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- Guideline: Management of drug-induced liver injury in HIV/TB co-infected patients
- HIV risk behaviour among TB patients in public primary healthcare
- Analysis of HIV-related mortality data in a tertiary neurology unit
- Optimal time to start ART after cryptococcal meningitis

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MESSAGE

From the Editor

Call for submissions: A decade of antiretroviral therapy in the public sector

For the last 13 years, the *Southern African Journal of HIV Medicine* (*SAJHIVMED*) has provided state-of-the art updates and indepth local insights into both the population-level impact of the HIV epidemic and the management of HIV-infected and at-risk individuals across Southern Africa. The history of the Journal is intertwined with the expansion of access to antiretroviral therapy (ART) across South Africa and the region. As 2014 marks the 10-year anniversary of the public sector roll-out of ART services in South Africa, *SAJHIVMED* is planning a special edition to reflect on the lessons and celebrate the achievements during this time.

As part of this, *SAJHIVMED* is calling for submissions from healthcare workers, policy makers and researchers for this special edition. Contributions of all shapes and sizes are welcome. We are particularly interested in 'reflections' from clinicians on the ground – providing insight into the realities of delivering ART to increasing numbers of patients under difficult circumstances. These submissions can take the form of short editorials of 500 - 1 000 words commenting on individual experiences of providing HIV care and treatment services at all levels of care. If you are interested, please submit these pieces by 1 December 2013 via the Journal website (http://www.sajhivmed.org.za), or feel free to email me directly at the address below.

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MESSAGE
From the Executive

Fellow HIV Clinicians, by now I am sure that most of you know that the World Health Organization (WHO) issued new guidelines. One of the most important differences is that these guidelines suggest initiating HIV-positive individuals on antiretroviral therapy (ART) at a $CD4^+$ count of 500 cells/μl. This has caused much debate. With fixed-dose combination (FDC) treatment (one pill once daily) and medications with low side-effect profiles now available, many of the arguments for delayed therapy have fallen away. However, there is no clear clinical evidence of a benefit to starting ART earlier. There is a transmission-prevention benefit in discordant couples as shown in the HPTN 052 study. The National Department of Health has not yet adopted the WHO guidelines, and for those of you who treat patients in the private sector, our advice is to provide careful adherence counselling, as you would to anyone initiating ART. If a patient has a $CD4^+$ count of 350 - 500 cells/μl and is committed to therapy, has thought through the issues around lifelong adherence and is committed, then – if funding permits – start. However, if there is any doubt about the capacity of an individual to adhere to treatment, delay ART until he/she is ready.

This edition contains a consensus statement on drug-induced liver injury (DILI) resultant from tuberculosis (TB) therapy. This statement has been a long time coming. We gathered together a group of specialists in the area, which was much like herding cats. We debated the various strategies and weighed the evidence, which is not extensive. A consensus was reached; we hope that you will find the statement useful. We will review the statement every couple of years; undoubtedly, there will be changes in the future. As we went through this process, I was struck by the paucity of research in the area of TB. Anyone of us who has treated TB has seen a case of DILI, but there are so few high-quality studies to help chose the best strategy for management.

Finally, I know it seems far away, but the Southern African HIV Clinicians Society's second clinical conference is scheduled for 24 - 27 September 2014. Please add this event to your diary and make plans to attend. The last one was outstanding and we are already working very hard to ensure that the next one is even better …

Francesca Conradie
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FORUM

Starting ART following cryptococcal meningitis: The optimal time has yet to be defined

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Ever since the public sector rollout of antiretroviral therapy (ART) in 2004, the question of the optimal time to start ART following diagnosis of an opportunistic infection has aroused controversy among South African HIV clinicians and researchers.

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Patients with cryptococcal meningitis (CM) in Southern Africa present with median CD4$^+$ counts <50 cells/μl,[1-4] with a high prevalence of co-morbidities such as tuberculosis (TB) and Kaposi's sarcoma. In this context, the challenge is to balance the competing risks of morbidity and mortality from each additional week of advanced immunosuppression – well demonstrated in South African (SA) HIV cohorts waiting to start antiretroviral therapy (ART)[5] – with those from immune reconstitution inflammatory syndrome (IRIS) occurring within the confined space of the central nervous system, when ART is commenced in the presence of a high fungal antigen load.[6,7]

The first Southern African CM guideline[8] published in 2008 recommended treatment with 1 mg/kg/day amphotericin B for 2 weeks – a regimen known to drive down the cryptococcal burden rapidly in cerebrospinal fluid (CSF), with many patients having sterile CSF by day 14.[1] At this time, given the lack of evidence regarding ART timing in CM, it was recommended to start ART 2 - 4 weeks after commencing amphotericin B.[8] This window pragmatically coincided with the timing of hospital discharge, and the switch from amphotericin induction therapy to consolidation with fluconazole, with the aim of having asymptomatic patients with sterile or almost-sterile CSF counselled and ready to start ART at outpatient follow-up 4 weeks into antifungal therapy.

Since 2007, two randomised controlled trials (RCTs) of ART timing following CM have been completed in Africa. In the first, conducted by Makadzange *et al.*[9] in Zimbabwe, patients receiving fluconazole monotherapy for CM were randomised to start ART at ≤72 h v. 10 weeks.[9] The study found excess mortality in the immediate ART arm, most probably due to IRIS, although this information was not collected systematically.[9] Notwithstanding this trial's small sample size and large early loss to follow-up,[10-12] it confirmed the clinical impression that starting ART extremely early was harmful, but it did not provide guidance on what to do in the context of amphotericin-based treatment, nor provide information on ART timing between 3 days and 10 weeks, which represent a far earlier and far later ART-initiation time-point, respectively, than most clinicians would consider in practice.

The Cryptococcal Optimal ART Timing (COAT) trial[13] conducted in Uganda and SA was designed to address these questions, randomising patients treated with amphotericin-based induction (1 mg/kg/day amphotericin B with 800 mg/day fluconazole) to early (1 - 2 weeks, median 8 days) v. deferred (4 - 6 weeks, median 36 days) ART. The trial was halted prematurely (N=177 patients randomised) due to excess mortality in the early ART arm, with the most pronounced difference in mortality occurring between days 8 and 30 after CM diagnosis: 21/75 (28%) early ART v. 8/80 (10%) deferred ART (hazard ratio 3.1; p<0.01). This difference occurred despite an apparently similar incidence of CM-IRIS in the two groups (13% v. 10%).[13]

Based on significant differences in mortality in an RCT conducted in an African context following amphotericin treatment, the 2013 Southern African HIV Clinicians Society guidelines committee felt compelled to move the recommended ART start window to 4 - 6 weeks, in line with the delayed ART group of the COAT trial. This generated some debate among panel members, with some favouring the 4-week time-point.

For all the clear advantages of RCT data, the two ART timing studies do not say anything about a preference between the better-performing study arm and intermediate time-points such as 2, 3 and 4 weeks – they only tell us that the worst-performing arms (i.e. during the first 2 weeks of induction therapy) do not represent the right time to start. Ten weeks

was not prioritised over 6 weeks in the Makadzange *et al*. study,[9] and 5 weeks was not prioritised over 3 or 4 weeks in the COAT trial.

We are unlikely to have any further ART timing RCTs for CM in the near future, given the large cohorts required to power an RCT of ART start at 2 v. 4 weeks post CM treatment. Thus, we may need to edge towards a preferred time based on observational clinical cohort data. In successive SA clinical trial cohorts between 2005 and 2010,[1-4] in which all patients received amphotericin-based induction treatment, with our SA partners we have gradually decreased the median time to ART start from CM diagnosis from 6 weeks[1] to just 23 days (in our latest trial).[4] Despite the concerns of confounding by historic trends in the severity of CM and HIV of patients at presentation, in all four studies[1-4] the median $CD4^+$ count was <50 cells/μl, the median baseline fungal burden was high (approximately 5 $\log_{10}$ CFU/ml in the CSF), and the percentage of altered mental status – the most significant indicator of poor prognosis in CM – ranged from 13% to 37%, with the latest trial[4] enrolling those with the highest rates.

One-year survival analysis of the combined cohort from the four trials (*N*=171 patients), who started ART at a median of 31 days (interquartile range 23 - 46) following a CM diagnosis, showed an earlier flattening of the survival curve in those who started ART within 1 month compared with those who started beyond 1 month.[7] Despite an association of day-14 fungal burden and subsequent CM-IRIS, there was no association of earlier ART initiation and IRIS, and patients who developed IRIS did not have a higher mortality. While CM was the presumed cause of 85% of the deaths in the first 2 weeks, the majority (67%) of deaths after 2 weeks were attributed to other illnesses related to advanced immunosuppression, which might have been prevented through earlier ART initiation.

The absence of RCT evidence favouring the 2 - 4-week time-points does not translate into evidence against these time-points. Our clinical cohort data and experience in managing HIV patients with CM in the SA setting makes us strong advocates of an ART start time of 4 weeks from CM diagnosis: a time-frame that is being applied in a recently commenced phase III randomised trial of CM treatment at four sites in Africa (ACTA trial, ISRCTN 45035509), and which we believe represents a pragmatic approach based on a synthesis of all available evidence.

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FORUM

Child privacy rights: A 'Cinderella' issue in HIV-prevention research

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Legal debates regarding child participation in HIV research have tended to focus on issues of informed consent. However, much less attention has been given to privacy; accordingly, we classify this as a 'Cinderella issue' that has been excluded from 'the ball' (academic debate). Here we argue that privacy issues are as important as consent issues in HIV-prevention research. We describe a child's right to privacy regarding certain health interventions in South African law, and identify four key norms that flow from the law and that could be applied to HIV-prevention research: (*i*) children cannot have an expectation of privacy regarding research participation if they have not given independent consent to the study; (*ii*) children may have an expectation of privacy regarding certain components of the study, such as HIV testing, if they consent independently to such services; (*iii*) children's rights to privacy in health research are limited by mandatory reporting obligations; (*iv*) children's rights to privacy in HIV-prevention research may be justifiably limited by the concept of the best interests of the child. We conclude with guidelines for researchers on how to implement these principles in HIV-related research studies.

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Health research among children (age <18 years), including HIV-prevention and -treatment research, is legally complex, because they have limited legal capacity and laws require them to be protected against their lack of experience and knowledge.[1] To date, legal debates have tended to focus on informed consent for child research. As a result, much of the literature has dealt with questions such as which parties should give consent to child research,[2-5] and what forms of research risk can be consented to on behalf of, or by children.[6-10] This article uses the analogy of Cinderella to describe the 'exclusion' of child privacy rights from academic debates on health research. It suggests that like Cinderella, who was left to clean the house rather than being invited to the ball, privacy has been overlooked or viewed as less important than the 'two ugly stepsisters' of *who* can consent and to *what* can be consented in child research.

It is argued here that the privacy rights of children participating in HIV-related research are as important as the consent rights for several reasons. Firstly, every child has the right to privacy.[11] It is argued that this right extends to ensuring that children have confidentiality regarding certain aspects of research participation. Secondly, South African courts have recognised that the failure to protect private medical information can have a direct public health impact, because without confidentiality, individuals are discouraged from seeking medical treatment or divulging personal information to healthcare providers.[12] It is argued, likewise, that undermining the confidential nature of the research relationship may erode public trust in research and researchers.

In previous articles, we argued that the privacy rights of adolescents (age 12 - 17 years) will have to be delineated carefully in HIV-prevention trials.[1,7] This article attempts to build on earlier work, by comprehensively setting out the nature and sources of a child's right to privacy regarding health interventions, and by developing four key norms which can be applied to a range of HIV-prevention studies. Adolescents are at risk of HIV infection, and in order to make new HIV-prevention products available to them, they will need to be enrolled in HIV-prevention trials – provided that rigorous ethical criteria are met.[13] For example, it is possible that, within the next 24 months, adolescent females will be enrolled in a clinical trial of a microbicide gel (FACTS 002), once sufficient safety and efficacy data have been obtained from adult participants.[14] There are also many other behavioural studies exploring aspects of HIV prevention in adolescents, e.g. explorations of knowledge, attitudes and practices among teenagers.

There are many complexities raised by a child's right to privacy within the context of trials of HIV-prevention products, as well as in related social-behavioural studies. Parents or guardians, who are aware of their child's involvement in such research through the consent process, may have expectations that personal health information reported to, or identified by researchers will be disclosed to parents. However, adolescents aged ≥12 years who have the capacity to consent independently to certain health interventions (such as testing for sexually transmitted infections) may have expectations of privacy regarding such interventions.[1,3,7]

The right to privacy in health-related matters

According to section 14 of the Constitution of the Republic of South Africa, everyone has a right to privacy.[11] This right enables individuals to be left alone or not to be observed by others.[15] It only extends to those aspects of a person's life that they and

society believe should be kept private.[16] Thus, an individual's right to privacy will exist if they have an expectation that the information would be kept private, and if such an expectation is regarded as reasonable by society.[16] Whether information can reasonably be regarded as private is established through an assessment of the impact of the violation on the individual's autonomous identity.[17] The right to privacy is also shaped by the grounds of justification. If a ground of justification exists (such as consent to the disclosure, necessity or where the law limits the right), the invasion of privacy will not be unlawful.[18]

A child's right to privacy in health-related matters

Constitutional and other rights apply in most instances to adults and children equally.[16] By implication, children are entitled to the right to privacy. However, a child's expectation of privacy may be limited, and in some instances, society would not recognise their expectation as reasonable.[1,7]

National Health Act (2003)

Currently, there is no legal guidance on how the right to privacy applies to child research participants, because the National Health Act (NHA)[19] is silent on this issue. However, section 14(1) of the NHA provides that a user (patient) has the right to confidentiality regarding health information, 'including information relating to his or her health status'.[19] However, such information may be disclosed in certain defined circumstances where the Act regards the disclosure as justifiable (section 14(2)(a)-(c) and 15(1), NHA).[19] It appears that the NHA does *not* create an independent right to privacy for children who do *not* have the capacity to consent to medical treatment, because if a parent or guardian consents on behalf of a child, then the parent/guardian is granted all the rights of the user, including the right to confidentiality (section 1, NHA).[19] This means that children, who cannot consent independently to a medical intervention would not have a right to keep information about such an intervention from the adult providing proxy consent.

