respondents, with almost identical average age, gender and educational profiles (Table 2). Respondents were asked to rank on a 10-point scale (with 10 being the best health that they had ever experienced)

their current health status as well as their recollections of their health at the time that they initiated ART, and three and six months later. The mean score for perceived health rose from 2.8 (standard deviation (SD) ±2.2) at ART initiation to 5.3 (SD ±2.0) three months later and 7.8 (SD ±1.7) six months later – an increase in line with improvements in clinical markers (e.g. CD4 cell counts) and quality-of-life indicators found in other studies of the same Khayelitsha cohort.[20,25-28]

Given the potential for ART to restore health and independence, we expected the ART rollout to result in changes in household characteristics, especially involving mothers and sisters. Accordingly, we hypothesised that mothers and sisters were more likely to be present in the households of patients initiating ART. We found that maternal presence in the household decreased significantly from 31% to 19% between wave 0 (ART initiation) and wave 2 (Table 3). Indeed, by wave 2, there was no significant difference between maternal presence in ART-patient households and those of the matched Khayelitsha residents. The trend was similar and statistically significant also for households with no mother but with a sister present.

An analysis of changes in paternal presence are reported in Table 3. We found that fathers were generally less present than mothers, in both the ART and matched Khayelitsha samples. However, as was the case with maternal presence, fathers were significantly more likely to be present in the household when ART respondents were sick with AIDS, rather than later. Whether fathers were actively playing any caring or supportive role could not be ascertained from the data. There was a statistically significant increase between wave 0 and wave 2 in the number of ART respondents who were themselves household heads (Table 4). More than half of the respondents in the ART sample were household heads by wave 2.

In addition, we examined changes in reported sexual partnerships over time, comparing ART patients with the general population. There was indeed a statistically significant increase in the number of ART patients with resident sexual partners (Table 5), but this remained significantly lower than for the matched Khayelitsha sample.

Table 2. Matched data sets

	ART panel	Khayelitsha matched sample
Women, %	80	80
Age (wave 1), years ± SD	33.2±6.5	33.6±7.4
Education (wave 1), years ± SD	9.7±2.8	9.9±2.5
Total, *N*	202	202

SD = standard deviation.

Discussion

We employed an innovative methodology to compare trends in a panel study of ART patients in Khayelitsha with a matched sample drawn from the local population. We confirmed the pattern found in the existing literature that people with AIDS rely on kin, especially mothers, for care and support.[2-5,9] A limitation of our study was that we could not ascertain whether it was the patient or the caregiver that moved households. Even so, we were able to establish that ART patients were more likely to be living in parent-headed households when they initiated treatment than

Table 3. The presence of mothers, sisters, fathers and parent-headed households

	ART start (wave 0)	ART (wave 2)	Khayelitsha (wave 2)
Mother present in the household	62 (30.7%)	39 (19.3%)	43 (21.3%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=93.58; *p*=000*; Fisher's exact: 0.000*		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=0.24; *p*=0.621; Fisher's exact: 0.711	
No mother but at least one sister in the household	40 (19.8%)	30 (14.9%)	26 (12.9%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=48.73; *p*=0.000*; Fisher's exact: 0.000*		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=0.33; *p*=0.565; Fisher's exact: 0.666	
Father present in the household	15 (7.4%)	9 (4.5%)	19 (9.4%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=48.09; *p*=000*; Fisher's exact: 0.000*		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=3.84; *p*=0.050†; Fisher's exact: 0.076†	
Parent-headed household	60 (70.3%)	35 (17.3%)	42 (20.8%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=84.57; *p*=0.000*; Fisher's exact: 0.000*		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=0.79; *p*=0.375; Fisher's exact: 0.447	

*$p<0.001$.
†$p<0.1$.

Table 4. Respondent-headed and single-person households

	ART start (wave 0)	ART (wave 2)	Khayelitsha (wave 2)
Respondent as head of household	65 (32.2%)	110 (54.5%)	85 (42.1%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=55.37; p=000*; Fisher's exact: 0.000*		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=6.20; p=0.013†; Fisher's exact: 0.017†	
Single-person households	8 (4%)	17 (8.4%)	7 (3.5%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=9.14; p=0.002†; Fisher's exact: 0.021†		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=4.33; p=0.038†; Fisher's exact: 0.056‡	

*p<0.001.
†p<0.05.
‡p<0.1.

Table 5. The presence of sexual partners in households

	ART start (wave 0)	ART (wave 2)	Khayelitsha (wave 2)
Partner present in the household	22 (10.9%)	69 (34.2%)	94 (46.5%)
Testing the statistical significance of the difference between wave 0 and wave 2 of the ART sample	Pearson chi²=12.71; p=000*; Fisher's exact: 0.001†		
Testing the statistical significance of the difference between wave 2 of the ART and Khayelitsha samples		Pearson chi²=6.43, p=0.011†; Fisher's exact: 0.015†	

*p<0.001.
†p<0.05.

they were after their health had been restored by ART. This implies that significant numbers had returned to the parental home to receive care when they were sick with AIDS.

Our study goes beyond the existing literature on the relationship between AIDS and household structure, by showing that ART reverses the burden of care on kin. Our analysis showed that by wave 2, i.e. when ART patients had been stabilised on treatment, the ART sample and the matched Khayelitsha sample were indistinguishable with regard to the presence of mothers and sisters and parent-headed households. The shift in living arrangements away from parent-headed households and the declining presence of uterine kin is strongly indicative of the effect of ART on restoring health and independence for young adults living with HIV.

Fathers were less present than mothers (consistent with the broader socio-economic literature[11,12-17]), but even so, ART patients were more likely to be living in households with a father present when they were sick with AIDS than they were once their health had been restored. It is possible that all or some of these fathers were providing the kind of care and support found in other studies,[8,18,19] but our data do not speak to this issue.

There is some evidence to suggest that HIV stigma, rather than falling as a result of the ART rollout, may well have risen in Cape Town in the early- to mid-2000s. Using data from the Cape Area Panel Study of young adults, Maughan-Brown[31] found that AIDS stigma increased in the African population between 2003 and 2006 and that fear of infection was the key driver. We therefore hypothesised that the presence of sexual partners in the households of ART patients was likely to have increased over time as health was restored, but in the context of ongoing AIDS stigma and fear of infection, ART patients were probably less likely than their counterparts in the general population to be living with a sexual partner. This hypothesis was supported by the data.

These results are consistent with what we know about the potential for ART to restore health and promote greater independence for PLWHA. However, there may also have been push factors at work – notably, some ART patients may have been forced/encouraged to leave by other household members once they were able to take care of themselves. The fact that there were statistically significantly more single-person households in wave 2 (compared with wave 0 of the ART sample, and wave 2 of the Khayelitsha sample) is consistent both with ART patients exercising greater independence *and* potentially experiencing persistent stigma and subsequent social isolation.

We found that the number of ART patients with sexual partners rose over time, but compared with the matched comparison sample, ART patients were more likely to be living alone and without sexual partners, even after their health had been restored. This is suggestive of the continued existence of stigma against PLWHA. Medical professionals should

remain alert to the possibility that stigma may be affecting some of their patients, especially those living alone, and that they may be suffering from social marginalisation.

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GUIDELINE

Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update

by the Southern African HIV Clinicians Society

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Six years after the first Society guidelines were published, cryptococcal meningitis (CM) remains an important cause of morbidity and mortality among HIV-infected adults in South Africa. Several important developments have spurred the publication of updated guidelines to manage this common fungal opportunistic infection. Recommendations described here include: (1) screening and pre-emptive treatment; (2) laboratory diagnosis and monitoring; (3) management of a first episode of CM; (4) amphotericin B deoxycholate toxicity prevention, monitoring and management; (5) timing of antiretroviral therapy among patients with CM; (6) management of raised intracranial pressure; (7) management of relapse episodes of CM.

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List of recommendations

1. Screening and pre-emptive treatment
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5. Timing of ART among patients with CM
6. Management of raised intracranial pressure
7. Management of relapse episodes of CM.

Six years after the first Society guidelines were published,[1] cryptococcal meningitis (CM) remains an important cause of morbidity and mortality among HIV-infected adults in South Africa (SA).[2] Several important developments have spurred the publication of updated guidelines to manage this common opportunistic fungal infection. First, for the first time in December 2011, the World Health Organization (WHO) published a Rapid Advice guideline focused on the management of HIV-associated CM in resource-limited settings.[3] Second, cryptococcal screening, an old strategy that has been revisited to detect cryptococcal disease earlier and pre-emptively reduce mortality, is being implemented in a phased manner in SA[4] and is being considered in other African countries. Third, the diagnostic landscape for CM has changed with the introduction of a United States Food and Drug Administration (FDA)-approved cryptococcal antigen (CrAg) lateral flow assay (LFA), which is simple, accurate and useful as a point-of-care test.[5] Finally, several clinical trials, many undertaken in Southern Africa, have improved our understanding of issues such as which first-line antifungal regimens are best suited to a resource-limited setting,[6-9] when to start antiretroviral therapy (ART),[10,11] and how to safely administer amphotericin B deoxycholate,[12] which has been used by many more SA clinicians as first-line induction-phase treatment for CM in the last 5 years.[13]

1. Screening and pre-emptive treatment

Refer to Table 1 for a summary of this recommendation.

1.1 Background

Early diagnosis of HIV infection and early initiation of ART before immunosuppression is the most important strategy to reduce the incidence of CM and associated mortality. In SA, patients should initiate ART according to the current national guidelines.[14,15] However, screening for early cryptococcal disease and pre-emptive antifungal treatment may be a useful adjunctive strategy, because the median CD4$^+$ T-lymphocyte

Table 1. Summary of recommendation 1: Screening and pre-emptive treatment

Scenario	Recommendations
HIV-infected adults with CD4⁺ T-lymphocyte count <100 cells/µl	• Screen for cryptococcal antigenaemia on serum or plasma by reflex laboratory or clinician-initiated testing • If clinician-initiated testing is performed, screening should be restricted to ART-naive adults with no prior CM • Either the LA or LFA may be used as a screening test
HIV-infected children or adolescents	• There are insufficient data to recommend screening in this population
Patients with a **positive** CrAg test result	• Refer to Fig. 1 and recommendations 1, 3 and 5 regarding further investigations, antifungal treatment and timing of ART • If ART was started *before* the CrAg-positive result was received, follow the algorithm in Fig. 1, continue ART and monitor the patient very carefully for symptoms and signs of cryptococcal IRIS
Patients with a **negative** CrAg test result	• Evaluate for other opportunistic infections and start ART as soon as possible

ART = antiretroviral therapy; LA = cryptococcal latex agglutination test; LFA = cryptococcal lateral flow assay (dipstick); CrAg = cryptococcal antigen; IRIS = immune reconstitution inflammatory syndrome.

count among patients at the time of ART initiation remains low in SA.[16] The WHO, in their recently issued Rapid Advice guideline, indicated that routine screening for cryptococcal disease in ART-naive adults with a CD4⁺ T-lymphocyte count <100 cells/µl may be considered prior to ART initiation in populations with a high prevalence of cryptococcal antigenaemia.[3] In two ART cohorts in SA, the prevalence of newly-diagnosed antigenaemia among patients with a CD4⁺ T-lymphocyte count <100 cells/µl was 4% and 7%, respectively.[17] This is greater than the threshold above which screening was found to be potentially cost-saving in a Ugandan study.[18,19] To reduce disability and deaths associated with HIV infection, screening and pre-emptive antifungal treatment of cryptococcal disease has been suggested for routine implementation as part of the South African National Strategic Plan for HIV, STIs and TB, 2012 - 2016.[4] Primary azole prophylaxis for cryptococcal disease, in the absence of a screening programme, is not routinely recommended by the WHO.[3]