Children's Act (2005)

The Children's Act, in contrast, provides that all children have a self-standing right to privacy regarding their 'health status' (section 13(1)(d), Children's Act).[20] 'Health status' is not defined, but it is assumed that this refers to a child's medical condition or diagnosis. The Act also provides that 'children are entitled to privacy from the age of 12 years regarding access to condoms, contraceptives and contraceptive advice' (sections 13(1)(d) and 134(3), Children's Act).[20] Furthermore, no person may disclose that a child is HIV-positive without the consent of the child (if they are aged ≥12 years), or another responsible adult if they are aged <12 years (section 133(1), Children's Act).[20]

The Children's Act provides that a child's rights to privacy regarding their health status may be limited where this is in their best interests (section 13(d), Children's Act).[20] Such rights may also be indirectly limited through mandatory reporting obligations. These require certain individuals such as medical practitioners, to report children who are abused, neglected or in need of care/protection (section 110, Children's Act).[1,7,20] The definitions of abuse, neglect and children in need of care and protection are very broad. Resultantly, reporting is required if, among others, children: (*i*) are performing child labour (i.e. working while aged <15 years); (*ii*) are dependent on drugs *and* they are 'without any support to obtain treatment for such dependency'; (*iii*) are being exploited, e.g. used by adults to commit crimes; or (*iv*) have been physically or sexually abused (section 150(2), Children's Act).[7,20]

The Choice of Termination of Pregnancy Act (1996)

The Choice of Termination of Pregnancy Act (CTPA) also deals expressly with the right to privacy, by providing that the 'identity of a woman who has requested or obtained a termination of pregnancy shall remain confidential at all times unless she herself chooses to disclose that information' (section 7(5), CTPA).[21] Woman in this context means a 'female person of any age' (section 1(xi), CTPA).[21] This provision is tempered by section 5(3), which provides that minors must be advised to 'consult with their parents, guardian, family members or friends' before the termination (section 5(3), CTPA).[3,21]

The Criminal Law (Sexual Offences and Related Matters) Amendment Act (2007)

The Sexual Offences Act (2007) limits a child's right to privacy by requiring the mandatory reporting of all sexual offences committed against children, including consensual crimes (section 54(1), Sexual Offences Act).[22]

Applying privacy laws to adolescent HIV-prevention studies

We argue that by applying the law on privacy to HIV-prevention studies, the following norms emerge:

A child does not have a right to privacy regarding participation in an HIV-prevention study unless they have consented independently to research participation. It is submitted that older adolescents may have expectations of privacy regarding participation in an HIV-prevention trial as they may have been recruited while independently accessing health services. However, this would not be regarded as reasonable given that ethical guidelines require parental consent for clinical trials,[23] and for more than minimal risk research.[24] Recently, section 71 of the NHA was operationalised, requiring parental or guardian consent for all forms of health research with minors.[19] While the section 71 requirements are overly broad, we argue that in the case of clinical trials, children do not have the right to keep their involvement private, because a parent or legal guardian should provide proxy consent.

In low-risk studies related to HIV prevention in adolescents, it is possible that research ethics committees (RECs) may grant approval for independent consent by adolescents despite the implementation of section 71 of the NHA, and in such cases, adolescents would also have an expectation of privacy for their enrolment in such studies. It is submitted that in this instance, such an expectation would be regarded as reasonable given that the REC has recognised their capacity to act without parental assistance.

An older child has the right to privacy regarding certain therapeutic health interventions that form part of the HIV-prevention study. We argue that where HIV-prevention studies involve a range of health services, older children may be entitled to privacy regarding these, for a number of reasons.[25] Firstly, in some circumstances *the law specifies that children are entitled to privacy* (see section above). As a result, children have the right to confidentiality regarding condoms, contraceptives and contraceptive advice, and their HIV status, from age 12 years.[3,20,25] Girl children are entitled to privacy regarding a termination of pregnancy at any age.[21] Secondly, in other situations, although the law does not

expressly set out that a child is entitled to confidentiality for that health intervention, e.g. medical treatment, it nevertheless provides that all children have the right to privacy regarding their health status.[20] This considered, it is argued that *when the law specifies that children have the capacity to consent independently to a particular intervention, they should have a corresponding right to privacy regarding their health status*. We argue that in such a situation the child would have an expectation of privacy, given their right to confidentiality regarding their health status, and that society would regard this as reasonable, as they are able to access the service without assistance.[1,25] Thirdly, in all other situations (where the law is silent on a child's right to privacy or it does not specify that they have the capacity to consent independently), the *general principles regarding the right to privacy would have to be applied.* This issue is discussed elsewhere.[1,25]

A child's right to privacy in the HIV-prevention study (where it exists) is limited by mandatory reporting obligations for abuse, neglect and sexual offences, and in some instances, ethical obligations to protect children. The Children's Act provides indirect limitations on a child's right to privacy by requiring the mandatory reporting of children who are abused, neglected, or those who are in need of care and protection.[1,7,20] This includes children performing child labour (i.e. working when aged <15 years) or those who are dependent on drugs *and* are not receiving any support for their addiction.[20] The Children's Act does not extend this obligation to report children in need of care and protection to third parties, i.e. other children whom child participants themselves may identify as being in a crisis situation. For example, if an adolescent research participant reports that a third party has been the 'victim' of a crime, or has 'committed' a crime, site staff will not have to report this information.[25] However, they may have ethical obligations to intervene if a child is in clear and imminent danger, e.g. from a violent and abusive parent. In such a case, they should assist the child participant to report this information to the appropriate authorities (local police or social workers) for further investigation.[25]

The Sexual Offences Act[22] also requires the mandatory reporting of sexual offences against children and this may affect a child's privacy rights within an HIV-prevention study.[25] This is discussed in detail elsewhere.[26]

A child's right to privacy regarding health status in HIV-prevention research may be limited by the concept of the best interests of the child. The right to privacy regarding a child's health status may be limited where maintaining confidentiality is not in the best interests of the child.[20] The Children's Act does not envisage an absolute concept of privacy, but rather a flexible approach in which a range of individual factors would need to be considered in establishing whether privacy is appropriate in the circumstances. For example, maintaining confidentiality – and not informing the child's parents – regarding a child's truancy from school may not be in the best interests of the child, because parents are under a legal duty to ensure that their children attend school until the end of the year in which they turn 15 years.[25]

Conclusion

It is argued that a child's right to privacy in research is a Cinderella issue that has received little direct attention in the literature, unlike the two consent stepsisters. This article has attempted to act as privacy's fairy Godmother and present this as a significant issue that requires urgent attention, to ensure that the privacy rights of adolescent participants are maintained without undermining their best interests.

We recommend that HIV-prevention researchers consider the following guidelines: (*i*) children should be advised during the recruitment stage of HIV-prevention trials or studies that they will have a limited right to privacy regarding their overall participation in the research if parental consent for enrolment is required; (*ii*) if parental consent is required, parents should be informed during the informed-consent process that, despite their consent, they will not receive direct feedback from researchers regarding many key components, because their children have legal rights to privacy for such components; (*iii*) standard operating procedures should be developed on the circumstances in which a child's right to privacy will be limited by mandatory reporting obligations.[1,25]

It is likely that some parents will not agree to enrolment because this approach may not be consistent with their values or preferences.[27] However, it is also likely that many will be willing to enrol their children in such studies when they receive assurances that children will be linked to appropriate counselling, support and health interventions to assist them.

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GUIDELINE

Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB

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Disclaimer. This consensus statement represents a consultative process with the authors and other experts in the field. At the time of publishing, this represented the best possible advice based on the data and experience of the group. We acknowledge that as more information is collected, both from randomised controlled trials and cohort data, this consensus statement will need to be updated. There will be at least a biennial review of the document.

Drug-induced liver injury (DILI) in HIV/tuberculosis (TB) co-infected patients is a common problem in the South African setting, and re-introduction of anti-TB drugs can be challenging for the healthcare worker. Although international guidelines on the re-introduction of TB treatment are available, the definition of DILI is not uniform, management of antiretroviral therapy (ART) in HIV co-infection is not mentioned, and the guidance on management is not uniform and lacks a practical approach. In this consensus statement, we summarise important aspects of DILI and provide practical guidance for healthcare workers for different patient groups and healthcare settings on the re-introduction of anti-TB drugs and ART in HIV/TB co-infected individuals presenting with DILI.

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1. Background

Globally, 34 million (31.4 - 35.9 million) people were living with HIV at the end of 2011. South Africa (SA) carries the highest burden, with 5.6 million people infected.[1] A major scale-up of public sector antiretroviral therapy (ART) has seen 1.6 million people start such therapy, and an increasing proportion of eligible individuals initiate treatment.[2] SA has the third highest tuberculosis (TB) burden in the world and the fourth highest multidrug-resistant (MDR) TB rate.[3] An estimated 60 - 80% of new TB cases in SA are HIV co-infected.[3,4] TB remains an important cause of morbidity and mortality among HIV-infected individuals, and undiagnosed TB is a major cause of death in the first months of ART.[5] Adherence to TB treatment is an important determinant of a favourable treatment outcome, and those who default treatment, especially if soon after treatment initiation, continue to be a source of infection and transmission within the community.[6,7] A two-fold higher relative risk of adverse events has been reported in HIV-infected individuals.[8,9]

Drug-induced liver injury (DILI) is a well-recognised adverse drug reaction of TB treatment and ART. DILI complicates TB treatment in 5 - 33% of patients. First-line anti-TB drugs associated with hepatotoxicity are isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA). Depending on the regimen, DILI develops in 9 - 30% of patients receiving ART.[11] Transaminitis can be associated with most ART, although nevirapine (NVP) is associated with the highest risk of DILI. A retrospective, observational study from SA showed an in-hospital and 3-month mortality among TB treatment or ART-associated DILI patients of 27% and 35%, respectively.[12]

Given the high HIV prevalence and TB incidence, DILI in TB/HIV co-infected patients is a common problem in the SA setting, and the re-introduction of anti-TB drugs can

be challenging for the healthcare worker. Although international guidelines on the re-introduction of TB treatment are available, the definition of DILI is not uniform, management of ART in HIV co-infection is not mentioned, and the guidance on management is not uniform and lacks a practical approach. In this consensus statement, we aim to summarise some important aspects of DILI and provide practical guidance for healthcare workers, for different patient groups and healthcare settings, on the re-introduction of anti-TB drugs and ART in HIV/TB co-infected individuals presenting with DILI.

2. Mechanism of DILI

Hepatotoxicity may result from direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells and/or liver vasculature. Predictable DILI is generally characterised by certain dose-related injury and tends to occur rapidly. Injurious free radicals cause hepatocyte necrosis in zones furthest away from the hepatic arterioles. Unpredictable or idiosyncratic reactions account for most types of DILI. These hypersensitivity reactions occur mostly independent of dose and relatively rarely for each drug, and may result in hepatocellular injury and/or portal tract inflammation with cholestasis.

RIF may occasionally cause dose-dependent interference with bilirubin uptake, resulting in subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage.[10] This may be transient and occur early in treatment or in some individuals with pre-existing liver disease.[10] Hepatocellular injury appears to be rare. PZA may induce both dose-dependent and idiosyncratic hepatotoxicity. PZA may induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis in a limited number of cases. INH is cleared mostly by the liver, primarily by acetylation by N-acetyltransferase 2. Mono-acetyl hydrazine is one of the main metabolites; its reactive metabolites are probably toxic to liver tissue through free radical generation. INH hepatotoxicity occurs generally within weeks to months, rather than days of starting the drug, as seen with hypersensitivity reactions. Unlike a classic hypersensitivity reaction, INH rechallenge does not always elicit a rapid recurrence of hepatotoxicity.[10]

Hepatotoxicity due to ART may be a result of immune restoration and the development of acute liver injury related to an enhanced immune response to TB or hepatitis B virus (HBV) immune reconstitution inflammatory syndrome (IRIS). HBV-IRIS presents as an acute hepatocellular injury, whereas TB-IRIS presents with an obstructive picture. Nucleoside reverse transcriptase inhibitors (NRTIs) are associated with a risk of mitochondrial toxicity and hepatic steatosis. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are also associated with hepatotoxicity. The hypersensitivity reaction observed with NVP can also include severe transaminitis.[11] NVP-DILI may be accompanied by a rash and fever. Hepatotoxicity is also observed with efavirenz (EFV), but the mechanism seems to be different.[13] The mechanism of protease inhibitor (PI)-associated hepatotoxicity is not known. Some studies have suggested an impaired drug metabolism, especially in individuals with underlying liver disease.[14]

To complicate matters, the HIV/TB co-infected patient is often exposed to other potentially hepatotoxic drugs and is prone to conditions associated with liver injury. Co-trimoxazole may be prescribed as preventive therapy or treatment for *Pneumocystis jirovecii* or toxoplasmosis. Cholestatic jaundice and hepatic necrosis are known side-effects and could be part of a systemic drug hypersensitivity syndrome that occurs independent of plasma drug concentrations.[15] Bacterial sepsis can also induce liver injury by various mechanisms, including the release of peroxynitrite by leucocytes, resulting in damage to the cell membranes; apoptosis of lymphocytes and gastrointestinal epithelial cells; and tissue ischaemia due to microvascular obstruction triggered by the release of pro-inflammatory mediators.[16] The pattern is generally mixed with increased bilirubin levels. TB itself and TB-IRIS can involve the liver. Hepatic TB-IRIS is probably more common than is appreciated clinically. Approximately 56% of patients with TB-IRIS have clinical hepatomegaly.[17] The hepatomegaly in TB-IRIS is frequently tender and patients may have symptoms of right-upper quadrant pain, nausea and vomiting.[18] The typical pattern of liver enzyme abnormality is mixed with moderate elevation of transaminases, but a far more significant rise in the canalicular enzymes.[18] Gamma-glutamyl transferase (GGT) is substantially more elevated in TB-IRIS patients than in HIV-negative patients with TB involving the liver. While bilirubin may increase, clinical jaundice is uncommon.[18]

Differentiating hepatic TB-IRIS from DILI attributed to a TB drug, ART or co-trimoxazole, poses a clinical conundrum. Unfortunately, there are no features absolutely predictive of either IRIS or DILI. Tender hepatomegaly, the preponderance of an elevation of the canalicular enzymes, the absence of jaundice, maintained synthetic liver function and TB-IRIS features in other organ systems may suggest TB-IRIS rather than DILI. The more definitive diagnostic route is to perform liver biopsy. However, this procedure is invasive and not readily available. Histological features observed in patients with TB-IRIS include significantly increased numbers of granulomas per liver core with abundant eosinophils palisading around these granulomas.[18] When there is doubt as to whether the liver function test (LFT) abnormalities represent TB-IRIS or DILI, it is safer to manage as DILI and monitor the response.

3. Risk factors for DILI

Risk factors for DILI in patients receiving TB treatment or ART are well described in the literature. The most important risk factors in individuals receiving TB treatment are: age >35 years; being a child; perhaps female gender; hepatitis B surface antigen (HBsAg) positivity, particularly if eAg-positive; use of alcohol; slow acetylator status; extensive TB disease; increase in baseline alanine transaminase (ALT); malnutrition; hepatitis C virus (HCV) co-infection; and HIV co-infection.[10,19,20] However, most data on TB-DILI in HIV-infected individuals come from observational studies or treatment trials, generally before the advent of effective ART. Definitions of hepatotoxicity and methodology varied among studies, and most lacked HIV-negative control groups. The overall influence of HIV infection alone on DILI during TB treatment was difficult to assess, but appeared to be slight, with the exception of one study where other confounding causes of DILI were present, such as injection drug use, alcoholism, ART and viral hepatitis.[10] One study from Ethiopia looked at TB-DILI in a population grouped by HIV status;[21] i.e. biochemical TB-DILI in HIV-positive and HIV-negative individuals. HIV-infection (odds ratio (OR) 3.6; 95% confidence interval (CI) 1.5 - 8.5), concomitant drug intake (OR 2.7; 95% CI 1.2 - 5.8) and a lower $CD4^+$ count (0 - 50 cells/µl: OR 21.3 (95% CI 2.2 - 204.9); $CD4^+$ 51 - 100 cells/µl: OR 5.2 (95% CI 0.6 - 46.0); $CD4^+$ 101 - 200 cells/µl: OR 4.3 (95% CI 0.4 - 42.4)) relative to a $CD4^+$ count >200 cells/µl, were identified as factors significantly associated with biochemical TB-DILI.[21] Risk factors associated with severe ART-related

Table 1. Overview of monitoring advice and cut-off levels for DILI according to existing guidelines

Authority	Monitoring in the presence of risk factors (especially liver diseases)	Cut-off levels for DILI and stopping drugs
ATS[10]	Yes	ALT >200 IU/l, or ALT >120 IU/l with symptoms
BTS[29]	Yes	ALT or AST >200 IU/l, rise in bilirubin
ERS, WHO, IUATLD[30]	-	ALT or AST >200 IU/l, icteric patient
HKTBS[31]	Yes	ALT >200 IU/l, bilirubin >40 µmol/l

DILI = drug-induced liver injury; ALT = alanine transaminase; AST = aspartate transaminase; ATS = American Thoracic Society; BTS = British Thoracic Society; ERS = European Respiratory Society; WHO = World Health Organization; IUATLD = International Union Against Tuberculosis and Lung Disease; HKTBS = Hong Kong Tuberculosis Service.

Table 2. DILI definition advocated in the SA setting

- ALT level >120 IU/l **and** symptomatic (nausea, vomiting, abdominal pain, jaundice); **or**
- ALT level >200 IU/l **and** asymptomatic; **or**
- Total serum bilirubin concentration >40 µmol/l

hepatotoxicity were a baseline elevation in serum aminotransferases, concomitant hepatotoxic medication, thrombocytopenia, renal insufficiency, chronic HBV or HVC co-infection and female gender.[22-25]

4. Definition of DILI

The definition of TB-DILI, according to the commonly used management guidelines, is summarised in Table 1. Asymptomatic transaminase elevations occur in 20% of patients started on standard anti-TB regimens prior to, or immediately after the start of treatment. Usually these elevations resolve spontaneously.[26-28] RIF may occasionally cause dose-dependent interference with bilirubin uptake, resulting in subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage. This may be transient and occur early in treatment or in some individuals with pre-existing liver disease.

Although similarities exist between the major guidelines, there are also differences. To achieve a uniform approach to DILI, a clear definition is required. None of the guidelines recommend routine monitoring of liver function in patients in whom there is no reason to suspect liver dysfunction. The definition for DILI in Table 2 has been advocated in the SA setting.

This definition applies to all TB patients including those with HIV co-infection. Although most guidelines suggest baseline LFT and laboratory monitoring of risk groups including HIV-positive individuals, this is generally not performed in low-resource countries with a high TB burden because of additional costs and low detection rates. Nevertheless, a healthcare worker should always enquire whether baseline laboratory parameters are available. In patients with a baseline ALT >120 IU/l or total bilirubin >40 µmol/l, it is recommended to start standard TB treatment and monitor closely, or to omit PZA initially in severe cases. If LFTs worsen on TB treatment, an alternative regimen should be started.

Elevated GGT and alkaline phosphatase (ALP) levels are not included in the DILI-definition of any of the major TB guidelines. Cholestasis is frequently observed in HIV-infected individuals and the cause can be multifactorial e.g. TB of the liver, TB-IRIS, drugs, opportunistic infections and fatty liver, but also HIV-related malignancies and biliary tract disease.[32] GGT and ALP levels should not be monitored routinely. Elevations of GGT alone do not reflect liver injury.

5. Management of TB-DILI: Existing guidelines and studies

Guidelines on the management of TB and adverse drug reactions have been published by the American Thoracic Society (ATS); the British Thoracic Society (BTS); the Task Force of the European Respiratory Society (ERS), the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD); and the Hong Kong Tuberculosis Service (HKTBS).[10,29-31,33] Most guidelines are based on expert opinion from a multidisciplinary team supported by literature searches. Good quality studies with adequate sample sizes on the preferred TB treatment regimen in patients presenting with DILI are scarce and will be discussed later. In the case of confirmed moderate or severe drug-induced hepatotoxicity, treatment should be interrupted and re-introduced after hepatotoxicity has resolved. When and how TB drugs should be re-introduced according to the various guidelines is summarised in Table 3.

However, in the SA setting, HIV/TB co-infected patients with DILI often have significant immune suppression and large mycobacterial loads, and the clinician may initiate a TB treatment backbone that excludes the first-line hepatotoxic drugs while the LFTs settle and until the patient is ready for rechallenge. Only the BTS guideline[29] provides guidance for these cases. Also, it is not clear what approach should be followed when the healthcare worker fails to re-introduce some of the first-line drugs, especially INH or RIF. The BTS guideline is reasonable and advises consultation with a fully trained physician, which is not always feasible in the Southern African setting.

Few published studies have focused on different re-introduction regimens of TB drugs.[34-37] All excluded HIV-positive patients and only two were randomised trials. A trial by Tahaoglu *et al.*[35] randomised 45 patients to INH, RIF, ethambutol (EMB) and streptomycin (STR) by gradually increasing the number and dosage of the drugs (n=20) or the standard regimen (INH, RIF, EMB and PZA) in the same dosage from the start of the rechallenge (n=25). Hepatotoxicity recurred in 0 and 6 (24%) patients (p=0.021), respectively. The time from withdrawal of TB drugs to resolution of hepatotoxicity was 18.7 days (standard deviation ±11.4).[35] Sharma *et al.*[36] randomised 175 patients with

Table 3. Overview of management of TB-DILI according to existing guidelines

Authority	Stopping TB drugs if clinical or symptomatic hepatitis	When to restart TB drugs	What TB drugs to start	Recommended LFT monitoring on rechallenge	If DILI recurs
ATS[10]	Yes	ALT <80 IU/l	• RIF +/- EMB full dose • After 3 - 7 days INH (full dose) • PZA only if mild DILI	• Check ALT 3 - 7 days after INH rechallenge	• Stop last drug added
BTS[29]	Yes	ALT within normal limits	• STR + EMB (if unwell or sputum is smear-positive within 2 weeks of commencing treatment) • INH (dose titration, every 2 - 3 days) • RIF (dose titration, every 2 - 3 days) • PZA (dose titration, every 2 - 3 days)	• Daily monitoring of LFT	• Stop offending drug, alternative regimen advised by fully trained physician
ERS, WHO, IUATLD[30]	Yes	LFT within normal limits	• Start all drugs at full dosage	• LFT monitoring (no recommendation on frequency)	• Stop all drugs, start STR + EMB and start other drugs one at a time
HKTBS[31]	Yes	-	-	-	-

TB = tuberculosis; DILI = drug-induced liver injury; LFT = liver function test; ALT = alanine transaminase; ATS = American Thoracic Society; BTS = British Thoracic Society; ERS = European Respiratory Society; WHO = World Health Organization; IUATLD = International Union Against Tuberculosis and Lung Disease; HKTBS = Hong Kong Tuberculosis Service; RIF = rifampicin; EMB= ethambutol; INH = isoniazid; PZA = pyrazinamide; STR = streptomycin.

Table 4. TB treatment regimen for patients with drug-susceptible TB when a first-line drug is omitted

Drug omitted	Intensive phase	Continuation phase
RIF	INH, MOX, EMB, STR × 2 months*	INH, MOX, EMB × 16 months
INH	RIF, MOX, EMB × 2 months*	RIF, MOX, EMB × 10 months
PZA	RIF, INH, EMB × 9 months	

TB = tuberculosis; RIF = rifampicin; INH = isoniazid; MOX = moxifloxacin; EMB = ethambutol; STR = streptomycin; PZA = pyrazinamide.
*May consider PZA rechallenge and use during the intensive phase, particularly if DILI occurred early during the intensive phase.

TB-DILI to one of three predefined re-introduction regimens. In the first arm, patients were given INH, RIF and PZA simultaneously at full dosage from day 1. In the second arm, drugs were re-introduced according to the ATS guideline with RIF at maximum dosage from day 1, INH at maximum dosage from day 8, and PZA at maximum dosage from day 15. In the third arm, drugs were administered in accordance with the BTS guidelines with 100 mg/day INH from day 1, (maximum dosage from day 4), 150 mg/day RIF from day 8 (maximum dosage from day 11) and 500 mg/day PZA from day 15 (maximum dosage from day 18). The recurrence rates were not significantly different between the three arms (around 10%). The median time from withdrawal of the TB drugs to resolution of hepatotoxicity was 18 days (interquartile range 14 - 28).[36] Some studies have looked at the use and safety of fluoroquinolones in TB-DILI patients. In these studies, the use of fluoroquinolones did not result in additional hepatotoxicity; however, the potential hepatotoxicity associated with fluoroquinolones (although infrequent) is something of which clinicians should be aware.[38,39] Szklo *et al.*[38] reported a cure rate of 85% and no treatment failures or relapses after 2 years of follow-up with fluoroquinolone regimens in patients who had DILI.

6. Management of TB-DILI in a high HIV burden setting: Recommendations

- Check TB diagnosis.
- Check results of TB culture and drug susceptibility testing.
- Reconsider TB diagnosis if not confirmed. If the patient has had a clinical response to the TB treatment including weight gain, improvement of symptoms that were compatible with a TB diagnosis and/or chest X-ray improvements, then the diagnosis can be assumed to be correct.
- Check if the patient is on the intensive or continuation phase of TB treatment.
- Consider other causes such as chronic alcohol consumption, pre-existing liver disease, viral hepatitis, other hepatotoxic medications, TB involvement of the liver, IRIS and bacterial sepsis.

6.1 Group 1: Intensive phase of TB treatment

6.1.1 Mild DILI: Clinically well with elevated ALT <200 IU/l and total bilirubin <40 µmol/l

- Continue TB drugs in the event of confirmed or probable TB.
- Continue ART if the patient is receiving ART.
- Repeat ALT and bilirubin in one week.
- If ALT and bilirubin have improved or normalised, stop laboratory monitoring.
- If ALT and bilirubin remain elevated but stable for 4 consecutive weeks, consider the other causes listed above, abdominal sonar and referral for further workup of liver dysfunction.
- If ALT and bilirubin increase further and meet the DILI definition, then move on to the relevant section below.