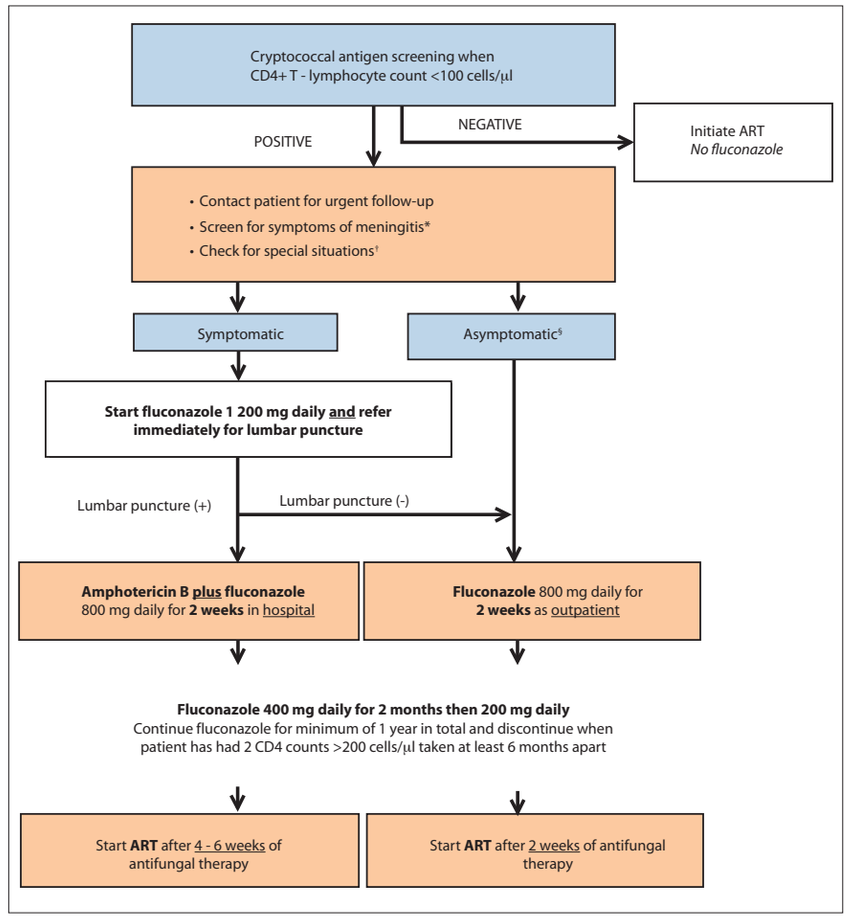

Fig. 1 Screen-and-treat algorithm for ART-naive adult patients with a CD4⁺ T-lymphocyte count <100 cells/µl.

** Symptomatic for meningitis if either of the following is present: headache; confusion.*

† Special situations include: prior cryptococcal meningitis; pregnancy or breastfeeding mothers; clinical liver disease.

§ A lumbar puncture may be considered if available.

1.2 Detailed recommendations

1.2.1 Who to screen

HIV-infected adults with a CD4⁺ T-lymphocyte count <100 cells/µl are recommended to be screened for cryptococcal antigenaemia. If screening is initiated by a clinician (medical practitioner or nurse trained in nurse-initiated management of ART (NIMART)) and not performed reflexively in the laboratory, then the expert panel recommends that screening be restricted to: ART-naive adults with CD4⁺ T-lymphocyte count <100 cells/µl **and** no prior CM. Although ART-experienced patients with a CD4⁺ T-lymphocyte count that remains <100 cells/µl may also be at risk for cryptococcal disease,[20] there is insufficient current evidence to routinely recommend screening ART-experienced adults. There are also insufficient data to recommend routine cryptococcal screening of HIV-infected children and adolescents, among whom the incidence of CM is much lower.[3, 21]

1.2.2 Screening strategies

The most cost-effective screening strategy has not yet been defined. Reflex laboratory screening, where blood samples with a $CD4^+$ T-lymphocyte count <100 cells/µl are automatically tested for CrAg, is being conducted at healthcare facilities in the Gauteng and Free State provinces in 2012/2013.[4] Screening initiated by clinicians is being conducted in other provinces such as the Western Cape.[4] Although the latex agglutination (LA) test has been more extensively evaluated for diagnosis of cryptococcal disease, the rapid LFA is equally valid as a screening test. The laboratory turnaround time is short for the CrAg screening test; however, initiation of ART should not be delayed unnecessarily while waiting for CrAg test results.

1.2.3 Management of CrAg-positive patients

The clinician should urgently evaluate CrAg-positive patients for symptoms and signs of meningitis, including headache and confusion (Fig. 1). For the management of symptomatic CrAg-positive patients, refer to recommendations 3, 4, 5 and 6. Patients *without* symptoms of meningitis may be offered a lumbar puncture (LP), if this is immediately accessible, to exclude early asymptomatic CM. For patients without suspected meningitis, oral fluconazole (800 mg for 2 weeks) followed by standard consolidation and maintenance treatment (refer to recommendation 3) is recommended; the same applies to patients with an LP that is cryptococcal test-negative. Among patients without signs or evidence of meningitis, ART is recommended to be started two weeks after antifungal therapy is initiated.

As part of the screen-and-treat algorithm (Fig. 1), CrAg-positive patients also need to be evaluated for the following clinical situations:

1.2.3.1 Prior CM

Patients with a history of CM do not need to be screened routinely as cerebrospinal fluid (CSF) and blood specimens may remain CrAg-positive for months to years. However, if a patient with prior CM is screened and found to be CrAg-positive and has new symptoms or signs of meningitis, a full evaluation should be undertaken for relapse disease (refer to recommendations 2 and 7). If the patient does not have new symptoms or signs of meningitis, the clinician should ensure that the patient has received or is receiving adequate fluconazole maintenance therapy (refer to recommendation 3). The serum/plasma (and CSF) CrAg test can remain positive for a prolonged period after successful treatment; therefore, if these tests are positive in the absence of symptoms and signs, this is not an indication of relapse.

1.2.3.2 Pregnant/breastfeeding women

Fluconazole is teratogenic (category D).[22] Women of child-bearing age who screen CrAg-positive should have a pregnancy test prior to starting fluconazole; those who are not pregnant and are started on fluconazole should be advised to avoid becoming pregnant during treatment. CrAg-positive patients who are pregnant should be offered an LP before a decision is made regarding management. If the patient has laboratory evidence of CM, then she should be treated for CM with amphotericin B. The risks, benefits and alternative to fluconazole treatment (i.e. ART and close clinical monitoring) should be discussed with the pregnant CrAg-positive patient *without* laboratory-confirmed CM and consultation with a medical practitioner who is experienced in the care of HIV-infected patients is recommended; in this context, consideration of factors such as the trimester and CrAg titre may be useful. For mothers who are breastfeeding, consultation with an experienced medical practitioner is also recommended as fluconazole can be transmitted in large amounts through breast milk to the infant.[22]

1.2.3.3 Clinical liver disease

Patients with a history of liver disease or with evidence of clinical liver disease deserve careful monitoring because fluconazole may cause liver injury. Consultation with a medical practitioner who is experienced in the care of HIV-infected patients is recommended.

2. Laboratory diagnosis and monitoring

Refer to Table 2 for a summary of this recommendation.

2.1 Background

Cryptococcus neoformans is the most commonly detected meningitis-causing pathogen in SA.[23] All adults with suspected meningitis should be investigated for CM. Patients with CM may present with fever as well as symptoms and signs related to inflamed meninges (including neck stiffness), raised intracranial pressure (including headache, confusion, altered level of consciousness, sixth cranial nerve palsies with diplopia and visual impairment, and papilloedema) and encephalitis (including memory loss and new-onset psychiatric symptoms).[24] Cutaneous lesions and pulmonary involvement (including cavitation, nodular infiltrates and consolidation) may also occur. Symptomatic relapses are common and are most often a result of inadequate or premature cessation of maintenance fluconazole treatment.[25] The incidence of CM is much lower among children;[21] African children with CM may present with an acute onset of illness and focal neurological signs may be less common.[26]

2.2 Detailed recommendations

2.2.1 Diagnosis of first CM episode

LP is required to establish an aetiological diagnosis of suspected meningitis. LP may also alleviate symptoms – such as headache, altered level of consciousness, and sixth cranial nerve palsies – that are a direct result of raised intracranial pressure. For a suspected first episode of CM, CSF should be submitted to the laboratory for a rapid test (either India ink or CrAg test) and fungal culture. If the India ink test is performed as the only rapid test and is negative, the laboratory should then perform a CrAg test (either LA or LFA). The sensitivity and specificity of CrAg tests (LA and LFA) are higher than of India ink.[3] *C. neoformans* can be cultured within 72 hours from the CSF of patients with a first episode. There is no need to routinely order a baseline CSF CrAg titre; most patients are diagnosed when the CSF fungal burden is high and antifungal treatment for a first episode is standardised and not influenced by the CrAg titre (refer to recommendation 3). If laboratory facilities are unavailable, a point-of-care LFA may be performed on CSF at the bedside.[5,27]

Antifungal susceptibility testing should not be requested for a first episode because antifungal drug minimum inhibitory concentrations (MICs) are invariably very low at first diagnosis[28] and, even if elevated, the relevance is difficult to interpret in this setting. If opening pressure was not measured at the time of the diagnostic LP, the LP should be repeated to measure the pressure once a diagnosis of CM is confirmed (refer to recommendation 6 for diagnosis and management of raised intracranial pressure).

2.2.2 Diagnosis of CM if focal neurological signs are present or if LP is not immediately available

Focal neurological signs are relatively uncommon in CM, except for sixth cranial nerve palsy. Where focal neurological signs are

Table 2. Summary of recommendation 2: Laboratory diagnosis and monitoring

Scenario	Recommendations
Diagnosis of first episode of suspected CM	• All adults with suspected meningitis should be investigated for CM • An LP should be performed to obtain CSF • CSF should be submitted to a laboratory for a rapid test (either India ink or CrAg test) and fungal culture • If opening pressure was not measured at the time of diagnostic LP, LP should be *repeated* to measure the pressure once a diagnosis of CM is confirmed (refer to recommendation 6 for the management of raised intracranial pressure) • The laboratory should routinely perform a CrAg test (either LA or LFA) when an India ink test is negative • If laboratory facilities are unavailable, a cryptococcal LFA may be performed at the bedside on drawing CSF • There is no need to routinely request a baseline CSF CrAg titre or antifungal susceptibility testing
Diagnosis of CM if LP is not immediately available or focal neurological signs are present	• Serum/plasma may be tested for CrAg to determine if the patient has disseminated cryptococcal disease • Patients with a positive serum/plasma CrAg test **and** symptoms and signs of meningitis should be empirically started on antifungal treatment (refer to recommendation 3) and referred to a centre where an LP and/or a CT brain scan can be performed
Diagnosis of subsequent episode of suspected CM	• A careful history should be taken and the patient should be assessed clinically for signs and symptoms of meningitis • An LP should be performed to obtain CSF • Opening pressure should be measured (refer to recommendation 6 for the management of raised intracranial pressure) • CSF should be submitted to a laboratory for prolonged fungal culture (minimum 14 days) (note: India ink and CrAg tests are not useful for the diagnosis of subsequent episodes of CM as they can stay positive for a prolonged period despite successful treatment) • Antifungal susceptibility testing may be considered in selected circumstances (see below and refer to recommendation 7)
Monitoring response to antifungal treatment	• Resolution of symptoms and signs can be used to monitor response to treatment • Unless there is a specific indication (e.g. persistent symptoms or signs suggesting late-onset raised intracranial pressure), LP should not be routinely performed after 14 days of antifungal treatment to document conversion of CSF from culture-positive to culture-negative* • CSF and serum/plasma CrAg titres should not be routinely monitored
Suspected antifungal drug-resistant isolate	• Consider antifungal susceptibility testing if a patient has had more than one relapse and the causes listed in Table 7 have been excluded (also refer to recommendation 7) • Fluconazole MICs should be determined at an academic or reference laboratory and interpreted by an experienced clinical microbiologist in conjunction with clinical findings
Screening for cryptococcal antigenaemia	• Refer to recommendation 1

CM = cryptococcal meningitis; LP = lumbar puncture; CSF = cerebrospinal fluid; CrAg = cryptococcal antigen; LA = latex agglutination test; LFA = lateral flow assay; MIC = minimum inhibitory concentration.

*If symptoms persist at or beyond 14 days, LP should be repeated to re-measure opening pressure, which may increase despite successful CSF sterilisation – refer to recommendation 6.