6.1.2 Moderate DILI: Clinically well and elevated ALT >200 IU/l irrespective of total bilirubin

- Discontinue the standard TB regimen.
- Start STR, moxifloxacin (MOX) and EMB (**note:** STR is contra-indicated if the glomerular filtration rate (GFR) is <60 ml/min).
- Discontinue co-trimoxazole prophylaxis and other hepatotoxic drugs.
- Stop ART. If the patient is on an NNRTI-based regimen, stop the NNRTI first and the NRTIs after 5 - 7 days. If the patient is on a PI-based regimen, stop all drugs at once. If the patient has been on a stable ART regimen for >6 months, consider continuing the therapy, as it is less likely that ART is the cause.
- Repeat ALT and bilirubin in 2 - 3 (inpatient) or 7 days (outpatient).
- When ALT is <100 IU/l and total bilirubin is normal, start the rechallenge.
- Day 1: RIF 450 or 600 mg daily, depending on weight.
- Day 3: Check ALT.
- Day 4 - 6: Add 300 mg INH daily.
- Day 7: Check ALT.
- Day 8: Consider a PZA rechallenge (especially in the case of TB meningitis or intolerance/resistance to other drugs) and check ALT at day 10.
- Once rechallenged, follow the guidance in Table 4.
- Monitor ALT weekly for 4 weeks after the rechallenge.

6.1.3 Moderate DILI: Isolated jaundice (ALT <120 IU/l and total bilirubin >40 µmol/l)

- Continue ART.
- Stop co-trimoxazole prophylaxis if ALP and GGT are also elevated.
- Stop RIF (RIF is the most likely cause of isolated jaundice).
- Continue INH, PZA and EMB and add MOX.
- Repeat ALT and bilirubin after 7 days. If bilirubin does not settle, then consult an expert.
- If the bilirubin settles, then follow the guidance in Table 4.
- The clinician may consider a full-dose RIF rechallenge 2 - 3 weeks after stopping RIF.
- Repeat ALT and bilirubin after 7 days. If ALT and bilirubin are stable, then stop MOX and continue with standard RIF, INH, PZA and EMB for 2 months, followed by 4 months of RIF and INH.
- If bilirubin increases to >40 µmol/l, stop RIF and continue INH, PZA, EMB and MOX. Follow the guidance in Table 4.
- Monitor ALT and bilirubin weekly for 4 weeks after the rechallenge.
- If ALT increases to >120 IU/l, perform abdominal ultrasound and refer for further investigation. Follow the guidance in sections 6.1.1 or 6.1.2.

6.1.4 Severe DILI: Clinically *not* well (nausea, vomiting, abdominal pain), meets DILI definition (Table 2)

- Admit the patient.
- Consult an infectious diseases or TB-treatment specialist, if available.
- Assess liver synthetic function with an international normalised ratio (INR) and monitor blood glucose (hypoglycaemia can complicate liver failure).
- Stop standard TB treatment, co-trimoxazole prophylaxis and all other hepatotoxic drugs.
- If the patient is on an NNRTI-based regimen, stop the NNRTI first and the NRTIs after 5 - 7 days. However, if the patient is in liver failure, stop all ART immediately.
- If the patient is on a PI-based regimen, stop all drugs at once.
- Start EMB, STR and MOX (**note:** STR is contraindicated if the GFR is <60 ml/min).
- Repeat ALT and bilirubin after 2 - 3 days.
- Rechallenge TB drugs when ALT is <100 IU/l and bilirubin is normal.
- Day 1: RIF 450 or 600 mg daily depending on weight.
- Day 3: Check ALT (should improve or become stable).
- Day 4 - 6: Add 300 mg INH daily.
- Day 7: Check ALT (ALT should improve or become stable).
- Stop STR and follow the guidance in Table 4.
- Consider PZA re-challenge (especially in the case of TB meningitis or intolerance/resistance to other drugs).
- Monitor ALT weekly for 4 weeks after rechallenge.

6.1.5 Management if RIF is not tolerated after rechallenge

- Stop RIF.
- Check ALT after 2 - 3 days.
- If ALT is <100 IU/l and bilirubin is normal, add 300 mg INH daily.
- Check ALT after 2 - 3 days.
- If ALT is stable, follow the guidance in Table 4.
- If ALT is worsening, stop INH and continue treatment in consultation with an infectious diseases or TB-treatment specialist.
- Consider PZA rechallenge where RIF has not been tolerated.
- Monitor ALT weekly for 4 weeks after rechallenge.

6.1.6 Management if INH is not tolerated after rechallenge

- Stop INH.
- Check ALT after 2 - 3 days.
- Continue RIF, MOX and EMB for 12 months in total.
- Consider PZA rechallenge in this setting where INH has not been tolerated.
- Monitor ALT weekly for 4 weeks after rechallenge.

6.2 Group 2: Continuation phase of TB treatment

- Confirm the start date and response to ART/TB treatment.
- Consider other diagnoses.
- If asymptomatic with elevated ALT <200 IU/l and bilirubin <40 µmol/l, then follow the approach in 6.1.1.
- If the patient has isolated jaundice (ALT <120 IU/l and total bilirubin >40 µmol/l), stop RIF, continue INH, EMB and MOX. Follow the guidance in Table 4.

- Continue ART. Stop co-trimoxazole prophylaxis if ALP and GGT are also elevated.
- The clinician may consider full-dose RIF rechallenge 2 - 3 weeks after stopping RIF.
- If the patient has moderate DILI (asymptomatic and elevated ALT >200 IU/l irrespective of total bilirubin) **or** severe DILI, then discontinue the standard TB regimen, co-trimoxazole prophylaxis and other hepatotoxic drugs.
- If the patient has severe DILI, assess liver synthetic function with an INR and monitor blood glucose.
- Stop ART. If the patient is on an NNRTI-based regimen, stop the NNRTI first and the NRTIs after 5 - 7 days (however, if the patient is in liver failure, stop all ART immediately). If the patient is on a PI-based regimen, stop all drugs at once.
- Monitor ALT and bilirubin in 2 - 3 days (inpatient) or 7 days (outpatient).
- Rechallenge TB drugs if ALT is <100 IU/l and bilirubin is normal.
- Day 1: 450 - 600 mg RIF daily depending on weight.
- Day 3: Check ALT (ALT should be stable).
- Day 4 - 6: Add 300 mg INH daily.
- Day 7: Check ALT.
- Continue RIF and INH to complete the continuation phase.
- If ALT and/or bilirubin worsen after RIF rechallenge, treat with INH, EMB and MOX. Further diagnostic tests and treatment duration in consultation with an infectious diseases or TB-treatment specialist may be needed.
- If ALT and/or bilirubin worsen after INH rechallenge, then treat with RIF, EMB and MOX. Further diagnostic tests and treatment duration in consultation with an infectious diseases or TB-treatment specialist may be needed.
- Monitor ALT weekly for 4 weeks after rechallenge.

6.3 General comments for all TB-DILI patients

- The re-introduction of first-line TB drugs in patients with TB-DILI is preferred over the use of second-line drugs.
- Rechallenge is **not** recommended for those who have had fulminant hepatitis (defined as hepatic encephalopathy with coagulopathy). Once ALT is <100 IU/ml and bilirubin has normalised, treat with an MDR-TB regimen, avoiding PZA and substituting PZA with EMB (i.e. STR or kanamycin, EMB, MOX, ethionamide and terizidone).
- If the patient cannot tolerate MOX, high-dose levofloxacin should be used. Ciprofloxacin should not be used in the treatment of TB.
- If STR is not available, then kanamycin or amikacin should be used.
- If the intensive phase of TB treatment is interrupted for any period, restart the full treatment course starting from the day that the alternative TB regimen is successfully re-introduced.
- Re-challenge with PZA was previously not recommended, but a recent trial has shown that most patients tolerate it.[36] PZA re-challenge should be considered in patients with severe TB (e.g. miliary, meningitis), drug resistance or intolerance to INH or RIF. Transaminase levels, especially ALT, should be monitored frequently (e.g. 3 times weekly) during rechallenge and weekly for a month following rechallenge.
- Patients with low body weight (<40 kg) should have their maximal doses calculated according to body weight.
- Monitor vision in all patients requiring a modified regimen, including signs of EMB toxicity.
- ART is indicated for all TB/HIV patients independent of $CD4^+$ cell count.

6.4 Rechallenge or initiation of ART

6.4.1 Patients who develop DILI while receiving TB medication only, not on ART

6.4.1.1 ART-naive

- $CD4^+$ count <100 cells/µl: start ART as soon as the complete standard or alternative regimen of TB drugs is re-introduced.[40]
- $CD4^+$ count >100 cells/µl: ART can be delayed until after the intensive phase of TB treatment, unless the patient has other serious HIV-related conditions (e.g. Kaposi's sarcoma or HIV encephalopathy).[40]
- After ART initiation, monitor ALT every 2 weeks for 2 months.

6.4.1.2 ART-experienced

- Collect information on treatment history, treatment response and reason for treatment interruption.
- Discuss the appropriate regimen with an infectious diseases or HIV-treatment specialist.
- After ART initiation, monitor ALT every 2 weeks for 2 months.

6.4.2 Patients who develop DILI while receiving TB treatment *and* ART

- If DILI developed on an NNRTI-based regimen with NVP, then rechallenge with an NNRTI-based regimen with EFV after the TB drug rechallenge.[13,40]
- If DILI developed on NNRTI-based regimen with EFV, then rechallenge EFV in the case of mild DILI after the TB drug rechallenge. In the case of severe or recurrent DILI, start a PI-based regimen with lopinavir/ritonavir (LOP/r) (with dose adjustment if receiving RIF).
- If the patient has mild DILI on EFV and LFTs resolve within 5 - 7 days after interrupting EFV, the clinician may consider restarting EFV before the TB drug rechallenge in order to avoid stopping ART.
- If DILI developed on PI-based regimen with double-dose LOP/r, then the preferred approach is to replace RIF with 150 mg rifabutin on alternate days and use this with atazanavir/ritonavir (or a standard dose of LOP/r). If this option is not available and double-dose LOP/r with RIF is used, then this should be recommenced with slow-dose escalation over 2 weeks: i.e. day 1 – 400/100 mg 12-hourly; day 7 – 600/150 mg 12-hourly; day 14 – 800/200 mg 12-hourly. This should be done after the TB drug rechallenge. **Note:** There is no need for double-dose LOP/r if there is **no RIF** in the final TB treatment regimen.
- In the case of all other regimens including newer PIs or drugs from other drug classes, discuss the approach with an infectious diseases or HIV-treatment specialist.
- After ART rechallenge, monitor ALT every 2 weeks for 2 months.

6.5 Rechallenge of co-trimoxazole

Co-trimoxazole therapy should not be rechallenged in HIV/TB patients taking primary or secondary co-trimoxazole prophylaxis and who experience severe liver toxicity. Dapsone should be used instead, but is less effective than co-trimoxazole in preventing *P. jirovecii* pneumonia and also lacks the broad antimicrobial activity of co-trimoxazole. It is therefore desirable to attempt rechallenge of co-trimoxazole in

patients with previous *P. jirovecii* pneumonia and with mild DILI after re-introduction of TB treatment and ART. Monitor ALT and bilirubin weekly for 1 month after rechallenge.

Conflict of interest. All authors submitted conflict of interest disclosure forms. Authors were required to report on financial support received from pharmaceutical companies and medical aids over the previous three years (updated 19 August 2013). F Conradie has received support from Aspen Pharmacare to attend conferences, research support from Janssen Pharacetic, and honoraria for speaking engagements from MSD, and acted as a consultant to Discovery Health. G Meintjes has received honoraria for speaking engagements from Sanofi Aventis and serves as a consultant for Aid for AIDS. R Bernhau, A Black, M-A John and E Jong report no conflicts of interest.

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ORIGINAL ARTICLE

Analysis of HIV-related mortality data in a tertiary South African neurology unit, 2006 - 2012

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Background. South Africa (SA) has a high prevalence of HIV infection with almost 11% of the population aged >2 years living with HIV. At the Steve Biko Academic Hospital, Pretoria, the Neurology Department has seen a steady increase in HIV-related neurology patients.

Objective. To evaluate the mortality data of this unit as it relates to HIV infection.

Methods. The study was a retrospective analysis of records. Patient mortality statistics for 2006, 2008, 2010 and 2012 were analysed regarding cause of death, sex, age and HIV status.

Results. During 2006, 85 patients died: 33% were HIV-positive, 13% were HIV-negative and 54% had not tested for HIV. By 2010, these figures were 50%, 22% and 28%, respectively, changing little in 2012 (48%, 28% and 24%, respectively). Causes of death in the HIV-positive group were meningitis in 58% – with tuberculous meningitis the most common aetiology – followed by strokes (14%), space-occupying lesions (8%) and status epilepticus (7%). Among HIV-positive patients aged 20 - 30 years, a larger proportion of young women died than men. In the combined untested and HIV-negative group, strokes accounted for the vast majority of deaths.

Conclusion. Neurological complications of HIV remain common in SA and contribute significantly to the overall mortality in our tertiary neurology unit, with TB posing a serious threat. A strong corps of clinical neurologists with training in infective neurology is needed urgently in the coming years to care for this growing number of patients.

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The AIDS epidemic in South Africa (SA) is continuing. The Department of Health estimated that the national HIV prevalence among women attending antenatal clinics was 29.4% in 2009 and 29.5% in 2011, with a higher prevalence in KwaZulu-Natal (37.4%) and Mpumalanga (36.7%) provinces.[1,2] Furthermore, an alarming HIV incidence of 10.9% has been reported among the population aged >2 years.[3] Death notification data in SA show that the death rate among young women (25 - 34 years) more than quadrupled between 1997 and 2004, and that among men (30 - 39 years) more than doubled, presumably in part due to HIV infection.[4] Unfortunately, mortality data are difficult to analyse, as the majority of HIV-related deaths are misclassified. Thus, the ascertainment of deaths related to HIV remains a big concern.[5,6]

Neurological complications of HIV infection are common. In the era prior to highly active antiretroviral therapy (HAART), neurological disorders were the first manifestation of AIDS in 7 - 20% of patients and prevalence rates of opportunistic neurological infections, including cryptococcal meningitis (CM), tuberculous meningitis and progressive multifocal leukoencephalopathy (PML), ranged from 39 - 70%. Toxoplasmic encephalitis and primary central nervous system (CNS) lymphoma were common causes of space-occupying lesions in HIV-positive patients.[7] In SA, the neurological complications that resulted in hospital admissions included bacterial and fungal meningitis, mass lesions – especially due to toxoplasmosis and tuberculosis (TB) – spinal cord disorders and peripheral nerve disorders. Primary CNS lymphoma was rarely seen.[8] One study showed TB as the most common cause of focal brain lesions in HIV-positive patients,[9] but very few cases of PML had been reported until a recent study showed that it was a common cause of white-matter lesions in an academic hospital in Pretoria.[10]

The clinical spectrum of neurological manifestations in HIV-positive patients has changed somewhat since the arrival of HAART, and several studies have confirmed that the incidence rates of neurological diseases, such as HIV-associated dementia and CNS opportunistic infections, are decreasing.[11] Even so, a Nigerian study showed that about one-third of patients receiving HAART presented to hospital with a neurological problem, including neurocognitive problems (53%), distal sensory neuropathy (16.4%), meningitis (6.4%), myopathies (5.2%), myelopathies (2.4%) and strokes (2%).[12]

In the Neurology Department of Steve Biko Academic Hospital, Pretoria, clinicians have the impression that there

has been a steady increase in HIV-related neurology cases. This article evaluates the mortality data of this tertiary neurology unit as it relates to HIV infection.

Methods

The patient mortality statistics of the neurology unit at Steve Biko Academic Hospital were reviewed for years 2006, 2008, 2010 and 2012; alternate years were chosen on the presumption that data would not change significantly from one year to the next. The hospital has 830 beds and serves as a major tertiary referral centre in Gauteng Province. The Department of Neurology admits patients from the emergency department, the neurology outpatient department and from referral hospitals. The statistics from the morbidity and mortality meetings are stored in the department and were analysed in this study in terms of cause of death, sex, age and HIV status. The HIV status of a patient is determined whenever a clinical indication exists and knowledge of the HIV infection would influence management. The cause of death was determined by the treating neurologists' best clinical opinion in the large majority of cases, since autopsies are often not feasible in our resource-limited setting. Ethics approval of the study was granted by the University of Pretoria.

Results

The total number of neurological admissions was 533, 446, 510 and 460 in 2006, 2008, 2010 and 2012, respectively. The total number of deaths was 85, 73, 80 and 61, respectively (Table 1).

Of the 85 patients who died in 2006, 28 (33%) were HIV-positive (12 females, 16 males), 11 (13%) were HIV-negative (6 females, 5 males) and 46 (54%) had not had their HIV status tested (26 females, 20 males). In the HIV-positive group, meningitis was the most common cause of death (75%), with TB the most common aetiology, followed by CM. Strokes were the second most common cause of death (14%). The HIV-negative group had miscellaneous causes of death (strokes, cancer-related and hypoxia). In 54%, the HIV status had not been determined; the most common cause of death in these patients was stroke (41%), followed by meningitis (17%).

Of the 73 patients who died in 2008, 31 (42%; 17 females, 14 males) were HIV-positive; again, infective causes of death were most common at 71%, with TB meningitis in 47% of meningitis cases, followed by CM in 26%. Strokes accounted for 23% of HIV-related deaths. The HIV-negative group included 13 patients (18%) with miscellaneous causes of death (strokes, complications of chronic neurological conditions, etc.). In 40% of patients, testing for HIV had not been requested; of these, two-thirds died as a result of stroke (66%), 17% from complications of status epilepticus and 10% from meningitis.

In 2010, 80 patients died. Most had been tested for HIV, and half were HIV-positive: 40 (50%; 22 females, 18 males) had a cause of death related to HIV infection. Meningitis and other infective disorders were the cause of death in 63% (TB 56%, cryptococcal 22%, *S. pneumoniae* 17%) and 18% died from seizure complications. Miscellaneous causes accounted for the rest of the deaths (strokes, various space-occupying lesions, etc.). $CD4^+$ counts were determined for nearly 70% of HIV-positive patients (mean 62×10^6 cells/l; range $2 - 200 \times 10^6$). Eighteen patients (22%) were HIV-negative, with miscellaneous causes of death (strokes 44%, meningitis, Wernicke encephalopathy, chronic neurological disorders, etc.). In 28% (22 patients), HIV testing had not been performed, and stroke was the most common cause of death (55%); 4 (14%) died of status epilepticus complications. Meningitis, metastatic disease and space-occupying lesions were other causes of death.

In 2012, 61 patients died: 29 (48%) were HIV-positive (20 females, 9 males), 17 (28%) were HIV-negative and 15 (24%) had not been tested. Again, the majority of HIV-positive patients died of infective causes (20; 69%), with TB meningitis being the most common cause of death in the meningitis group (80%). Strokes accounted for 17% of deaths. $CD4^+$ counts were available in 21/29 patients and ranged from $13 - 1\,021 \times 10^6$ cells/l (mean 145×10^6). From the retrospective data, it was possible to ascertain that 14 patients had not been receiving antiretroviral therapy (ART), 4 were receiving ART, and this information was not available for 11. Of the 17 deceased patients (28% of total) who were HIV-negative, the majority died from strokes (8/17; 47%), meningitis (4/17; 24%) and other miscellaneous causes. HIV testing had not been performed in 15 (24%) patients; most of these patients died from strokes (10/15; 67%) and meningitis (3/15; 20%). Fig. 1 shows the HIV status of patients over the period that the study was conducted.

Over the study period, 71 female and 57 male HIV-positive patients died. Their age ranges were 14 - 64 and 17 - 61 years for females and males, respectively. The age profiles showed a clear difference in the age at death between the sexes, with a much higher proportion of women dying at age 20 - 30 years than men in the HIV-positive group (19 v. 5, respectively) (Fig. 2).

When combining the results of the 4 years of the study, the causes of death in the HIV-positive patients included meningitis (58%), strokes (14%), space-occupying lesions (8%), status epilepticus (7%) and PML (5%) (Fig. 3). Meningitis was most commonly tuberculous (50%), followed by cryptococcal (30%) and bacterial (12%). Causes of death in the combined HIV-negative and HIV-unknown group are shown in Fig. 4.

Discussion

It is well-known that HIV leads to a wide spectrum of neurological complications, ranging from immunological dysregulation to diseases caused by immunosuppression, such as cerebral toxoplasmosis, PML and primary CNS lymphoma, and to HIV-driven disorders such as dementia and polyneuropathies.[13,14] Secondary conditions related to HAART and reactive psychiatric disorders also occur. Up to 40% of HIV-infected patients may have a neurological disorder[15] and post-

Table 1. Patient admissions, deaths and HIV status over the study period

	2006	2008	2010	2012
Patients admitted, *N*	533	446	510	460
Deaths, *n* (%)	85 (15.9)	83 (16.3)	80 (15.6)	61 (13.2)
Deceased who were HIV-positive, %	33	42	50	48

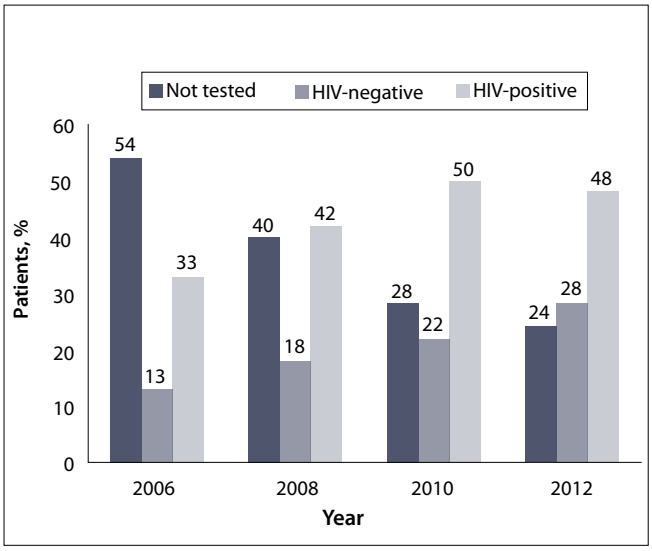

Fig. 1. HIV status of patients over the study period, indicating a positive trend for HIV infection.

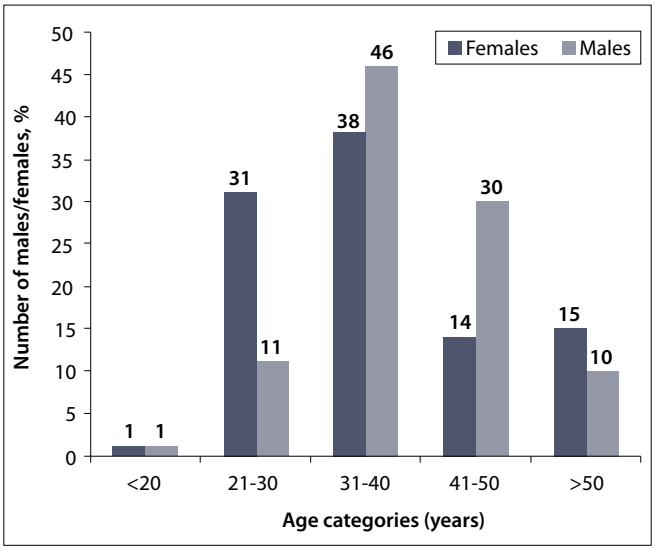

Fig. 2. Age categories of HIV-positive patients, suggesting that females died of neurological complications of HIV infection at a younger age than their male counterparts.

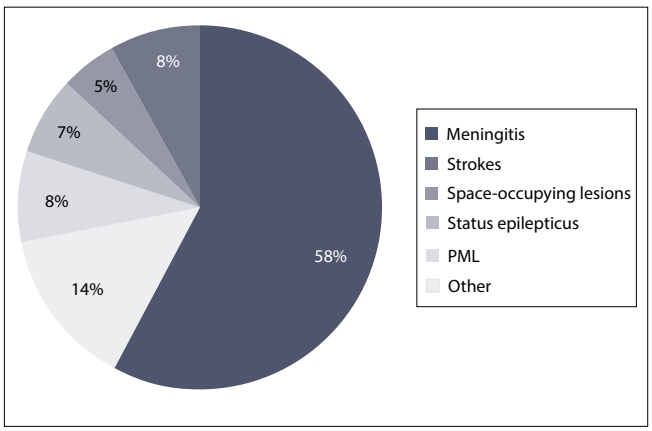

Fig. 3. Cause of death in the HIV-positive patients.

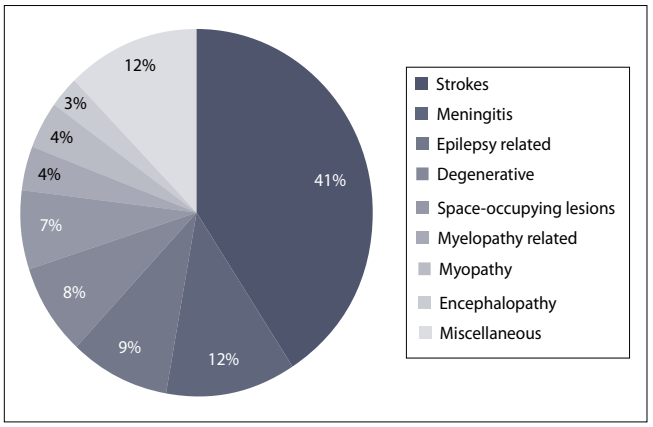

Fig. 4. Cause of death in the combined HIV-negative and HIV-unknown patients.

mortem studies show an even higher proportion of CNS pathology with HIV infection.[16]

Over the study period, an increasing number of patients had been tested for HIV infection – from 45% in 2006 to 70% in 2010 and almost 80% in 2012, with HIV infection proven in 34% in 2006 and approximately 50% in 2010 and 2012. Thus, HIV-related neurological disorders are the leading cause of death in our tertiary unit, with at least half of all deaths currently directly related to HIV infection. According to the South African National HIV Survey of 2008, 10.9% of South Africans aged >2 years were infected with HIV in 2008, which compared with 11.4% in 2002 and 10.8% in 2005, showed some stabilisation.[3] However, the prevalence was still growing in people aged >25 years (from 15.6% in 2005 to 16.8% in 2008), which may be reflected by our findings. Many people were unaware of their HIV status and were not receiving HAART, although this was not formally assessed in this study. Patients were also often referred late in the course of their neurological illness, making reversal of established pathology a challenge.