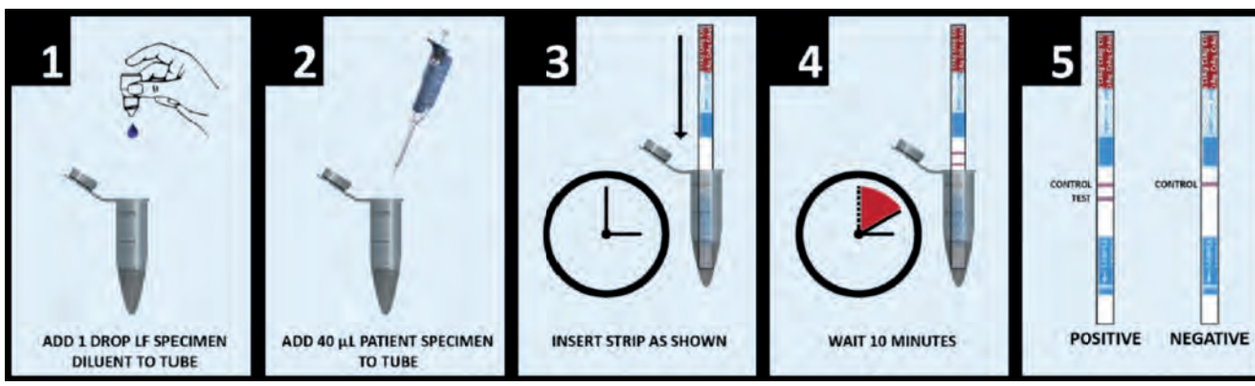

Fig. 2. Laboratory procedure to set up and read the cryptococcal antigen lateral flow assay (Immuno-Mycologics, Norman, OK) (source: Immy CrAg LFA package insert; reprinted with permission).

present, a CT brain scan should be performed first to exclude the presence of space-occupying lesions. If a CT brain scan cannot be performed immediately in the case of focal neurological signs, or if LP is not immediately available to make a diagnosis of meningitis, then serum/plasma may be tested for CrAg to determine if the patient has disseminated cryptococcal disease. Patients with a positive serum/plasma CrAg test **and** symptoms and signs of meningitis are very likely to have CM and should be started empirically on antifungal treatment (refer to recommendation 3). Patients without focal neurological signs should then be referred to a centre where LP can be performed, while patients with focal neurological signs first need to have a computed tomography (CT) brain scan, followed by an LP (if this is not contra-indicated by CT brain findings). Although aware that it may be difficult to access a CT brain scan in rural settings, the panel cannot recommend that an LP be performed in a patient with focal neurological signs without a scan.

2.2.3 Diagnosis of a subsequent episode of CM

A careful history should be taken including dates of previous episodes of CM and the patient should be assessed clinically for signs and symptoms of meningitis. An LP is indicated if the patient has signs and symptoms of meningitis. CSF should be submitted for fungal culture with plates incubated for at least 14 days to detect slow fungal growth. Rapid tests are not useful for diagnosis of subsequent episodes because both India ink and CrAg tests may remain positive for months to years even if treatment has been successful. Antifungal susceptibility testing may be considered in certain circumstances (see below and refer to recommendation 7).

2.2.4 Monitoring response to treatment

Resolution of symptoms and signs should be used to monitor response to treatment. LP should not be routinely performed after 14 days of antifungal treatment to document conversion of CSF from culture-positive to culture-negative, because the expert panel advises routinely changing from induction to consolidation phase treatment at 14 days. Given that the culture result takes several days (up to 14 days) to become available, the culture result will not affect the timing of this change. If symptoms persist at day 14, LP should be repeated to re-measure opening pressure, which may increase despite successful CSF sterilisation. Patients with raised intracranial pressure should be managed according to recommendation 6. CSF CrAg may remain positive for months to years and CrAg titres are not recommended to be routinely measured to monitor response to treatment. Serum/plasma CrAg titres are also not useful to monitor response to treatment.[29]

2.2.5 Suspected antifungal drug-resistant isolate

Antifungal susceptibility testing may be considered if the patient has had more than one relapse episode and the causes listed in Table 7 have been excluded. Isolates with elevated fluconazole MICs have been described occasionally from relapse episodes – especially where fluconazole monotherapy is initially given – and are unusual if amphotericin B-based induction treatment was administered during the first episode. As there are no established clinical breakpoints for *C. neoformans* and fluconazole, it is useful to test isolates from the initial and subsequent episodes in parallel at an academic or reference laboratory and document a four-fold (double-dilution) change in MIC,[14,16] which may suggest resistance. This requires storage of the initial isolate, which may not always be possible at a diagnostic laboratory. MICs should be interpreted by an experienced clinical microbiologist, in conjunction with the clinical history. Refer to recommendation 7 for the management of patients with fluconazole-resistant isolates. Non-susceptibility to amphotericin B is very unusual and susceptibility testing to this drug should not be requested.

3. Management of first episode of CM

Refer to Table 3 for a summary of this recommendation.

3.1 Detailed recommendations

The antifungal treatment of CM is divided into 3 phases: induction, consolidation and maintenance.

3.1.1 Induction phase (2 weeks)

Guidelines of the Infectious Disease Society of America (IDSA) and the WHO recommend the first choice for induction-phase treatment as: amphotericin B (0.7 - 1.0 mg/kg/dose) **and** flucytosine (100 mg/kg/day).[3,30] Unfortunately, flucytosine is not currently available in Southern Africa. The panel supports international advocacy efforts to provide greater access to flucytosine in resource-limited settings, particularly in light of the findings of a recently-published clinical trial in Vietnam showing improved survival among patients with CM treated with amphotericin B plus flucytosine v. amphotericin B alone.[9]

In the absence of flucytosine, the expert panel advocates that Southern African patients should be treated with the following induction therapy for the first two weeks: amphotericin B deoxycholate (1 mg/kg/day intravenous (IV) administration) plus fluconazole (800 mg *per os* (PO) daily). Among SA adults, the 1 mg/kg/day dose of amphotericin B is well tolerated.[31] The panel advises adding fluconazole (800 mg/day) during the induction phase in line with the WHO guideline; this is supported by evidence from a clinical trial that this combination is associated with a marginally superior rate of CSF clearance compared with amphotericin B alone, and evidence from two trials showing a non-significant decrease in mortality and neurological morbidity.[3,6,9,32]

Table 3. Summary of recommendation 3: Management of first episode of CM

Phase	Duration	Treatment
Induction	• 2 weeks	• Amphotericin B (1 mg/kg/day IV) **and** fluconazole (800 mg daily PO)
Consolidation	• 8 weeks	• Fluconazole (400 mg daily PO)
Maintenance	• Until the $CD4^+$ T-lymphocyte count >200 cells/μl for 6 months on ART and most recent viral load is suppressed (minimum 10 months)	• Fluconazole (200 mg daily PO)

IV = intravenous; PO = *per os*.

Where amphotericin B is unavailable or cannot be given safely, the patient should be transferred to a hospital where amphotericin B is available. It is reasonable to give a fluconazole dose of 1 200 mg PO daily while transfer is awaited.

In countries where amphotericin B is unavailable, the panel would advise clinicians to follow the WHO guideline with respect to high-dose fluconazole options.[3] However, in SA, all patients diagnosed with CM should have access to amphotericin B-based induction-phase treatment.

3.1.2 Consolidation phase (further 8 weeks)

The panel recommends 400 mg fluconazole PO daily for 8 weeks.

3.1.3 Maintenance phase

This is also termed secondary prophylaxis. The panel recommends 200 mg fluconazole PO daily for at least a further 10 months (i.e. until at least 12 months after treatment for CM was started). Maintenance fluconazole should only be stopped when the $CD4^+$ T-lymphocyte count is >200 cells/µl for at least 6 months and the most recent HIV-1 viral load is suppressed. Patients with CM should have 6-monthly $CD4^+$ T-lymphocyte measurements until fluconazole can be stopped.

3.1.4 Adolescents and children

A dose of 1 mg/kg/day amphotericin B should be prescribed during the induction phase. Fluconazole doses should also be calculated according to body weight. Induction phase: 12 mg/kg/day (up to 800 mg daily); consolidation phase: 6 - 12 mg/kg/day (up to 400 mg daily); maintenance phase: 6 mg/kg/day (up to 200 mg daily).

3.1.5 Baseline renal impairment

If patients have renal impairment at the time of diagnosis, this is not a contraindication to receiving amphotericin B deoxycholate at the standard dose (i.e. 1 mg/kg/day); however, creatinine should be monitored frequently and if it deteriorates significantly, then amphotericin B may need to be stopped and treatment continued with fluconazole monotherapy. When used as monotherapy during induction, the fluconazole dose would be 1 200 mg daily with normal renal function. With a creatinine clearance of 10 - 50 ml/min, the dose of fluconazole used as monotherapy should be reduced by 50% to 600 mg daily, and if creatinine clearance is <10 ml/min, fluconazole should be reduced to 400 mg daily. If the baseline renal impairment is thought to be due to dehydration, then intensive IV rehydration efforts should occur while starting amphotericin B. For the prevention, monitoring and management of renal impairment that develops during amphotericin B deoxycholate administration, refer to recommendation 4.

3.1.6 Patients receiving TB treatment

In contrast to previous guidelines, the panel does not recommend a fluconazole dose increase in patients receiving rifampicin, as the induction of fluconazole metabolism by rifampicin causes only moderate reductions in fluconazole exposure,[33] and because of the high doses of fluconazole that are initially being used.

3.1.7 Adjunctive corticosteroid therapy

The panel does not currently recommend adjunctive corticosteroid therapy in the initial management of CM. There is an ongoing international clinical trial that aims to address this question.[34] Refer to recommendation 7 for the use of corticosteroids in patients with immune inflammatory reconstitution syndrome (IRIS).

3.1.8 Immunological failure on ART

In patients who develop immunological failure while receiving ART and where the $CD4^+$ T-lymphocyte count drops <200 cells/µl after secondary prophylaxis has been stopped, the panel advises restarting fluconazole at 200 mg daily. Refer to the above section on maintenance-phase treatment for the duration of treatment.

3.1.9 Non-adherence to maintenance treatment

In patients who stop taking fluconazole maintenance prematurely and then return for care but are asymptomatic, the panel advises simply restarting fluconazole (200 mg daily) and monitoring closely for the recurrence of meningitis. Refer to the above section on maintenance-phase treatment for the duration of treatment.

3.1.10 Analgesia

Therapeutic LP is the best form of 'analgesia' for headaches associated with raised intracranial pressure. Paracetamol can be used, but not non-steroidal anti-inflammatory drugs (NSAIDs), due to the nephrotoxicity concern with amphotericin B deoxycholate. Morphine may also be appropriate and is not contraindicated in the presence of raised intracranial pressure.

4. Amphotericin B toxicity prevention, monitoring and management

Refer to Table 4 for a summary of this recommendation.

4.1 Background

Major adverse effects of amphotericin B deoxycholate include renal impairment due to renal tubular toxicity (usually in the second week of therapy), hypokalaemia, hypomagnesaemia, anaemia, febrile reactions and chemical phlebitis. Nephrotoxicity and electrolyte abnormalities may be prevented by pre-hydration, by avoiding concurrent use of other nephrotoxins (e.g. NSAIDs and aminoglycosides) and by routine administration of potassium and magnesium supplements. Phlebitis is very common in patients receiving amphotericin B and increases the risk of localised cellulitis as well as sepsis. Anaemia commonly occurs among patients receiving amphotericin B and can be clinically significant, particularly among those with a low baseline haemoglobin level. Haemoglobin decreases >2 g/dl occurred in 50 - 71% of patients over 2 weeks of treatment in an SA trial.[7] It is important also to exclude other treatable causes of anaemia and consider transfusion in symptomatic patients.