In this study, infective causes of death in HIV-positive patients were preponderant, with TB the most common aetiology. Several previous post-mortem studies have shown that infections as a cause of death constitute the largest proportion in HIV-positive individuals. A study from Botswana[17] concluded that TB was the leading cause of death in HIV-positive adults, followed by pneumonia and Kaposi's sarcoma. Another study compared causes of death and mortality rates during the pre-, early and late HAART eras, finding that even with HAART, infections remained the leading cause of death in HIV-positive patients.[18] A recent study[19] showed that the presence of neurological disorders in treated HIV/AIDS patients negatively affected survival, with the highest mortality hazard ratio occurring in those patients who had opportunistic infections of the CNS.[19]

A high index of suspicion should be maintained for CM and tuberculous meningitis in the primary healthcare (PHC) setting, since many patients were referred with neurological problems that were already irreversible. The new guidelines for the prevention, diagnosis and management of CM[20] may go a long way in addressing the problem of late diagnosis of CM, and routine screening for cryptococcal antigen and urgent follow-up in patients with a $CD4^+$ count <100 cells/µl should be seen as a necessity in all PHC facilities. Tuberculous meningitis is often misdiagnosed, even if a lumbar puncture is performed, since cerebrospinal fluid (CSF) results are not always typical. A high index of suspicion is essential, and patients

should be started empirically on anti-TB treatment, even if it means that some patients may be treated unnecessarily.[21]

Our mortality data did not include information on ART. This information should, in future, be added to our statistics for analysis, as the current impression is that many patients are still unaware of their HIV status and are treatment-naive. Earlier awareness and initiation of ART before immunosuppression should lead to reduced mortality.

Among the HIV-positive patients in the 20 - 29-year age group, the proportion of women who passed away was much higher than men. This finding may be related to the results of the South African National HIV Survey of 2008,[3] which revealed that the HIV prevalence is disproportionally high for females compared with males, peaking in the 25 - 29-year age group, with one-third being HIV-positive. In males, the prevalence was found to peak in the 30 - 35-year age group (25% HIV-positive), which is also comparable to our findings where most male deaths occurred at age 30 - 39 years. Intergenerational sex may be a contributory factor to the high HIV prevalence in young women, many of whom have partners who are ≥5 years older – this number has increased from 9.6% in 2005 to 14.5% in 2008. Young girls may be particularly vulnerable in such relationships since they lack the skills and power to insist on condom use.[3,22]

Conclusion

Our findings show that neurological complications of HIV infection remain common in SA and contribute significantly to the overall mortality in our tertiary neurology unit. TB remains a significant threat, with many young patients dying as a result of this infection. In the next few years, a strong corps of clinical neurologists with special training in infective disorders is urgently needed to provide optimal care for this large number of patients.

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ORIGINAL ARTICLE

HIV risk behaviour among public primary healthcare patients with tuberculosis in South Africa

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Objective. To identify factors associated with HIV in tuberculosis (TB) patients in a public primary healthcare (PHC) setting in South Africa (SA).
Method. Among 4 900 consecutively selected TB patients (54.5% men; women 45.5%) from 42 public PHC clinics in 3 districts in SA, a cross-sectional survey was performed to assess new TB and new TB retreatment patients within one month of anti-TB treatment.
Results. The sample comprised 76.6% new TB patients and 23.4% TB retreatment patients. Of those who had tested for HIV, 59.9% were HIV-positive; 9.6% had never tested for HIV. In multivariate analysis, older age (odds ratio (OR) 5.86; confidence interval (CI) 4.07 - 8.44), female gender (OR 0.47; CI 0.37 - 0.59), residing in an informal settlement (OR 1.55; CI 1.13 - 2.12), being a TB retreatment patient (OR 0.55; CI 0.42 - 0.72), occasions of sexual intercourse with condom use (OR 1.07; CI 1.02 - 1.13) and having a sexual partner receiving antiretroviral treatment (ART) (OR 7.09, CI 4.35 - 11.57) were associated with an HIV-positive status in TB patients.
Conclusion. This study revealed high HIV risk behaviour (e.g. unprotected last sexual intercourse and alcohol and drug use in the context of sexual intercourse) among TB patients in SA. Various factors were associated with HIV risk behaviour. Condom use and substance use risk reduction need to be considered as HIV-prevention measures when planning such strategies for TB patients.

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South Africa (SA) has 0.7% of the world's population and 28% of the world's population of HIV/tuberculosis (TB) co-infected individuals.[1] It has been estimated that approximately 60% of people with TB are co-infected with HIV.[1] Co-infected patients have almost double the chance of acquiring multidrug- (MDR-TB) and extensively drug-resistant TB (XDR-TB), and have a high mortality rate.[2]

Several studies have found a high level of HIV risk behaviour (e.g. multiple sexual partners, lack of condom use, intravenous drug use) among TB/HIV co-infected patients receiving anti-TB treatment.[3-6] Factors associated with HIV status in TB patients have included female gender, age 26 - 35 years, unmarried marital status, a higher income, belonging to a specific population group and engaging in high-risk practices.[3,4,7]

The aim of this study was to identify factors associated with HIV in TB patients in public primary healthcare (PHC) in SA.

Methods

A cross-sectional survey was conducted among TB patients in public PHC clinics in SA, in the three provinces with the highest TB caseload. One district with the highest TB caseload per province (*N*=3) was ultimately included in the study: Siyanda in the Northern Cape, Nelson Mandela Metropole in the Eastern Cape, and eThekwini in KwaZulu-Natal. Within each district, 14 PHC facilities (PHC clinics or community health centres) were selected (*N*=42) on the basis of the highest TB caseload per clinic. Healthcare providers identified all new TB treatment and retreatment patients aged ≥18 years, informed them about the study and referred them for participation, if interested. Recruited patients were consecutively interviewed within one month of anti-TB treatment. Interviews were conducted by trained external research assistants over a period of 6 months in 2011 in all 42 clinics. The research assistants asked for permission/consent from the recruited patients to participate in the interview. Ethical approval was granted by the Research Ethics Committee of the Human Sciences Research Council (protocol REC 1/16/02/11) and by the National Department of Health.

Measures

Socioeconomic characteristics

A researcher-designed questionnaire was used to record information on participant age, gender, educational level, marital status, income, employment status, dwelling characteristics and residential status. Poverty was assessed with 5 items on the availability or non-availability of shelter, fuel or electricity, clean water, food and cash income in the past week. Response options ranged from 1 = 'not one day' to 4 = 'every day of the week'. Poverty was defined as having a higher score on non-availability of essential items. The total score ranged from 5 to 20; 5 = low, 6 - 12 = medium and 13 - 20 = high poverty. Cronbach's α for the poverty index was 0.89 in this sample.

Table 1. Socioeconomic characteristics of the sample

Characteristic	Total (*N*=4 900)	Men (*n*=2 671; 54.5%)	Women (*n*=2 229; 45.5%)	χ^2 or *t*	*p*-value
Age (years) (range 18 - 93), mean (±SD)	36.2 (±11.5)	37.2 (±11.5)	34.8 (±11.4)	7.29	0.000
Age group (years), *n* (%)				75.43	0.000
18 - 24	643 (13.3)	276 (10.6)	358 (16.5)		
25 - 34	1 841 (38.1)	928 (35.7)	899 (41.4)		
35 - 44	1 313 (27.1)	780 (30.0)	515 (23.7)		
45 - 54	671 (13.9)	399 (15.3)	259 (11.9)		
55 - 64	265 (5.5)	161 (6.2)	95 (4.4)		
≥65	104 (2.2)	58 (2.2)	45 (2.1)		
Population group, *n* (%)					
Black	4 078 (84.6)	2 175 (83.9)	1 845 (85.3)	1.66	0.198
Coloured	634 (13.1)	345 (13.3)	281 (13.0)	0.11	0.742
Indian/Asian/white/other	114 (2.3)	71 (2.7)	37 (1.7)	5.63	0.018
Marital status					
Never married	3 323 (72.7)	1 734 (70.2)	1 589 (75.6)	16.68	0.000
Married/co-habitating	982 (21.5)	594 (24.1)	388 (18.5)	21.03	0.000
Separated/divorced/widowed	265 (5.8)	141 (5.7)	124 (5.9)	0.08	0.783
Education, *n* (%)					
≤Grade 7	1 269 (26.3)	745 (28.8)	502 (23.2)	19.49	0.000
Grade 8 - 11	2 213 (45.9)	1 126 (47.4)	960 (44.3)	4.63	0.031
≥Grade 12	1 336 (27.7)	613 (23.7)	704 (32.5)	45.32	0.000
Poverty index (5 - 20), *n* (%)				2.22	0.329
Low (5)	1 592 (35.0)	882 (35.2)	710 (34.4)		
Medium (6 - 12)	2 195 (48.2)	1 117 (47.2)	1 018 (49.3)		
High (13 - 20)	768 (16.9)	433 (17.4)	335 (16.2)		
Geolocality, *n* (%)					
Urban residence	3 151 (66.2)	1 691 (65.4)	1 460 (67.2)	1.56	0.212
Rural residence	877 (18.4)	480 (18.6)	397 (18.3)	0.08	0.780
Informal settlement	730 (15.3)	413 (16.0)	317 (14.6)	1.79	0.181

Psychological distress

The Kessler psychological distress scale (K-10) was used to measure global psychological distress, including significant pathology that did not meet the formal criteria for a psychiatric illness.[8,9] The following symptoms were assessed by asking: 'In the past 30 days, how often did you feel: nervous; so nervous that nothing could calm you down; hopeless; restless or fidgety; so restless that you could not sit still; depressed; that everything was an effort; so sad that nothing could cheer you up; worthless; tired out for no good reason?' The frequency with which each of item was experienced was recorded using a five-point Likert scale ranging from 0 = 'none of the time' to 5 = 'all the time'. This score was summed, with increasing scores reflecting an increasing degree of psychological distress. This scale serves to identify individuals who are likely to meet formal definitions of anxiety and/or depressive disorders, as well as to identify individuals with sub-clinical illness who may not meet formal definitions for a specific disorder.[8] The scale has been validated in HIV-positive individuals in SA.[10] There was significant agreement between the K-10 and the MINI-defined depressive and anxiety disorders. A receiver operating characteristic (ROC) curve analysis indicated that the K-10 showed agreeable sensitivity and specificity in detecting depression (area under the ROC curve (AUC) 0.77), generalised anxiety disorder (AUC 0.78) and post-traumatic stress disorder (AUC 0.77).[10] The K-10 scale was used as a binary variable comparing scores ≥30 or <30. The internal reliability coefficient for the K-10 was α=0.92.

Alcohol consumption

The 10-item alcohol use disorders identification test (AUDIT)[11] assesses alcohol consumption level (3 items), symptoms of alcohol dependence (3 items) and problems associated with alcohol use (4 items). Heavy episodic drinking is defined as the consumption of ≥6 standard drinks (10 g alcohol) on a single occasion.[11] A standard drink in SA is equivalent to 12 g of alcohol. Because the AUDIT is reported to be less sensitive at identifying risk drinking in women, as recommended by Freeborn *et al.*,[12] the cut-off point for binge drinking in women (4 units) was reduced by one unit compared with that for men (5 units). Responses to items on the AUDIT are rated on a 4-point Likert scale from 0 to 4 (maximum score 40 points). A higher AUDIT score indicates a more severe level of risk: a score ≥8 indicates a tendency to problematic drinking. The AUDIT has been validated in HIV-positive patients in SA, showing excellent sensitivity and specificity in detecting MINI-defined dependence/abuse (AUC 0.96),[13] and among TB and

Table 2. Health and HIV risk characteristics

Characteristic	Total (*N*=4 900)	Men (*n*=2 671)	Women (*n*=2 229)	χ^2 or *t*	*p*-value
TB status, *n* (%)					
New TB treatment patient	3 650 (76.6)	1 946 (75.2)	1 704 (78.4)		
TB retreatment patient	1 113 (23.4)	643 (24.8)	470 (21.6)	6.83	0.009
HIV status, *n* (%)				87.83	0.000
HIV-positive	2 585 (59.9)	1 222 (53.4)	1363 (67.4)		
HIV-negative	1 728 (40.1)	1 068 (46.6)	660 (32.6)		
Never tested for HIV, *n* (%)	449 (9.6)	311 (12.3)	138 (6.5)	43.69	0.000
Perceived health status, *n* (%)				4.72	0.095
Excellent/very good	912 (19.1)	524 (20.2)	388 (17.8)		
Good	1 646 (34.6)	874 (33.8)	772 (35.5)		
Fair/poor	2 205 (46.3)	1 190 (46.0)	1 015 (46.7)		
Severe psychological distress (based on Kessler 10), *n* (%)	1 183 (26.3)	660 (26.9)	523 (25.6)	0.90	0.341
HIV risk behaviour					
Sexually active in the past 3 months, *n* (%)	2 318 (51.3)	1 336 (54.1)	982 (48.0)	16.63	0.000
Last sexual intercourse unprotected, *n* (%)	2 319 (54.9)	1 243 (54.0)	1 076 (56.0)	1.67	0.196
Sexual intercourse with condom use (occasions), mean (±SD)	1.72 (±0.8)	1.69 (±0.8)	1.77 (±0.8)	-2.66	0.008
Sexual intercourse without condom use (occasions), mean (±SD)	1.53 (±0.7)	1.55 (±0.7)	1.49 (±0.7)	2.05	0.040
Alchol, drug and tobacco use, *n* (%)					
AUDIT				234.10	0.000
Low (0 - 7)	3 637 (76.8)	1 759 (68.2)	1 878 (87.0)		
Medium (8 - 19)	785 (16.6)	579 (22.5)	206 (9.5)		
High (20 - 40)	315 (6.6)	241 (9.3)	74 (3.4)		
Alcohol before sexual intercourse	537 (20.9)	376 (25.6)	161 (14.7)	43.67	0.000
Drugs before sexual intercourse	237 (9.3)	148 (10.1)	89 (8.2)	2.75	0.098
Current tobacco use	1 290 (27.6)	1 006 (39.6)	284 (13.3)	399.29	0.000
Sexual partner, *n* (%)					
Disclosed HIV status to partner	2 729 (63.9)	1 479 (63.5)	1 250 (63.6)	0.01	0.923
Partner HIV-positive v. HIV-negative or unknown	1 192 (27.2)	600 (25.0)	592 (29.8)	12.70	0.000
Sexual partner receiving ART	434 (11.1)	244 (11.5)	190 (10.7)	0.75	0.387

TB = tuberculosis; AUDIT = alcohol use disorders identification test; SD = standard deviation; ART = antiretroviral therapy; OR = odds ratio; CI = confidence interval.

HIV patients in PHC in Zambia, demonstrating good discriminatory ability in detecting MINI-defined current alcohol use disorders (AUDIT 0.98 for women and 0.75 for men).[14] Cronbach's α for the AUDIT in this sample was 0.92, indicating excellent reliability.

Tobacco use

Two questions were asked about the use of tobacco products: (*i*) 'Do you currently use one or more of the following tobacco products (cigarettes, snuff, chewing tobacco, cigars, etc.)?' (response options were 'yes' and 'no'); and (*ii*) 'In the past month, how often have you used one or more of the following tobacco products (cigarettes, snuff, chewing tobacco, cigars, etc.)?' (response options were: 'once or twice', 'weekly', 'almost daily' and 'daily'). Current tobacco use was defined as having used any tobacco product in the past month.

Perceived general health

Participants were asked: 'In general, would you say your health is: excellent, very good, good, fair or poor?' This measure was categorised based on participant response (very good = excellent/very good; good; and poor = fair/poor).

TB treatment, HIV and antiretroviral therapy (ART) status were assessed by self-report and from medical information. HIV risk behaviour was assessed in terms of the following: whether or not the participant was sexually active in the past 3 months; whether or not the last occasion of sexual intercourse was unprotected; the number of occasions of sexual intercourse with condom use in the past 3 months; the number of occasions of sexual intercourse without condom use in the past 3 months; alcohol use before sexual intercourse in the past 3 months; illegal drug use before sexual intercourse in the past 3 months; whether or not the participant had disclosed his/her HIV status to the sexual partner; the HIV status of the sexual partner; and the ART status of the sexual partner.

Data analysis

Data were analysed using SPSS software (version 19.0). Frequencies, means and standard deviations (SDs) were calculated to describe the

sample. Data were checked for normality distribution and outliers. For non-normal distribution, non-parametric tests were used. Associations of HIV status were identified using logistic regression analyses. Following each univariate regression, multivariate regression models were constructed. Independent variables from the univariate analyses were entered into the multivariate model if significant at $p<0.05$. For each model, the R^2 values were calculated to describe the amount of variance explained by the multivariate model. A p-value <0.05 was regarded as statistically significant.

Results

From the sample (N=4 935) approached for inclusion in the study, 35 (0.7%) patients declined the request to participate. The final sample included 4 900 patients (54.5% men; 45.5% women) of mean age 36.2 years (SD ±11.5; range 18 - 93). Almost two-thirds (65.2%) were aged 25 - 44 years, most (72.7%) were never married, 27.7% had completed secondary education, 17% scored high on the poverty index, 24.2% had a formal salary as a main household income, and 58.9% were unemployed. A significant number of participants (15.3%) lived in informal settlements (Table 1).

Health and HIV risk characteristics

Of the total sample, 76.6% were new TB patients and 23.4% were TB retreatment patients. Of those who had tested for HIV, 59.9% were HIV-positive; 9.6% had never tested for HIV. More than 1/4 patients (27.6%) were current (past month) tobacco users, 26.3% had severe psychological distress, and 46.3% perceived their health status as fair or poor. Regarding sexual risk behaviour, 54.9% had had unprotected sexual intercourse on the last occasion thereof, and 20.9% had used alcohol and 9.3% illegal drugs before sexual intercourse in the past 3 months. Two-thirds (63.9%) of the participants had disclosed their HIV status, 27.2% had a sexual partner who was HIV-positive and 11.1% had a sexual partner who was receiving ART (Table 2).

HIV status, socioeconomic factors, health status and HIV risk behaviour

In univariate analysis, the following were associated with an HIV-positive status among TB patients: older age; female gender; not being poor; black race; residing in an informal settlement; being a TB retreatment patient; poor perceived health status; not currently using tobacco products; not being sexually active in the past 3 months; having unprotected sexual intercourse on the last occasion thereof; the number of occasions of sexual intercourse with condom use; hazardous or harmful alcohol use; alcohol use before sexual intercourse in the past 3 months; drug use before sexual intercourse in the past 3 months; and having a sexual partner who was receiving ART. In multivariate analysis, the following were associated with an HIV-positive status in TB patients (Table 3): older age; female gender; residing in an informal settlement; a TB retreatment status; number of occasions of sexual intercourse with condom use; and having a sexual partner who was receiving ART.

Discussion

This study revealed a high prevalence (59.9%) of co-infection with HIV among a large sample of TB patients in public PHC in SA, similar to the findings of other studies (60%).[1] Further, there was a high level of HIV risk behaviour (last occasion of sexual intercourse unprotected, and alcohol and drug use in the context of sexual intercourse), in agreement with other studies.[3-6] This is alarming, given the high rate of HIV/TB co-infection at a national level in SA.[1] The dual epidemics of HIV and TB have become a public health priority, and this is beginning to receive increasing attention from the National Department of Health as specified in the National Strategic Plan 2012 - 2016.[15] TB cannot, therefore, be managed as a single disease entity. A comprehensive treatment and prevention programme for TB, HIV and indeed other co-morbid disorders is required to meet this public health challenge. In the context of this study, condom use and substance use risk reduction need to be considered as HIV-prevention measures when planning HIV-prevention programmes for TB patients.

In multivariate analysis, older age, female gender, residing in an informal settlement, being a TB retreatment patient, occasions of sexual intercourse with condom use, and having a sexual partner receiving ART were associated with HIV-positive status in TB patients. In agreement with other studies,[3] sociodemographic variables (female gender and older age) were associated with HIV status in TB patients. In contrast, unlike in other studies,[3,4,7] marital status, income, population group and engaging in high-risk practices were not associated with an HIV-positive status. Furthermore, TB retreatment patients were more likely to be HIV-positive than new TB treatment patients. These data provide information to inform HIV-prevention strategies.

Study limitations

Caution should be taken when interpreting the results of this study because of certain limitations. As this was a cross-sectional study, causality between the compared variables cannot be concluded. A further limitation was that most variables were assessed by self-report and desirable responses may have been given. The population surveyed originated predominantly from urban areas, and may not be representative of other settings in SA.

Conclusion

This study revealed a high HIV risk behaviour among TB patients in SA. Various factors were identified associated with this behaviour, providing information for HIV-prevention strategies. Condom use and substance use risk reduction need to be considered as HIV-prevention measures when planning HIV-prevention programmes for TB patients.

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Table 3. Association between HIV status, socioeconomic factors, health status and HIV risk behaviour

Socioeconomic factor	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Age group (years)		
18 - 24	1.00	1.00
24 - 34	3.26 (2.68 - 3.96)‡	3.19 (2.29 - 4.43)‡
35 - 44	4.01 (3.25 - 4.94)‡	5.86 (4.07 - 8.44)‡
≥45	1.58 (1.27 - 1.95)‡	2.37 (1.60 - 3.49)‡
Male v. female	0.55 (0.49 - 0.63)‡	0.47 (0.37 - 0.59)‡
Marital status		-
Never married	1.00	
Married/co-habitating	0.88 (0.76 - 1.02)	
Separated/divorced/widowed	0.71 (0.55 - 0.93)	-
Education		
≤Grade 7	1.00	
Grade 8 - 11	1.14 (0.98 - 1.32)	
≥Grade 12	1.04 (0.88 - 1.23)	
Poverty index		
Low	1.00	1.00
Medium	1.12 (0.88 - 1.17)	0.90 (0.70 - 1.14)
High	0.45 (0.37 - 0.54)‡	0.77 (0.55 - 1.09)
Population group		
Black	1.00	1.00
Coloured	0.21 (0.17 - 0.26)‡	0.29 (0.20 - 0.41)
Indian/Asian/white/other	0.26 (0.17 - 0.39)‡	0.26 (0.12 - 0.58)
Geolocality		
Urban residence	1.00	1.00
Rural residence	0.95 (0.82 - 1.12)	0.82 (0.61 - 1.10)
Informal settlement	1.43 (1.19 - 1.71)‡	1.55 (1.13 - 2.12)*
New TB treatment v. retreatment patient	0.72 (0.62 - 0.83)‡	0.55 (0.42 - 0.72)‡
Perceived health status		
Excellent/very good	1.00	1.00
Good	2.33 (1.95 - 2.77)‡	2.51 (1.89 - 3.34)
Fair/poor	4.34 (3.66 - 5.16)‡	4.83 (3.61 - 6.46)
Severe psychological distress	1.02 (0.89 - 1.18)	-
HIV risk behaviour		
Sexually active in the past 3 month	0.83 (0.73 - 0.94)†	1.06 (0.70 - 1.59)
Last sexual intercourse unprotected	1.26 (1.11 - 1.44)‡	1.56 (1.23 - 1.99)
Occasions of sexual intercourse with condom use	1.09 (1.06 - 1.13)‡	1.07 (1.02 - 1.13)*
Occasions of sexual intercourse without condom use	1.01 (0.97 - 1.05)	-
Alcohol, drug and tobacco use		
AUDIT		
Low	1.00	1.00
Medium	0.85 (0.72 - 1.00)*	1.01 (0.75 - 1.37)
High	0.74 (0.58 - 0.94)*	0.96 (0.62 - 1.48)
Alcohol before sexual intercourse	1.09 (1.02 - 1.17)*	0.92 (0.81 - 1.04)
Drugs before sexual intercourse	1.22 (1.13 - 1.32)‡	1.08 (0.93 - 1.25)
Current tobacco use	0.60 (0.52 - 0.68)‡	0.98 (0.76 - 1.27)
Sexual partner		
Disclosed HIV status to sexual partner	0.99 (0.86 - 114)	-
Sexual partner receiving ART	4.09 (3.09 - 5.41)‡	7.09 (4.35 - 11.57)‡

TB = tuberculosis; AUDIT = alcohol use disorders identification test; SD = standard deviation; ART = antiretroviral therapy.

[a] Using 'enter' LR selection of variables; [b] Hosmer and Lemeshow chi-square 15.41, df 8, 0.052; Cox and Snell R^2 0.25; Nagelkerke R^2 0.34.

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

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CONFERENCE REPORT

'Feedback: Where data finally get thrilling' – tools for facility managers to use data for improved health outcomes in the prevention of mother-to-child transmission of HIV and antiretroviral therapy

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Data use and data quality continue to be a challenge for government sector health facilities and districts across South Africa. Led by the National Department of Health, key stakeholders, such as the Anova Health Institute and district health management teams, are aligning efforts to address these gaps. Coverage and correct implementation of existing tools – including TIER.net, routine data collection forms and the South African District Health Information System – must be ensured. This conference report provides an overview of such tools and summarises suggestions for quality improvement, data use and systematic evaluation of data-related interventions.

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There is increasing recognition of the importance of a functional information-management system to improve health outcomes in South Africa (SA). This is gaining attention through a number of local and international policy documents, including the SA District Health Management Information System (DHMIS) Policy (2011),[1] the Aid Effectiveness Framework (2012)[2] and the US President's Emergency Plan for AIDS Relief (PEPFAR) Partnership Framework.[3] With ongoing evaluation and improvement of the SA District Health Information System (DHIS), patients, clinicians and policymakers are ideally positioned to benefit from the improved quality and increased use of routinely collected data at facility, sub-district and district levels. In the case of HIV services, the DHIS can be particularly valuable in determining the number of clients receiving antiretroviral therapy (ART) and in identifying gaps in the prevention of mother-to-child transmission (PMTCT) of HIV services.

The Anova Health Institute (Anova) recently gathered 160 delegates in Johannesburg for the symposium 'Feedback: Where data finally get thrilling', to provide an overview of best practice for information use in assessment and improvement of health services, with an emphasis on HIV treatment and PMTCT. The target audience included facility managers across Gauteng Province, with a focus on Johannesburg. Anova partnered with information and programme managers from provincial and district government, as well as a variety of non-governmental organisations (NGOs), to maximise expertise and objectivity on the issue.

Magnitude of the issue

The DHMIS Policy calls for more than just addressing data quality; it denotes that information should be used in programme planning and in clarifying the main roles and responsibilities 'for ensuring data completeness, data quality, and data use and "ownership" at all levels of the health system.'[4] One finding of this symposium was voiced by those in attendance: the DHMIS Policy is not available or followed by all facility managers, especially in the areas of data use for programme decisions and feedback between all levels (facility to sub-district/district and *vice versa*). The DHIS, which since 1996 has been the sole government repository of health-related data in SA, has not reached optimal levels of quality, as documented[5] and anecdotally reported. This holds true for PMTCT as documented by Mate *et al.*,[6] as well as for ART data which are not as well documented. Particular areas of concern include data accuracy, completeness and reliability. Fortunately, the National Department of Health (NDoH), facility managers, district DoH structures and NGO partners have begun the implementation of tools like TIER.net, the Prevention of Mother-to-Child Transmission Action Framework and the District Health Barometer (DHB) to interrogate and better

utilise information. In this context, this conference report is not a declaration of success, but rather a brief description of the status of our progress in using tools to strengthen data quality and ease of use.