4.2 Detailed recommendations

4.2.1 Administration of amphotericin B deoxycholate

Amphotericin B deoxycholate powder (50 mg vials) should be refrigerated between 2°C and 8°C and protected from light.[35] The total daily dose of amphotericin B is calculated based on a dose of 1 mg/kg/day; amphotericin B deoxycholate powder from each 50 mg vial should be aseptically reconstituted in 10 ml of sterile water. The calculated volume of the concentrate (i.e. reconstituted drug in sterile water) should be injected into a 1 litre bag of 5% dextrose water and shaken to mix. Amphotericin B deoxycholate should **never** be mixed with normal saline or half-normal saline as it will precipitate. Once mixed, the solution (≤0.1 mg amphotericin B per 1 ml

Table 4. Summary of recommendation 4: Amphotericin B toxicity prevention, monitoring and management

Scenario	Recommendations
Administration of amphotericin B deoxycholate*	• Amphotericin B powder should be reconstituted in sterile water; inject the calculated volume of reconstituted drug in water into 1 litre of **5% dextrose water** and administer within 24 hours • Amphotericin B can be administered via peripheral IV line if the solution contains ≤0.1 mg amphotericin B in 1 ml of 5% dextrose water • A test dose is unnecessary • The solution should be infused over at least 4 hours
Prevention of amphotericin B deoxycholate-related toxicities	• Patients should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol) infused over 2 hours **before** the amphotericin B infusion† • Twice-daily oral potassium and daily oral magnesium supplementation should be administered (adults) • To minimise the risk of phlebitis, lines should be flushed with normal saline after amphotericin B infusion is complete and the infusion bag should not be left attached to the IV administration set after infusion is complete
Monitoring	• Baseline and twice-weekly creatinine and potassium (and magnesium, if available) • Baseline and weekly haemoglobin • Fluid input and output monitoring
Management of toxicities	• If creatinine doubles, then 1 dose of amphotericin B may be omitted or pre-hydration can be increased to to 1 litre 8-hourly. If creatinine remains elevated or repeatedly rises, then amphotericin B should be stopped and fluconazole used as suggested in recommendation 3 (baseline renal impairment section). • Febrile reactions can be treated with paracetamol (1 g) 30 minutes before infusion (if severe, hydrocortisone (25 mg IV) can be given before subsequent infusions)

IV = intravenous.

* For adolescents and children, drugs should be calculated by body weight.

† For children and adolescents, normal saline, with 1 ampoule of potassium chloride (20 mmol) added per litre of fluid, should be infused at 10 - 15 ml/kg over 2 - 4 hours (not more than 1 litre) prior to amphotericin B administration. If saline is unavailable, then other parenteral rehydration solutions, e.g. Darrow's solution or Ringer's lactate that already contain potassium can be used.

5% dextrose water for infusion through a peripheral IV line[22]) must be infused within 24 hours of preparation or discarded. A test dose is not recommended.[3] Protection from light with a brown bag is unnecessary.[35] The line that is used for amphotericin B infusion should not be used to administer other drugs simultaneously. The solution should be infused over 4 hours or more (infusion over <4 hours can result in cardiac complications). Once the infusion is complete, the line should be flushed with normal saline.

4.2.2 Prevention of amphotericin B deoxycholate-related toxicities

Patients should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol K^+ per 10 ml ampoule) infused over 2 hours before administration of amphotericin B deoxycholate. This reduces renal toxicity and hypokalaemia. Patients should be given 1 200 mg of potassium chloride twice daily (equivalent to 16 mmol of oral potassium, e.g. two Slow-K 600 mg tablets twice daily, 8 mmol K^+ per tablet) and up to one 500 mg magnesium chloride daily (e.g. two Slow-Mag 535 mg tablets daily, 5.33 mmol Mg^{2+} per tablet) for the duration of treatment with amphotericin B deoxycholate. Routine pre-emptive potassium supplementation should not be given to patients with pre-existing renal impairment or hyperkalaemia. To minimise the risk of phlebitis, lines should be flushed with normal saline after amphotericin B infusion is complete. The empty bag should not be left attached to the IV line. The IV line should be removed if the patient develops a fever after the infusion, or at the first sign of redness or discomfort at the insertion site. Febrile reactions may occur; to prevent recurrence, the infusion should be administered at a slow rate over the first half-hour while observing the patient closely, as treatment such as paracetamol may be required.

4.2.3 Clinical and laboratory monitoring

At minimum, for the duration of amphotericin B deoxycholate treatment, baseline and twice-weekly monitoring of serum creatinine and potassium, and baseline and weekly monitoring of haemoglobin are recommended. Renal toxicity is more likely to develop in the second week of treatment. Fluid input and output should be monitored carefully. Chemical phlebitis is often complicated by infection at the IV line insertion site, which can result in bacteraemia; the insertion site should be monitored by regular clinical examination, and febrile patients with a suspected insertion site infection should be appropriately investigated and managed.

4.2.4 Management of toxicities

For patients with significant hypokalaemia (serum K^+ <3.3 mmol/l), IV replacement is required: 2 ampoules of potassium chloride (20 mmol K^+ per 10 ml ampoule) in 1 litre of normal saline 8-hourly. Among those who develop hypokalaemia, serum potassium should be monitored daily until resolved. If hypokalaemia remains uncorrected, serum magnesium should be checked (if this test is available) and/or oral magnesium supplementation doubled. IV magnesium sulphate may be considered for persistent hypokalaemia and hypomagnesaemia. If serum creatinine doubles from baseline, one dose of amphotericin B deoxycholate may be omitted and/or pre-hydration may be increased to 1 litre of normal saline 8-hourly; serum creatinine should then be monitored daily. If serum creatinine improves, amphotericin B may be restarted at a dose of

0.7 mg/kg/day and alternate-day treatment could be considered. If creatinine remains elevated or repeatedly rises, amphotericin B should be stopped and fluconazole used as suggested in recommendation 3 (baseline renal impairment section). If febrile reactions occur, paracetamol (1 g) may be given 30 minutes before infusion, or for severe reactions, hydrocortisone (25 mg IV) can be administered before subsequent infusions.[22]

5. Timing of ART among patients with CM

Refer to Table 5 for a summary of this recommendation.

5.1 Detailed recommendations

All HIV-infected patients who are diagnosed with CM are eligible for co-trimoxazole preventative therapy and ART.

The panel recommends commencing ART 4 - 6 weeks after CM diagnosis, and strongly advises that ART not be delayed beyond 6 weeks after diagnosis; some panel members advise that clinicians should aim to start exactly 4 weeks after diagnosis of CM. Although most patients with CM have advanced immunosuppression with very low $CD4^+$ T-lymphocyte counts, two randomised clinical trials in sub-Saharan Africa have shown excess early mortality when ART was commenced while patients were still receiving induction-phase treatment for CM.[10,11] In the latter trial, conducted in Uganda and SA, patients who started ART 1 - 2 weeks after CM diagnosis had a 15% higher mortality rate than those who deferred ART until 5 - 6 weeks.[11] Another small trial showed possible excess IRIS in those patients who started early.[36]

The long in-hospital stay associated with amphotericin B therapy should be utilised for pre-ART counselling, identification of a treatment supporter and early referral to an ART clinic. Clinicians should aim to set up an ART clinic appointment within one week of discharge from hospital; this prevents delays in ART initiation beyond what is advised in this guideline. Patients initiated on ART should be counselled regarding the risk of developing IRIS. If a patient is referred to another facility for ART, then the need for fluconazole maintenance therapy should be communicated.

The panel recommends standard first-line ART regimens among patients with CM.[14,15] If nephrotoxicity occurred on amphotericin B, the renal function should be checked before starting ART to ensure that it has improved (creatinine clearance >60 ml/min) before commencing tenofovir. There are potential interactions between nevirapine and fluconazole, but studies have shown that these interactions do not affect the efficacy or toxicity of therapy.[37,38] The panel recommends checking ALT if symptoms of hepatitis or jaundice develop while patients are receiving fluconazole, but routine alanine transaminase (ALT) monitoring is not indicated.

The panel advises that, among patients who present with relapse of CM or a first CM episode after defaulting ART, ART is also restarted after 4 - 6 weeks.

One situation where ART may be delayed further is if a patient is still symptomatic with headaches at the visit when ART is due to be started. In such a situation, an LP should be repeated to measure pressure and fungal culture should be used to exclude persistent culture-positivity. ART should be deferred and such patients may require further LPs or amphotericin B therapy to ensure control of symptoms before starting ART.

Among patients who are serum/plasma CrAg-positive on screening, but do not have symptoms of meningitis and thus do not have an LP performed or have an LP that excludes CM, the panel advises starting ART 2 weeks after starting fluconazole (Fig. 1).

6. Management of raised intracranial pressure

Refer to Table 6 for a summary of this recommendation.

6.1 Background

Raised intracranial pressure occurs in ≤75% of patients with CM and is thought to result from obstruction of CSF outflow, resulting in build-up of CSF pressure.[39] It may be present at diagnosis of CM or develop while the patient is receiving treatment. It may cause severe headaches, vomiting, confusion or a depressed level of consciousness, ophthalmoplegia (particularly sixth cranial nerve palsies) and visual disturbance/loss. Clinicians need to consider raised intracranial pressure as part of the differential diagnosis and act appro-

Table 5. Summary of recommendation 5: Timing of ART among patients with CM

Recommendations
• Start ART 4 - 6 weeks after diagnosis of CM. The panel strongly advises that ART not be delayed beyond 6 weeks after diagnosis; some members of the panel advise that clinicians should aim to initiate ART exactly 4 weeks after diagnosis of CM.
• No adjustment in first-line ART regimen is required for patients who are ART-naive (unless renal dysfunction precludes the use of tenofovir).

Table 6. Summary of recommendation 6: Management of raised intracranial pressure

Recommendations
• Measure baseline opening pressure
• If opening pressure >25 cm H_2O, remove 10 - 30 ml of CSF
• Repeat LP whenever there are symptoms or signs of raised intracranial pressure (headache, vomiting, drowsiness, confusion, sixth cranial nerve palsy, visual disturbance)
• Daily therapeutic LPs may be required

CSF = cerebrospinal fluid; LP = lumbar puncture.

priately if a patient exhibits these symptoms or signs at any stage of CM management. To alleviate raised pressure, therapeutic LPs are indicated. New-onset hypertension may be a sign of increased intracranial pressure (i.e. Cushing's triad) and should prompt an LP to measure opening pressure instead of anti-hypertensive medications.

6.2 Detailed recommendations

It is good practice to measure the CSF opening pressure whenever a diagnostic LP is done. However, in practice the opening pressure will not have been measured at the initial diagnostic LP in CM. Thus, once the diagnosis of CM is made, an LP should be repeated to measure CSF opening pressure, particularly if the patient still has a headache (which is usually the case). The pressure should be measured with the patient lying down and without excessive spinal flexion. If the opening pressure is raised (>25 cm H_2O), then 10 - 30 ml of CSF should be drained (to normalise pressure to <20 cm H_2O or decrease the pressure by at least 50% – based on repeat measurements of closing pressure). Thereafter, the need for pressure relief should be dictated by the recurrence of symptoms of raised intracranial pressure. Patients may require daily LPs. Patients with raised intracranial pressure experience considerable relief of symptoms following therapeutic LPs. Approximately 15% of patients with initially normal intracranial pressure will develop raised intracranial pressure during treatment; therefore, all patients should be monitored daily for headache or signs of raised pressure that should prompt an LP.

Patients with persistent pressure symptoms and who fail to respond to serial lumbar punctures may require lumbar drain insertion or shunting procedures. Neurosurgical consultation should be sought.

In situations where manometers are not available, the panel suggests using a central venous pressure set manometer and attaching this to the LP needle using aseptic technique. In situations where this is also unavailable, if there are symptoms or signs of raised intracranial pressure due to CM (severe headache, drowsiness, sixth cranial nerve palsies), then the panel recommends performing an LP and removing 20 ml of CSF and repeating daily, if necessary.

Manometers can be ordered from Rocket Medical PLC (Tyne and Wear, UK) through Summit Surgical (Gauteng) (email: phil@acroteq.co.za or jim@wycliffe.edu; fax: +27 (0)86 565 6347).

7. Management of relapse episodes of CM

There are several possible reasons for the recurrence of symptoms of meningitis in patients treated for CM. In certain cases, recurrence is due to microbiological relapse, but situations exist where there is symptom recurrence but CSF fungal cultures are negative. The causes are summarised in Table 7.

When a patient presents with a recurrence, it is not always possible immediately to be sure of the aetiology. Assessment should include:

- Assessment of adherence to fluconazole consolidation and maintenance-phase treatment (self-reported and pharmacy refill data)
- To support an IRIS diagnosis, an enquiry as to whether the patient recently started ART
- An LP to measure opening pressure, assess CSF inflammation and for a prolonged fungal culture (14 days) – there is no role for India ink staining or CSF/serum/plasma CrAg assays in establishing the cause of recurrence, as these may remain positive for months (years even) in patients after successful treatment (refer to recommendation 2)
- If the CSF is culture-positive and non-adherence does not appear to be the cause, then fluconazole susceptibility testing should be considered (refer to recommendation 2) and should be performed in a reference laboratory; the panel recommends this especially when there has been more than one relapse, despite reported good adherence.

If the cause of the recurrence is attributed to non-adherence, then the patient should be treated as for the first episode. The reasons for non-adherence should be explored and the patient should receive additional adherence counselling, preferably with a treatment supporter. If the patient also defaulted ART, this should be re-initiated 4 - 6 weeks after presentation. ART may need to be adjusted if there is concern that there has been virological failure on first-line ART.

Paradoxical cryptococcal IRIS occurs among patients treated for cryptococcal disease who start ART and develop a recurrence or worsening of the clinical manifestations of cryptococcal disease. IRIS is thought to be the result of an immunopathological reaction directed at residual cryptococcal antigen at sites of the disease.[40] IRIS occurs, on average, 6 weeks after ART is commenced, but delayed cases (even more than a year after ART initiation) are described.[41] IRIS affects approximately 20% of patients with cryptococcal disease who start ART, and mortality may be substantial.[42] The most frequent manifestation is a recurrence of the symptoms of meningitis, often with raised intracranial pressure. Typically, the CSF fungal culture is negative at the time of IRIS presentation; IRIS represents

Table 7. Possible causes of recurrent symptoms and signs of meningitis in CM

- Non-adherence to fluconazole consolidation or maintenance treatment
- Non-adherence to ART
- Paradoxical IRIS
- 'Breakthrough' of *C. neoformans* growth in CSF without laboratory evidence of resistance
- Ongoing raised intracranial pressure without one of the above (i.e. isolated mechanical problem)
- Virological failure on ART after having stopped fluconazole maintenance treatment
- Resistance to fluconazole (this is uncommon if amphotericin B induction therapy is used)
- Other diagnoses (e.g. TB meningitis)

ART = antiretroviral therapy; CSF = cerebrospinal fluid; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis.

an immunological reaction rather than a microbiological recurrence. However, in cases where induction therapy was recent (<2 months), the CSF fungal culture may still be positive. Other cryptococcal IRIS manifestations include lymphadenitis and cryptococcomas.[40]

In all patients with **suspected paradoxical CM IRIS**, an LP should be performed to measure pressure and obtain a fungal culture incubated for up to 14 days. It is not possible to make a diagnosis of IRIS with certainty prior to excluding microbiological relapse on CSF fungal culture. **If the symptoms are mild**, the panel recommends performing therapeutic LPs if there is raised intracranial pressure, providing analgesia and increasing the fluconazole dose to 1 200 mg daily with regular review and follow-up of the CSF fungal culture result. If the CSF fungal culture is negative, the dose of fluconazole can be reduced back to what it was (400 mg or 200 mg daily depending on the timing of the CM IRIS event). **If patients with suspected CM IRIS have severe symptoms** or deteriorate with the approach above, the panel recommends treating with amphotericin B (1 mg/kg/day IV) plus fluconazole (800 mg PO daily) until the CSF culture is confirmed as negative. If the CSF culture is still negative after 7 days of incubation, amphotericin B can be stopped. If the fungal culture is positive by 7 days, then amphotericin B should be continued for 14 days. Daily therapeutic LPs may be required if the opening pressure is raised. A CT head scan should be considered, as mass lesions and cerebral oedema can occur with IRIS. Analgesia should be provided. For patients with severe IRIS who do not respond to the above treatment, corticosteroids (e.g. prednisone 1mg/kg/day PO or dexamethasone IV) should be considered. The panel recommends that corticosteroids preferably be used among patients with IRIS who are documented to be CSF fungal culture-negative and when other aetiologies are excluded; however, if there is life-threatening neurological deterioration, corticosteroids should be started immediately.

In patients with CM due to fluconazole-resistant isolates, subsequent management should be discussed with a medical practitioner experienced in the treatment of CM. Such patients should receive induction therapy with amphotericin B again. Consolidation and maintenance options depend on the fluconazole MIC and include high-dose fluconazole with or without weekly amphotericin B infusions or voriconazole.

In patients with multiple relapses, it is important to document the conversion of CSF from culture-positive to culture-negative before stopping amphotericin B. Such cases should be discussed with an experienced medical practitioner and fluconazole susceptibility testing should be performed (refer to recommendation 2).

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CASE REPORT

Managing AIDS-related Kaposi's sarcoma and pregnancy

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An estimated 30 - 40% of HIV-infected patients are likely to develop cancer during the progression of their disease. The occurrence of malignancy among these patients represents a difficult challenge in their care. Kaposi's sarcoma (KS) – currently the most common tumour observed with an estimated incidence of 15 - 20% – represents the first manifestation of AIDS in 30 - 40% of patients. Any organ may be involved, but the gastrointestinal tract and lung remain the most frequently involved locations. The case described here presented a clinical and ethical dilemma where visceral KS, pregnancy and medical complications required multi-disciplinary management.

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A 24-year-old woman was referred to the Division of Oncology at a large academic hospital. She had presented recently at a local hospital with a history of progressive shortness of breath, and had received treatment for atypical, multilobular pneumonia. She was diagnosed with HIV in 2009 when she presented with severe mucocutaneous Kaposi's sarcoma (KS) as her AIDS-defining disease. She was pregnant at the time of her initial diagnosis, and received 4 cycles of bleomycin/vincristine chemotherapy after delivering a healthy term infant. This was followed by an additional 14 cycles of chemotherapy, which was discontinued when her KS lesions demonstrated a good clinical response.

She returned 6 months later with KS progression and was re-challenged with the ABV regime (doxorubicin, bleomycin and vincristine) for 6 cycles. She reached the tolerance dose of bleomycin, and chemotherapy was discontinued. A large lesion behind her left earlobe was treated with a short course of palliative external beam radiotherapy (EBRT).

In February 2012, KS progression was visible, this time involving the genital area, mouth and lymph nodes. Again, she was challenged with combination chemotherapy containing doxorubicin and vincristine for 4 cycles, with no clinical benefit, and palliative EBRT was offered to problematic lesions of the vulva and left foot.

In June 2012 she was admitted to the high-care unit with a 2-month history of progressive, grade IV dyspnoea, intermittent cough, and bleeding from a palatial KS lesion in her mouth. She was 27 weeks pregnant and had been treated at a local hospital for pneumonia and started on anti-tuberculosis (TB) treatment 2 weeks earlier.

On inspection, the patient was acutely ill with signs of a hyper-dynamic circulation and peripheral oedema. Physical examination revealed bilateral coarse crepitations, wheezes and the use of accessory respiratory muscles. A large, bleeding, nodular KS lesion was observed, involving most of the hard palate and oropharynx. Abnormal laboratory studies revealed reduced haemoglobin (7.8 g/dl), raised C-reactive protein (75.0 mg/l), low albumin (26 g/l), raised fibrinogen (4.4 g/l), raised D-dimer (1.34 mg/l) and raised lactate dehydrogenase (368 U/l) levels and a low CD4 count (137 cells/µl). A standard blood culture was negative. A routine chest X-ray (CXR) revealed bilateral opacities infiltrating predominantly the perihilar peribronchovascular interstitium of both lungs (Fig. 1).

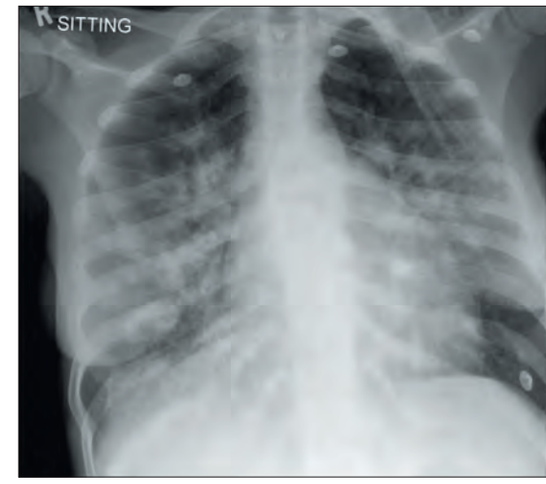

Fig. 1. Chest X-ray showing bilateral KS opacities infiltrating predominantly the perihilar peribronchovascular interstitium (these may often be mistaken for opportunistic infections).

According to the AIDS Clinical Trials Group (ACTG) staging system, the patient was classified as a poor-risk stage IV (T1,I1,S1)

HIV/AIDS patient with a problem list of: (*i*) HIV-infected since 2009, receiving antiretroviral therapy (ART); (*ii*) CD4 count of 137 cells/µl; (*iii*) 2 weeks of anti-TB treatment; (*iv*) KS since 2009 (for which she received multiple cycles of chemotherapy and palliative EBRT); (*v*) current presentation of bilateral, multi-lobular infiltrates on a CXR with a high index of suspicion of lung KS involvement; (*vi*) early signs of early diffuse intravascular coagulation (DIC); and (*vii*) pregnancy (28 weeks).

Management

A multi-disciplinary team (MDT), comprising a high-care medical team, oncologist, obstetrician and the HIV/infectious diseases personnel, was required for optimal management.

Intravenous antibiotic therapy (clarithromycin), concurrent ART (tenofovir, efavirenz and lamivudine) and anti-TB (rifafour) supportive treatment were continued, with the addition of trimetroprim-sulfamethoxazole as *Pneumocystis jyroveci* prophylaxis, as the patient's current CD4 count was <200 cells/µl. Continuous positive airway pressure (CPAP) was required as she became entirely dependent on the support system to maintain breathing. Sub-cutaneous heparin was administered during her hospital stay.

On day two post admission, she reported no fetal activity and an obstetric consult confirmed an intra-uterine death. She went into spontaneous labour and delivered a premature, stillborn microcephalic fetus (weighing 1 380 g).

Her bleeding KS mouth lesion was controlled with adrenaline gauze. Due to her poor performance status, low CD4 count, resistant KS, extent of KS disease and poor prognosis, no active chemotherapy management was offered. She died 3 hours post delivery due to extensive KS and respiratory failure.

Discussion

In sub-Saharan Africa, where many patients access ART with advanced HIV disease, AIDS-related KS presents with a high tumour burden and rapid disease progression, resulting in a life expectancy of <6 months.[1] KS involving the lung presents as shortness of breath, fever, cough, chest pain and haemoptysis, or as an incidental finding on a CXR.[2]

A prognostic index can guide therapeutic options for AIDS-related KS, including: immune status (CD4 count); patient age; AIDS-defining disease on presentation; and the presence of co-morbid conditions. Patients with a favourable prognostic index can be treated initially with ART alone. Systemic chemotherapy is warranted in advanced, systemic or rapid, progressive KS disease. Several chemotherapeutic agents – e.g. bleomycin, vincristine, vinblastine, and an anthracycline (doxorubicin) – have activity in the treatment of KS, but in the developed world, liposomal doxorubicin and a taxane group constitute the backbone of current systemic chemotherapy against KS.[1,3,4] In all cases, an objective response of 70 - 80% can be obtained with various combinations of chemotherapy. Partial responses and clinical benefit are frequently observed, but relapses often occur when treatment is stopped.[3,5]

Our patient initially received a combination of bleomycin and vincristine, and was re-challenged with the ABV combination when her KS progressed. Unfortunately, treatment with systemic chemotherapy comes at a cost: both bleomycin and doxorubicin have a maximum tolerable dose before long-term complications become evident. In addition, bleomycin may induce alveolitis and pulmonary fibrosis, and there is evidence of accelerated pulmonary dysfunction in lung KS patients who received bleomycin.[6] Doxorubicin is associated with irreversible cardiac damage (congestive heart failure and cardiomyopathy) when the maximum dose of ≥450 mg/m^2 is exceeded.

The patient described here had reached the maximum tolerable dose of both bleomycin and doxorubicin. She developed progressive KS during the last 4 cycles of doxorubicin-based therapy; therefore, it may be postulated that her KS became resistant to anthracycline chemotherapy. As both liposomal doxorubicin and the taxane drugs are not available in the public healthcare sector, second-line chemotherapy could not be offered.

The incidence of pregnancy-associated malignancy ranges from 0.02 - 0.10%; the most common malignancies diagnosed during pregnancy are gynaecological, haematological and skin cancers (malignant melanoma). Malignancies in pregnancy present the MDT with an ethical conflict between the optimum management of the cancer and preservation of the pregnancy.[7] For most of these cancers, chemotherapy is necessary to achieve a cure or efficient palliation of cancer-related symptoms. The consequence of chemotherapy and/or EBRT during the first trimester is high (congenital malformation or spontaneous abortion), and termination of pregnancy v. delayed treatment should be discussed with the patient. Chemotherapy treatment during the second and third trimesters follows the standard chemotherapy guidelines, but delivery should be timed during a non-neutropaenic period and care should be taken to time the last cycle of treatment at 32 weeks of gestation. However, patients remain at high risk and this warrants careful monitoring.[8]

The patient described in this case presented with a 28-week pregnancy, but had received chemotherapy and EBRT during the first trimester when she was unaware of her pregnant status. This resulted in an intra-uterine death and early clinical DIC that concluded in a spontaneous delivery, probably due to maternal hypoxia and the abnormal fetus (microcephaly). Few studies are available concerning *in utero* chemotherapy-exposed neonates. In one study, the mean gestational age at delivery was 35.8 weeks, the mean birth weight was 2 647 g, and 4% of infants were born with a congenital abnormality.[8,9]

Conclusion

This case highlights the clinical complications and ethical dilemma associated with advanced KS in pregnancy. The MDT plays an important role in securing optimal care for patients with advanced HIV disease, malignancy and associated pregnancy.

Conflict of interest. None.

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CASE REPORT

HIV sero-conversion during late pregnancy – when to retest

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The South African National Prevention of Mother-to-Child Transmission of HIV programme has resulted in significant reductions in vertical transmission, but new infant HIV infections continue to occur. We present two cases of HIV seroconversion during late pregnancy, demonstrating the limitations of the current programme. These could be mitigated by expanding the programme to include maternal testing at delivery and at immunisation clinic visits as we pursue the elimination of mother-to-child transmission.

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In order to identify HIV-infected women and offer antiretroviral (ARV) prophylaxis, the South African National Prevention of Mother-To-Child Transmission (PMTCT) of HIV programme recommends 2 HIV tests during pregnancy: at the first antenatal visit and at 32 weeks of gestation.[1] We present two cases that suggest that additional HIV testing strategies are needed to help eliminate the mother-to-child transmission of HIV.

In a longitudinal study on HIV-exposed infants, we recruited infants whose mothers were known to be HIV-infected post partum along with a control group of infants born to HIV-negative women. All women delivering at the Kraaifontein Midwife Obstetric Unit were eligible for enrolment. HIV-exposed infants were matched with HIV-unexposed controls within one month of birth. Mother-infant pairs were recruited within three days of delivery and a $CD4^+$ T-cell count was performed on all women regardless of HIV status. In accordance with the study protocol, the infants were reviewed at 2 weeks of age and regularly thereafter. At the 2-week visit, the HIV status of the uninfected mothers was confirmed with an HIV rapid assay using finger-prick blood (Alere Determine HIV 1/2).

Recently, HIV infection was identified on the rapid tests at the 2-week visit in 2 women (Table 1). According to antenatal clinic documentation, both tested negative during pregnancy: at booking (at 21 weeks and 28 weeks of gestation, respectively) and at 32 weeks of gestation, as recommended in the national guideline.[1] Neither infant was born before 38 weeks of gestation. The HIV rapid assay in use in the antenatal clinic at the time was the First Response HIV1-2-0 Card Test (Premier Medical Corporation Ltd, India). According to policy, only a single test is required to screen for HIV. Positive screening tests are confirmed with a second rapid assay (ABON HIV 1/2/0 Tri-Line HIV Rapid Test Device).

Both women elected to breastfeed, although one mother switched to infant formula after one week owing to poor feeding. Her $CD4^+$ T-cell count at delivery was 680 x 10^6 cells/l. Her infant was symptomatic at age 2 weeks and was immediately hospitalised, requiring transfer to the intensive care unit. An HIV DNA polymerase chain reaction (PCR) test (Amplicor HIV-1 DNA prototype assay 1.5) at 2 weeks was positive.

The $CD4^+$ count of the second woman was 157 x 10^6 cells/l at delivery. Her baby was well and the HIV DNA PCR at 2 weeks was negative. Daily nevirapine (NVP) for the infant was initiated and the mother was referred for combination antiretroviral therapy (cART) which was commenced within 2 weeks.

Discussion

These two cases raise concerns about antenatal HIV screening and the implications for vertical transmission. As expected, neither woman received any ARV prophylaxis.

A recent Medical Research Council (MRC) report on the effectiveness of the national PMTCT programme in South Africa[2] demonstrated that, among mothers who reported being HIV-negative, 4.1% had infants who were HIV-exposed at 4 - 8 weeks (measured by the presence of HIV antibodies in the infants' blood). A 2007 surveillance study in KwaZulu-Natal (KZN) found that 6.9% of infants whose mothers reported a negative HIV status had similar evidence of exposure (i.e. the

Table 1. Patient characteristics

Patient	Maternal age (years)	Gestational age, first ANC (weeks)	Gestational age, first HIV test (weeks)	Gestational age, second HIV test (weeks)	Infant date of birth	Maternal CD4$^+$ count at birth (x10^{6}cells/l)	Feeding choice	Infant PCR test at 2 weeks
1	29	21	21	32	31/10/2012	680	Breast	Positive
2	23	28	28	32	05/11/2012	157	Breast	Negative

ANC = antenatal clinic visit; PCR = polymerase chain reaction.

presence of HIV antibodies in the infants' blood).[3] Of concern is that the vertical transmission rate in this group was high (31% v. an overall rate of 20.2% at that time).

It is possible that some women knew, but did not admit their HIV-positive status. However, the KZN study was anonymous, and the MRC report demonstrated a high uptake of HIV testing and disclosure, making it unlikely that this scenario contributed significantly to the observations.[2,3] Moreover, the two subjects described here each had HIV-negative results for rapid tests on two different occasions.

Alternatively, there may have been a problem with the HIV rapid antibody assay, including that the tests were conducted within the window period. Antibodies to HIV can be detected at 2 - 3 weeks after infection by fourth-generation laboratory enzyme-linked immunosorbent assay (ELISA) tests, which detect both antibody to HIV and p24Ag (Fiebig stage II and III).[4] The third-generation rapid tests have a window period of three to four weeks post infection (Fiebig stage III).[4,5] Testing during this time will yield a false-negative result. The reported sensitivity and specificity of the First Response HIV 1-2-0 Card Test are 100% and 98.8% when used correctly[5] within the WHO recommended range of >98%.[6] In our subjects, this explanation could only apply to the second assay at 32 weeks, and would indicate recent acquisition of infection. The rapid assay may have recorded a false-negative result for the second test. All batches of rapid tests are validated by the National Institute for Communicable Diseases (NICD) on a panel of laboratory samples, but they have not been validated in pregnant women specifically or in the field. Assay sensitivities have been reported between 87% to 95% in clinics depending on the product.[2,7] More data are therefore required to assess and validate HIV rapid assays in pregnant women, and to ensure the quality of testing at clinic level. Importantly, there is no quality-control procedure for negative rapid tests.

The most likely explanation for our findings is true acquisition of HIV during pregnancy and breastfeeding. Pregnancy poses an increased risk for HIV acquisition by women, even after adjustment for behavioural and other factors; it is possible that the hormonal and other biological changes associated with pregnancy play a role.[8] High viral loads during primary HIV infection increase the risk of vertical transmission *in utero*, peri partum and post partum,[9,10] especially in the absence of ARV prophylaxis. In studies in Botswana and SA, new mothers with negative HIV test results or of unknown HIV status were tested immediately post partum or at infant immunisation visits. The results demonstrated a seroconversion rate of 2.4 - 7.9% during pregnancy and post partum.[2,7,11,12] These women are at high risk of vertical transmission.[13-15] In addition, they are more likely to use mixed feeding practices, placing their infants at greater risk for HIV infection.[2,16-18] 'Mixed feeding' refers to the use of breast milk in addition to other fluids (infant formula, water, tea) for infant feeding. The increased incidence of mixed feeding observed in these women is presumably because, having tested HIV-negative, they perceive no risk.

Repeat HIV testing of mothers during late pregnancy, at delivery or at the clinic immunisation visits, would identify women who acquire HIV during pregnancy and in the early post-partum period. The HIV diagnosis of infants whose mothers tested negative during pregnancy is often delayed,[18] with significant implications for morbidity and mortality.[19] Most SA women deliver at a healthcare facility[20] and 99% attend the 6-week vaccination visit.[2] Moreover, testing at these time-points shows high uptake,[11,21,22] while offering HIV tests to both partners may identify discordant couples and allow counselling on HIV prevention.[2] A proviso to this is increasing evidence that, even within discordant partnerships, a significant number of new HIV infections arise from extra-couple transmission.[23]

Conclusion

While the elimination of mother-to-child transmission of HIV is feasible, it will require a modification of current protocols/guidelines to include repeat HIV testing of women at delivery and/or post partum, a quality-control strategy for laboratory testing of a small percentage of negative rapid tests, involvement of male partners in testing and counselling, and an emphasis on exclusive feeding practices, regardless of HIV status.

Ethics approval. The Mother Infant Health Study (MIHS) is approved by the Ethics Committees of Stellenbosch University and the University of British Columbia.

Conflict of interest. None.

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CASE REPORT

Progressive HIV infection in the presence of a raised CD4$^+$ count: HIV/HTLV-1 co-infection

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There are a number of pathophysiological causes for a normal or raised CD4 count in the context of progressive HIV infection. These include various co-infections, previous splenectomy, and lymphoproliferative disorders. Such circumstances can both confound HIV diagnosis and delay initiation of chemoprophylaxis and highly active antiretroviral therapy (HAART). We describe the case of a patient co-infected with HIV and human T-cell lymphotropic virus type 1 (HTLV-1) who, prior to HAART initiation, was found to have progressive immune deficiency associated with a raised CD4 count.

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A 51-year-old married man from Gauteng province, South Africa (SA), originally from the Northern Cape, tested HIV-positive on an enzyme-linked immunosorbent assay (ELISA) in March 2002 as part of a routine medical examination for insurance purposes. His CD4$^+$ count was 794 cells/µl and his HIV viral load was 19 365 copies/ml. He gave no history of any infectious diseases, but was receiving treatment for hypertension. On examination he was generally healthy, with normal vital signs and all systems proved unremarkable. On account of being asymptomatic with a CD4$^+$ count within normal range, he was neither initiated on highly active antiretroviral therapy (HAART) nor chemoprophylaxis, and was told to follow-up with his general practitioner for regular immune monitoring (Table 1).

An abnormally high CD4$^+$ count was detected on follow-up in September 2002 prompting T-cell receptor polymerase chain reaction (PCR) studies, which revealed no

Table 1. CD4⁺ and HIV viral load monitoring (2002 - 2009)

Date	CD4⁺ count (cells/µl)	CD4⁺ (%)	HIV-1 viral load (copies/ml)
March 2002	794	15.0	19 365
September 2002	6 043	15.6	59 900
March 2003	4 891	13.9	31 400
September 2003	7 775	17.0	37 200
November 2003	7 799	21.0	58 300
June 2004	5 893	15.0	252 000
April 2006	13 820	23.1	133 281
September 2008	12 731	23.6	1 226 897
January 2009	2 875	73.0	494 510
April 2009	6 939	72.0	1 920
October 2009	1 973	61.1	Undetectable (<20)

evidence of a clonal T-cell lymphoproliferative disorder. A bone-marrow biopsy was also performed and showed non-malignant T-cell hyperplasia. No further studies were conducted and expert opinion from HIV clinicians recommended that no antiretroviral therapy (ART) be given at that stage.

In January 2009 the patient was referred to us with a history of weight loss, fatigue and night sweats. On examination, he had increased reflexes affecting the right leg, with weakness in both arms; otherwise, examination was essentially normal. Magnetic resonance imaging of the spine revealed a collapsed vertebra at T9; a biopsy showed a chronic inflammatory process but no granulomata. On account of the history and clinical presentation, spinal tuberculosis (TB) was considered and TB treatment was commenced. Furthermore, despite the high CD4⁺ count, it was felt that the patient would benefit from ART on account of being clinically immune-compromised and having a high HIV viral load. He was initiated on a regimen of Truvada (tenofovir/emtricitabine) and efavirenz (EFV) to which he responded well with a drop in RNA copies/ml of >2 $\log_{10}$ after three months of treatment and an undetectable HIV viral load six months thereafter. As the CD4⁺ count remained above normal limits, repeat bone marrow and flow cytometry studies were carried out, identifying a population of T-lymphocytes with abnormal flow characteristics. T-cell receptor PCR showed the presence of a clonal cell population and bone marrow histology revealed infiltration by tumour cells with scattered atypical uninucleated cells and binucleated Reed-Sternberg cells. Immunophenotypic analysis showed no overt evidence of a B-cell lymphoproliferative disorder. Antibodies to human T-cell lymphotropic virus type 1/2 (HTLV-1/2) were detected by ELISA and the patient was diagnosed with a smouldering type of adult T-cell leukaemia/lymphoma (ATLL) secondary to HTLV-1 infection (HTLV-2 not being associated with this condition). He was treated with four cycles of infusional chemotherapy consisting of etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (EPOCH), which he tolerated well. Interferon-alpha therapy was subsequently commenced and mantained three times per week. At the time of writing, the patient is clinically well with no neurological deficits, an undetectable HIV viral load and a CD4⁺ count of 4 430 cells/µl.

Discussion

HTLV-1 was the first retrovirus to be identified in humans and is structurally related to other viruses within the retroviridae family, such as HIV-1 and HIV-2, sharing similar routes of transmission. Since its discovery in 1979 three additional human deltaretroviruses (HTLV-2, HTLV-3 and HTLV-4) have been found, but only HTLV-1 and HTLV-2 have so far been associated with human disease. Antibodies to HTLV-1 were first identified in SA in 1984 and the first report of isolation of the virus was published in 1988.[1,2] Subsequently, a number of seroprevalence studies have been conducted in SA, where HTLV-1 has been found to be endemic in areas of Mpumalanga, the Eastern Cape, Free State and KwaZulu-Natal (KZN).[3,4] However, there are no recent representative data regarding prevalence in the general SA population or specific patient subgroups.[5]

Like other human retroviruses, HTLV-1 causes a lifelong infection of T-lymphocytes, in particular CD4⁺ cells. However, unlike HIV, the immunological hallmark of HTLV-1-infected individuals is a sustained proliferation of T-cells driven by the HTLV-1-encoded Tax protein.[6] The subsequent transactivation of cellular genes by the Tax-encoded region can result in malignant transformation, although this is rare.[7] In the majority of cases, cytotoxic T-cells effectively control the virus by lysis of infected lymphocytes, which in turn results in the release of inflammatory cytokines that can be pathogenic.[6] On account of these various pathophysiological mechanisms, HTLV-1 is associated with a diverse range of pathology, including malignant disease, inflammatory syndromes and infective complications.[6] A number of these conditions have been described in SA, including ATLL, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infectious dermatitis.[8-10] Although the life-time risk for HTLV-1-associated diseases in general is considered close to 10%, an indication of a long history of viral-human co-evolution,[6] this may be an under-representation when the interaction between HTLV-1 and other infective agents is considered. TB has been found to occur more frequently in patients infected with HTLV-1 and is also thought to be associated with a worse prognosis.[6] HTLV-1 has been shown to up-regulate hepatitis C viral replication and is implicated as a co-factor in the development of hepatocellular carcinoma. Furthermore, two studies have demonstrated an increased rate of cervical carcinoma in HTLV-1-infected patients.[7] Whether HIV-1 co-infection with HTLV-1 is associated with a faster progression to AIDS remains a contentious issue, although a number of studies have suggested as much.[11] What is, however, less controversial and perhaps of greater relevance is the effect of HTLV-1 on T-lymphocytes, and in particular, its association with CD4⁺ lymphocytosis in HIV-1 co-infected patients.[12,13]

In general, lymphocytosis can be classified as belonging to one of two groups: either a reactive polyclonal proliferation, which can be caused by a variety of infective agents, hypersensitivity reactions, autoimmune conditions and splenectomy, or a clonal expansion as a result of a lymphoproliferative disorder. In the context of HIV co-infection, lymphocytosis has been described during early seroconversion associated with CMV, as well as in HIV/HTLV-1 co-infection where $CD4^+$ lymphocytosis can be caused by both a reactive or clonal expansion. Consequently, patients with untreated HIV-1 who are co-infected with HTLV-1 show a dissociation between immunological and virological markers. That is to say, HIV-1/HTLV-1 co-infected patients have been found to progress to AIDS with a high HIV viral load, but in the presence of a normal or higher than normal $CD4^+$ count (both absolute and percentage).[12] A recent study in Mozambique demonstrated that co-infected pre-HAART adult patients were seven times more likely to have $CD4^+$ counts >500 cells/µl (median 525 cells/µl) than HIV mono-infected patients.[13] However, as these $CD4^+$ cells are likely to be functionally altered, associated with a loss of naive cells and a higher activation pattern, $CD4^+$ lymphocyte counts in HIV-1/ HTLV-1 co-infected patients cannot be considered to be a reliable marker of immunological competence.[12] Furthermore, $CD4^+$ counts can be dramatically raised on account of ATLL (i.e. clonal expansion), which occurs in ≤5% of HTLV-1 infections.[6] As most cases of ATLL develop in individuals infected early in life through breastfeeding,[6] it is probable that our patient was already infected with HTLV-1 when he first presented in 2002 with a $CD4^+$ count of 794 cells/µl. Whether initiation of HAART at this juncture would have prevented the development of ATLL cannot be determined. However, it is thought that zidovudine (AZT) may protect HTLV-1-infected peripheral blood mononuclear cells from immortalisation on account of its genotoxic/mutagenic properties.[14]

The last sizeable HTLV-1 seroprevalence study in SA was conducted in northern KZN in 1993; a prevalence of 2.6% was found among the general population.[4] In the same study an HIV-1 prevalence of 3.5% was noted. As the risk factors for HTLV-1 and HIV are shared, an epidemiological association between these two retroviruses is to be expected. In 1996, HTLV-1 was found in 2% of asymptomatic urban black people in the Free State, but in 6% of HIV-seropositive patients from the same region.[3] More recently, and alarmingly, in a small retrospective study of 170 HIV-positive plasma specimens collected between 2007 and 2008 from Limpopo, 24% of specimens tested positive for HTLV-1/2 antibodies by ELISA.[15] Unfortunately, further testing to confirm the diagnosis or differentiate between HTLV-1 and HTLV-2 infection was not performed. Nevertheless, these findings highlight the evident gap in current knowledge and the need for clinicians to be aware of retroviruses other than just HIV.

Conclusion

A $CD4^+$ lymphocyte count cannot always be considered to be a reliable marker of immunological competence in HIV-infected people, especially in patients co-infected with HTLV-1. Normal or raised $CD4^+$ counts in such persons can be on account of reactive or clonal expansion of T-lymphocytes and can confound HIV diagnosis and delay initiation of chemoprophylaxis and HAART. As we lack up-to-date epidemiological data but know that certain areas in SA are endemic for HTLV-1, we suggest maintaining a high index of suspicion of HTLV-1 infection in all HIV-positive adult patients in Southern Africa. In particular, HIV-positive persons who are clinically immune-compromised and have a raised $CD4^+$ count should be tested for HTLV-1, as well as patients who present with clinical features in keeping with ATLL, HAM/TSP or infective dermatitis. As locally available serological tests are unable to differentiate HTLV-1 and -2, a PCR or western blot analysis may be required subsequent to a positive HTLV-1/2 ELISA test to confirm the diagnosis and distinguish between HTLV-1 and -2. Furthermore, the decision to initiate HAART in co-infected patients is better determined by clinical stage and HIV viral load than $CD4^+$ count.

More research is needed to understand the epidemiology of HTLV-1 infection in Southern Africa; not only with regard to co-infections such as HIV-1/ HTLV-1 and TB/ HTLV-1, but also in terms of the wider public health impact, including implications for PMTCT practices and safety of the blood supply.

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CASE SERIES

Clinical challenge: Deteriorating liver function in TB and HIV co-treatment

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Editor's note: In this section of the *Journal*, we present complex, real-world HIV medicine cases to two experienced clinicians working in very different environments, and ask them to describe the approach that they would take if they saw the case in their local hospital setting. In our first edition, a patient with deteriorating liver function is presented by Prof. Francois Venter and Dr Ntsakisi Masingi, and then discussed by Dr Sarah Stacey in Johannesburg and Dr Sarah Fidler in London.

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Case

Prof. F Venter and Dr N Masingi

A 30-year old male taxi driver (CD4$^+$ count 5 cells/µl) presented with a vague history of weight loss and night sweats. He had received tuberculosis (TB) treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) for one month. He was initiated on antiretroviral therapy (ART) including tenofovir, lamivudine and efavirenz.

The clinician involved was concerned about the low CD4$^+$ cell count, and brought the patient back for follow-up after 4 weeks. At that time, the patient said he felt much better. Objectively, the patient had gained 4 kg and was slightly jaundiced. He had no hepatomegaly and there were no other clinical findings. The clinician phoned the patient after receiving his 4-week blood test results, and asked him to return for follow-up. His blood test results before and after ART initiation are summarised in Table 1. Five weeks after ART initiation, the clinical examination results were unchanged. The patient refused inpatient care, as he had to drive his taxi.

With this background, we put the following questions to our clinical experts in Johannesburg and London:

- How would you practically manage this patient at your institution, with available resources?
- What would be your top differential diagnoses?
- What would make you change your management plan, if anything, as you implement it?
- Is there anything that may emerge over time that would worry you?

Response

Dr S Stacey (Johannesburg)

I would consider, as possible causes of this common problem:

- A drug reaction to:
  - TB therapy
  - ART
  - prophylactic co-trimoxazole
- TB-IRIS reaction
- Ingestion of other hepatotoxic substances including traditional medicines
- Acute viral infections.

I would prefer to investigate and manage the patient as an inpatient in the infectious diseases ward, especially because of the long waiting list for outpatient investigations, but would not insist on admission if the patient adamantly refused.

I would stop the TB therapy and co-trimoxazole and repeat the liver function tests (LFTs) after 5 - 7 days. Co-trimoxazole can cause a cholestatic picture alone or a hepatocellular and cholestatic pattern together. Due to the very rapid rise in liver enzymes, I would also stop ART. Although I think the prescribed antiretrovirals (ARVs) are the less likely suspects and he is asymptomatic, he is also jaundiced and his enzymes are more than five times the baseline value. Efavirenz has been associated with liver failure and liver fatalities.

Other blood tests would include repeat viral hepatitis serology for types A, B and C to exclude recently acquired acute hepatitis, a cytomegalovirus (CMV) polymerase chain recation (PCR) test, full blood count and differential and inflammatory markers.

I would question the patient about the use of over-the-counter and traditional medicines and alcohol, and advise him to discontinue their use.

In the meantime, I would use a liver-sparing regimen for TB therapy, consisting of an aminoglycoside, moxifloxacin and ethambutol. I have chosen these drugs because although none of them are as effective as rifampicin or isoniazid (INH), I would like to

Table 1. Patient blood test results before and after ART initiation

	Time relevant to ART initiation		
Result	**1 week before**	**4 weeks after**	**5 weeks after**
Hb (g/dl) (normal 12 - 15)	9	8.5	8
Platelets (normal 140 - 400)	500	480	450
Bilirubin	Normal	10 x normal	10 x normal
AST	2 x normal	8 x normal	10 x normal
ALT	3 x normal	8 x normal	10 x normal
GGT	2 x normal	10 x normal	10 x normal
ALP	2 x normal	10 x normal	10 x normal
INR			Normal (1.1)
Creatinine clearance	Normal	Normal	Normal
Urine dipstix	Normal	Bilirubin, protein	Bilirubin, protein
Hepatitis B/C screening serology	Negative		
Viral load (copies/ml)	1 000 000	2 000	
$CD4^+$ cell count (cells/µl)	5	50	

ART = antiretroviral therapy; Hb = haemoglobin; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; INR = international normalised ratio.

ensure that I am still providing a combination that is effective in the continuation phase. I would substitute dapsone for co-trimoxazole, because dapsone is not associated with liver injury.

If the patient's liver enzymes showed signs of improvement on this regimen, I would wait until they approached normal and then reintroduce the TB drugs one at a time (although we are usually anxious to restart full TB therapy as soon as possible because we believe that liver-sparing treatment is less effective than standard therapy). We still do not restart pyrazinamide in these patients, but I would attempt to reintroduce both INH and rifampicin, although we have noticed that some patients tolerate reintroduction of full TB therapy with the fixed-dose combination (FDC). It is also much more practical to prescribe the FDC, as single drugs are only available at tertiary sites and, even there, are not stocked consistently. If the patient tolerated TB therapy, I would attempt to reintroduce ART using the same regimen.

I would request an ultrasound of the liver as well, but booked on an outpatient basis, this investigation may be several weeks away at our hospital. Hypodense lesions in the liver, associated with lymphadenopathy, and splenic lesions could suggest TB-immune reconstitution inflammatory syndrome (TB-IRIS), although the initial diagnosis of TB was sufficiently vague to make other (unmasked) infections of the liver worth considering, such as fungal infections, non-tuberculous mycobacterial infections and viral infections like CMV. Depending on the results of the ultrasound, I would proceed to recommend a liver biopsy and/or magnetic resonance cholangiopancreatography (MRCP) if the patient's liver functions did not improve off medication.

Response

Dr S Fidler (London)

First, I would take a full history – plus a sexual history – to exclude other sexually transmitted infections (STIs) that could affect liver function (e.g. hepatitis B and C virus, which could be acute infections even though he was initially antibody-negative), and ask about travel to consider other acquired co-infections, other family or close contacts who were unwell, other medications, over-the-counter medications, recreational drugs and especially alcohol. I would ask about malaena, gastrointestinal symptoms, nausea, vomiting and fevers.

Blood tests to add: repeat hepatitis A, B and C; CMV PCR; Epstein-Barr virus (EBV); toxoplasmosis; STI screen; syphilis; drug levels (efavirenz, rifampicin); and bacterial and mycobacterial blood cultures.

My differential diagnosis would include: a drug reaction to either co-trimaoxazole, any TB drug or ART – most likely efavirenz or tenofovir, alcohol or other medication not disclosed.

Other causes, if all of the above were excluded, could include lymphoma (a very low $CD4^+$ cell count suggests long-standing untreated HIV).

I would admit the patient to hospital for investigation and observation, exclude other causes, and treat as diagnosed. If he declined admission and his liver dysfunction continued, I would advise him to stop driving his taxi – especially if alcohol abuse was suspected, or LFT results were increasingly abnormal. If he continued to decline admission, I would repeat his LFTs and clotting three times a week. I would arrange an urgent liver ultrasound scan, and potentially magnetic resonance imaging (MRI), depending on the outcome of the ultrasound. I would do a regular review of the patient in the outpatient clinic to ensure that there was no clinical evidence of hepatic failure

or encephalopathy. If there was any evidence of liver failure, I would admit the patient.

As the patient's LFTs were increasingly abnormal, I would stop all drugs. The goal is to reintroduce drugs, preferably individually, prioritising TB treatment first, but preventing other opportunistic infections in view of the patient's severe immunosuppression. I would anticipate that once all drugs were stopped, the LFT results would return to within normal limits.

I would then review the patient's treatment options for both TB and HIV. This would include the use of GeneXpert for determining TB drug sensitivities and HIV genotyping, including integrase and tropism (this should be available from the baseline sample taken on all new HIV-positive individuals) prior to restarting therapy. The first priority would be TB treatment: based on the test results, I would restart an effective regimen for TB, introducing single agents with close monitoring of LFTs and clotting (three times weekly). Once the patient was established on TB treatment, I would re-start his ART regimen: I would check the viral genotype to confirm whether or not there was any drug resistance and determine the potential for other ART options. Ideally, tenofovir/emtricitabine/efavirenz would be the preferred option in view of TB drug interactions and available safety data, but I would monitor LFTs and therapeutic drug levels. If efavirenz was the potential cause of abnormal LFTs, I would consider triple nucleosides while the patient was receiving TB drugs or potentially, but cautiously, raltegravir with tenofovir/emtricitabine, although there are fewer data on interactions, so the patient would require close monitoring of viral load (VL). I would avoid PIs altogether due to drug interactions. If, despite starting ART, there was clinical or ultrasound evidence suggestive of TB-IRIS, I would consider adding steroids to treat the suspected IRIS, while continuing TB treatment and ARVs unchanged.

Final outcome

Prof. F Venter and Dr N Masingi

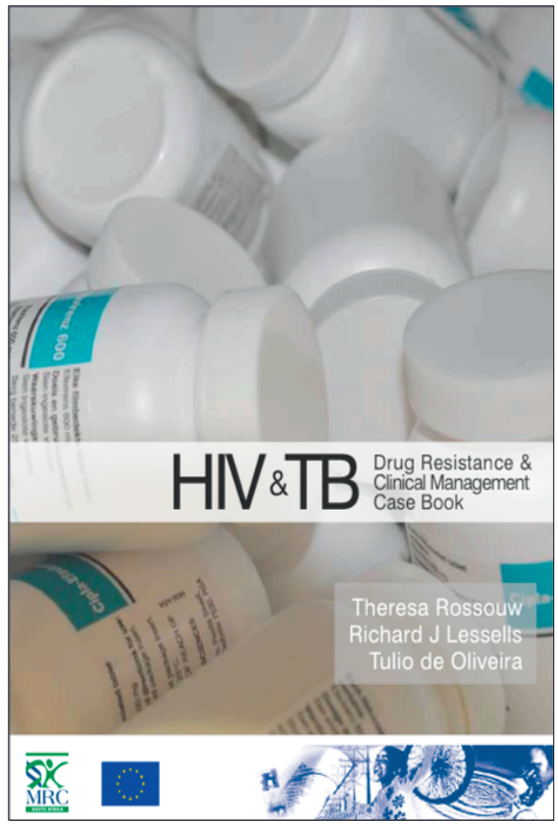
We elected to continue the ARVs and TB continuation phase treatment, phoning the patient daily to make sure he was alright. We were a little suspicious about the use of traditional medicines (he seemed unsure when we asked him), so we asked a counsellor to speak to him, who agreed that he may be using something. We then gave him general counselling about unknown drug interactions, and showed him his LFT results and how they were deteriorating. We were worried about the patient driving a taxi (on efavirenz, potentially encephalopathic), but he had no objective signs of liver failure, his international normalised ratio (INR) remained normal, suggesting his liver synthetic function was still alright – and he was not prepared to stop driving. An ultrasound three weeks later showed liver and splenic micro-abscesses, so the patient could also have had a TB-IRIS reaction. He is fine now, with a $CD4^+$ count >300 cells/µl, an undetectable VL 8 months later, he is still driving his taxi, but we never proved TB.

These cases are hard, but access to additional and repeated laboratory investigations and rapid radiology can help. The differential diagnosis of drug toxicity, TB-IRIS, toxin or new opportunistic illness all look alike, and if the patient's LFTs had continued to decline, we would have stopped all treatment and slowly re-introduced his TB medication, then ART, once his LFTs had settled.

BOOK REVIEW

'HIV & TB Drug Resistance & Clinical Management Case Book'

by T Rossouw, R J Lessells, T de Oliveira. Cape Town: South African Medical Research Council, 2013. ISBN 978-1-920014-91-9.



South Africa (SA) is home to the highest number of HIV-infected people in any country, and has the largest HIV treatment program worldwide, with 2 million patients currently receiving combination antiretroviral therapy (ART). The country also has a massive tuberculosis (TB) epidemic, and TB/HIV co-infection is a common challenge for clinicians. The increasing number of patients who are infected with drug-resistant strains of TB and/or HIV in Southern Africa poses a mounting threat to successful treatment. Drug-resistance testing for patients failing therapy is available at reference laboratories, which contrasts the situation in many countries in sub-Saharan Africa. This provides an important tool to protect the sustained effectiveness of available TB and HIV therapies; however, interpretation of drug resistance reports is complex and expert guidance to clinicians may be required for optimal clinical management.

In this context, the recently published *HIV & TB Drug Resistance & Clinical Management Case Book* by Rossouw, Lessells and de Oliveira, is an important aid to clinicians in SA and beyond, who are managing complex cases of patients with HIV and TB drug resistance. It provides a comprehensive background to the development of drug resistance as well as up-to-date clinical knowledge on how to diagnose and manage drug-resistant infections. The book uses an instructive case-based learning approach, with 14 HIV and 6 TB cases. After a brief review of technical details, each clinical case is presented in a structured manner. The description of the case is followed by the clinical chart and drug-resistance results. The drug-resistance report is translated into a clear and evidence-based recommendation for clinical management. Lessons from each case are excellently summarised in 'key learning points'. The cases cover diverse and illustrative examples of adult and paediatric patients with therapy failure, thus addressing actual problems that clinicians will deal with in daily practice.

Many of the cases in the book highlight errors in management that contributed to the emergence of drug resistance. These 'preventable' cases of drug resistance provide important lessons; avoiding these mistakes will advance clinical practice and benefit patients. Preventing acquired drug resistance in patients receiving treatment will also have major public health consequences, as these cases are the source of onward transmission of drug resistance to newly infected individuals.

A common feature of the HIV cases is that they used the SATuRN RegaDB drug resistance database to construct a complete clinical chart and resistance report for each patient. This database conveniently summarises all clinical and laboratory information into a clinical chart including treatment history, CD4 counts and viral load results. It also interprets the drug-resistance genotype using the Stanford HIVDB algorithm. The SATuRN information management system provides an excellent example of how bioinformatics tools can be utilised to the benefit of the physician and patient.

In conclusion, this book is an excellent practical compendium of knowledge in the field of HIV and TB drug resistance, set in the highly relevant context of Southern Africa where drug-resistant strains of HIV and TB are increasingly reported. It provides expert guidance in difficult clinical situations and explains the steps to be taken to prevent the emergence and transmission of drug resistance. This book highlights the fact that education and training are fundamental steps in the implementation of technologies such as viral-load and drug-resistance testing, so that they can be used to full advantage.

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Conflict of interest. Both authors are clinicians and investigators in the PharmAccess African Studies to Evaluate Resistance (PASER) network established in sub-Saharan Africa to monitor HIV drug resistance.

CPD QUESTIONNAIRE

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True (A) or false (B):

Regarding 'men who have sex with men (MSM)-appropriate' health services in South Africa (SA):

1. Local evidence suggests that there are high rates of HIV among the population of MSM.
2. Biologically, unprotected vaginal sex is more likely than unprotected receptive anal sex to transmit HIV.
3. For a health-provision site to be considered MSM-appropriate, services need to be friendly, sensitive and competent.

With regard to managing AIDS-related Kaposi's sarcoma (KS) and pregnancy:

4. In sub-Saharan Africa, KS with pulmonary manifestations generally has an associated life expectancy of <6 months.
5. Patients with a favourable prognostic index should be treated with a combination of antiretroviral therapy (ART) and systematic chemotherapy immediately.
6. Liposomal doxorubicin and a taxane group constitute the backbone of current systemic chemotherapy against KS in the developed world.

Regarding screening for suicide risk among HIV-infected persons in the immediate post-diagnosis period:

7. HIV-infected individuals are at higher risk of suicidality than the general population in SA.
8. A number of psychometric, clinical and biological measures to detect suicide risk have made it simple to measure and predict this risk accurately.
9. Self-reported screening tools provide an adequate evaluation of suicidality.

Regarding the challenges to delivering quality care in a prevention of mother-to-child transmission (PMTCT) of HIV programme in Soweto, SA:

10. Knowledge of PMTCT interventions in SA is high among pregnant women and healthcare providers.
11. Challenges in scaling up PMTCT services in the SA public healthcare sector relate to coverage at different steps of the PMTCT cascade, and also to the quality of care rendered in the PMTCT services.
12. ART initiated pre-conception decreases the risk of mother-to-child transmission of HIV significantly.
13. Disclosure of HIV status is unrelated to PMTCT intervention uptake and adherence among women.

Regarding HIV sero-conversion during late pregnancy and when to retest:

14. Pregnancy poses an increased risk for HIV acquisition by women.
15. High viral loads during primary HIV infection increase risk of vertical transmission *in utero*, peripartum and post partum.
16. The two HIV tests recommended during pregnancy – one at the first antenatal visit and one at 32 weeks of gestation – are adequate to identify all new HIV infections in pregnant women.

Regarding HIV/human T-cell lymphotropic virus type 1 (HTLV-1) co-infection:

17. Co-infections, previous splenectomy, and lymphoproliferative disorders are among the pathophysiological causes for a normal or raised $CD4^+$ count in the background of a progressive HIV infection.
18. HIV-1/HTLV-1 co-infected patients have been found to progress to advanced clinical disease with a high HIV viral load but in the presence of a normal or higher than normal $CD4^+$ count.

Regarding parental presence within households and the impact of ART in Khayelitsha, SA:

19. Young adults with advanced HIV disease are likely to rely on and live with their families for support, but this can be reversed after initiation of ART.

Regarding ART adherence clubs as a long-term retention strategy for clinically stable patients receiving ART:

20. The ART adherence club model leads to better adherence and long-term retention in care for clinically stable ART patients compared to usual clinical services.

INSTRUCTIONS

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

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