Conference content

Keynote speaker, Winnie Moleko from the Wits Reproductive Health and HIV Institute (WRHI)/NDoH, presented 'Data feedback towards quality improvement in service delivery'. Moleko discussed the state of data quality in SA and the role that this plays in quality improvement and implementation of the National Core Standards.[7] Practitioners and policy makers can use data to identify gaps in service delivery, resources and facility needs. For data to be useful, they must be correct and accurate; data that are incorrect or presented misleadingly can be detrimental to service delivery and planning. One suggestion that Moleko made, which can be implemented in service facilities, is to post the facility's data on improvements and achievements in a public place in the facility. This allows staff and clinicians to engage the public and clients in the facility's data-improvement process.

All presentations are available online (http://www.anovahealth.co.za/resources/entry/feedback_where_data_finally_gets_thrilling/). Table 1 summarises the lessons learnt for clinicians and facility managers working in the field of HIV. The body of the symposium covered three main areas: (*i*) review of data quality and challenges; (*ii*) best practice review of data use for quality improvement; and (*iii*) data tools available to facilities, clinicians and policy makers.

Review of data quality and challenges

Mokgadi Morokolo represented Johannesburg Health Information and gave an overview of the DHMIS. She reminded the facility managers in the audience of their responsibility for the data signoff process. This includes a review of the source data such as facility registers, critical analysis of the data outputs, and timely submission of reports and corrections. She emphasised that this is the responsibility of sub-district managers, district directors and hospital chief executive officers (CEOs). These managers are also responsible for improving their knowledge of indicators and maintaining current data-collection tools. District directors are responsible for ensuring that facilities have the current and correct stationery.

Goodwill Kachingwe and Nowinile Dube presented recent district-level data and highlighted where data can and should be used at all phases

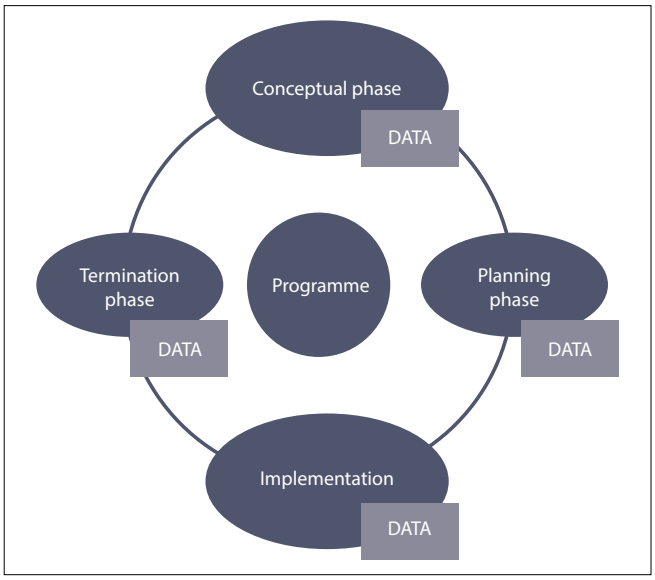

Fig. 1. Flowchart indicating where data can and should be used at all phases of the DHMIS programme cycle.

Table 1. Relevance of the DHMIS for clinicians and facility managers working in HIV-related fields

Why data and information matter	• Generally in SA, ART and PMTCT service data are not of optimal quality • Facility managers hold the ability and responsibility to demand data quality • Quality data are necessary to create usable information to improve service delivery
Key policies for the facility, sub-district and district	• NDoH ART monitoring data management SOPs (2012): http://www.anovahealth.co.za/images/uploads/ART%20ME%20SOP%20FINAL%204%204%202012.pdf • DHMIS Policy (2011): http://www.doh.gov.za/docs/policy/2012/dhmis.pdf

Benefits of information use	• Access to essential information (e.g. number of clients receiving ART; number of treatment defaulters)
	• Knowledge of progress on indicators towards the National Strategic Plan on HIV, STIs and TB 2012 - 2016 (http://www.doh.gov.za/docs/stratdocs/2012/NSPfull.pdf) and other relevant targets, e.g.:
	  • percentage of people per annum becoming eligible to receive ART
	  • patients alive and receiving ART at 6, 12, 24, 36, 48 and 60 months
	  • mother-to-child transmission rate (6 weeks and 18 months)
	• Better understanding of the PMTCT/HIV care cascade
	  • PMTCT gaps, e.g.:
	  • HAART initiation among pregnant mothers v. HAART eligible
	  • HIV antibody testing at 18 months v. tested for PCR at 6 weeks
	  • ART gaps between those who test HIV-positive and those who receive:
	  • $CD4^+$ testing
	  • pre-ART care
	  • ART initiation

DHMIS = District Health Management Information System; SA = South Africa; ART = antiretroviral therapy; NDoH = National Department of Health; PMTCT = prevention of mother-to-child transmission; SOPs = standard operating procedures; HAART = highly active antiretroviral therapy; PCR = polymerase chain reaction; TB = tuberculosis.

of the programme cycle (Fig. 1). Data are used in the conceptual phase to help determine what health outcomes need to be addressed through the programme. Data can be used in the planning phase to provide insight into where resources need to be distributed or to provide a baseline for future evaluation. In the implementation phase, data are used to monitor the programme implementation or to ensure that target populations are being reached by the programme. In the termination phase, data are used to evaluate the success of the programme, or to determine how the programme has contributed to district, provincial or national targets.

Best practice review of data use for quality improvement

Maria Sibanyoni from the WRHI reported on the implementation of a quality-improvement intervention in Johannesburg.[8] The intervention incorporated quality-improvement meetings with staff, collaborative learning workshops, process mapping and a data dashboard to improve initiation and adherence to ART. This effort succeeded in creating an inter-facility referral network and focused on data-driven processes that provided clear and achievable targets for meeting client needs. These achievements can be replicated in other locations.

Theunis Hurter, from Anova's Cape Winelands project, demystified TIER.net reporting for the audience. TIER.net is being expanded into facilities throughout the country (Fig. 2 shows its growing use in Johannesburg). In the Winelands, TIER.net has helped clinicians and policy makers at facilities and the district level to identify defaulters, track and trace patients, and even identify PMTCT programme gaps. Specific to PMTCT, Hurter and DoH colleagues in the Cape Winelands identified, through the use of routine data, that facilities in the district had initiated ART in more under-2-year-olds than had been offered PMTCT services – a clear service-delivery gap. Like this example, one key element in using data for effective programme and data quality improvement is the presence of facility managers who empower their data capturers and others to give feedback on the data and make note of any trends, issues or remarkable issues in the data.

Existing data tools available to facilities, clinicians and policy makers

Existing tools, organisations and methodologies are in abundance, but greater coverage and use of these tools is still needed. The DHIS, for example, can be used to identify data quality issues through *min/max out-of-range graphs* and *data completeness reports*. The Prevention of Mother-to-Child Transmission Action Framework is effective for target-setting and monitoring programme performance. As much of this information was new to the conference audience, we suggest that raising awareness of these tools is still necessary.

Mashudu Rampilo shared the results of an informal Data Quality Audit comparing source documents (registers) to facility reports and DHIS data specific to HIV testing, the PMTCT programme and ART in Mopani, Limpopo Province. Although from a different setting, the audience was both familiar and shocked with the results. Rampilo's results showed wide variation and regular disagreement between each of the three data points (the source, facility report and the DHIS). As noted in the DHMIS overview, data accuracy is the responsibility of the staff at facility, sub-district and district level.

One method to improve service delivery at the facility level is treatment-gap modelling. This uses baseline data, national targets and comparisons between people receiving treatment and those eligible for treatment, to estimate where the biggest gaps in service coverage exist, and where more needs to be done to meet local, provincial and national health indicator targets. This approach was adapted from the work of Barker and Venter.[10]

The available, but under-utilised (as remarked from conference attendees) DHB contains a comprehensive set of indicators to inform planning at all levels in the government and NGO sectors. Candy Day from the Health Systems Trust highlighted how the DHB can be used to provide an overall view of district health performance at the primary healthcare level, and to provide comparative data to monitor the overall quality of service within a district.

One final strategy for data use is the Three Tier ART Monitoring and Evaluation (M&E) Strategy, of which the ART M&E standard operating procedures (SOPs) are a key element. Catherine White presented this tool, which is essential to quality data collection and use of M&E of ART.

Fig. 2. Mapping TIER.net progress in Johannesburg, May 2012.[9]

Recommendations

While facilitating the final discussion, Dr Cephas Chikanda, Anova's Head of Health Systems Strengthening, and Prince Dulaze, Anova's M&E co-ordinator for Johannesburg, solicited participant feedback to consolidate the key points that the audience had derived from the day's presentations. The participants' recommendations included:

- There is a need for better communication about the data within facilities between clinicians, facility managers and data collectors, as well as between the different levels of the health system. For example, facility and district managers need to communicate what the data tell them about service delivery and resources.
- Accountability for the data is the responsibility of everyone, from facility and district

data collectors, to district managers and policy makers at the national level. Accountability includes knowing the data elements, what the data reveal about health service delivery and outcomes, and how to accurately and efficiently use data to improve the health system.

- The continuous revision of data-collection tools and systems is a concern. Standardisation of tools and systems according to the DHMIS would facilitate correct and timely completion of collection tools, assist users in becoming familiar and comfortable with the data tools, and make it easier for users and collectors to identify issues and errors. Standardisation is one way to contribute to continuous quality improvement, as well as the development and use of tools and strategies for the immediate- and long-term.
- In order for the health system to use data most efficiently for its best effect, it is important to value good quality data as central to quality healthcare provision and worthy of investing time and resources. This includes sharing the results of data collection and interpretation with health services and the public. Data must also be prioritised within the system to highlight its worth as a valuable tool to improve health service delivery.

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CASE REPORT

Combined antiretroviral and anti-tuberculosis drug resistance following incarceration

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We describe a case of HIV/tuberculosis (TB) co-infection from KwaZulu-Natal, South Africa, characterised by drug resistance in both pathogens. The development of drug resistance was linked temporally to two periods of incarceration. This highlights the urgent need for improved integration of HIV/TB control strategies within prison health systems and within the broader public health framework.

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The twin epidemics of HIV and tuberculosis (TB) have had a devastating impact on individuals, families and communities in South Africa (SA) over the past two decades.[1] SA alone is responsible for almost one-third of the global burden of HIV-associated TB.[2] While much progress has been made in the last few years with robust responses to these epidemics, many challenges remain.[3] Antiretroviral and anti-TB drug resistance pose considerable threats to the control of these epidemics.[4,5] The breakdown in HIV/TB control within prisons is another emerging threat.[6,7] We describe one of the first reports of combined antiretroviral and anti-TB drug resistance, where the development of resistance was closely associated with two periods of incarceration.

Case report

A 34-year-old unemployed male presented to a primary healthcare (PHC) clinic in Hlabisa sub-district, KwaZulu-Natal, in February 2012 with a cough, night sweats and weight loss. He had been diagnosed with HIV infection in 2002, but had not accessed HIV care until April 2009 when he presented with his first episode of smear-negative pulmonary TB. At that time, his CD4$^+$ cell count was 85 cells/μl and he was initiated on a standard first-line antiretroviral therapy (ART) regimen of stavudine (d4T), lamivudine (3TC), and efavirenz (EFV). He achieved complete virological suppression (HIV viral load <50 copies/ml) and a good immunological response (CD4$^+$ count 482 cells/μl) after 5 months of ART (Fig. 1). In May 2010, he was incarcerated (in a correctional facility approximately 50 km from home) and as a result of non-disclosure of HIV status to prison officials, his ART was interrupted. Following release in September 2010, he had re-engaged with care at the PHC clinic and had been restarted on ART (tenofovir (TDF), 3TC and EFV). Within 6 months, he was once again detained in prison and his ART was interrupted once again for several months. He reported that he shared a cell with up to 50 people during this second spell in prison, several of whom were coughing and one had apparently stated that he had multidrug-resistant TB (MDR-TB).

Xpert® MTB/RIF was performed on sputum and detected *Mycobacterium tuberculosis* resistant to rifampicin. He was referred to the provincial drug-resistant TB unit (approximately 250 km from home) and was commenced on a standardised regimen of kanamycin, moxifloxacin, ethionamide, terizidone, pyrazinamide and isoniazid. Two weeks later, he was re-initiated on ART (TDF, 3TC and EFV). He completed the intensive phase of drug-resistant TB treatment with a good treatment response (acid-fast bacilli smear and culture negative after 2 months) and no evidence of nephrotoxicity, but there was no virological response to ART (viral load 390 845 copies/ml 6 months after restarting ART), despite documented good adherence.

Genotypic resistance testing was performed and revealed non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations (K103N and V106M) and nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations (K65R and M184V), conferring high-level resistance to EFV and 3TC, and intermediate-level resistance to TDF. Hepatitis B surface antigen (HBsAg) was negative and haemoglobin was 12.7 g/dl. As a result, he was switched to a second-line ART regimen consisting of co-formulated zidovudine (AZT) and 3TC with lopinavir/ritonavir (LPV/r). At this stage, the total number of pills taken daily was 27 (including co-trimoxazole and pyridoxine). As of June 2013, he continues to be followed up at his local PHC clinic (2 km from home) and at the drug-resistant TB unit.

Consent

Written informed consent was given by the patient prior to publication.

Discussion

The issue of TB control in SA prisons has recently received much attention, as a result of the successful legal action against the Minister of Correctional Services by a former prison inmate who contracted TB while in a correctional facility awaiting trial.[8] Here we have described a case where acquisition of drug-resistant TB most likely occurred in prison and the clinical course was compounded by the emergence of antiretroviral drug resistance. This has significance, not only for individual health, with increased treatment complexity and adverse clinical outcomes, but also for the health of the wider community, with the risk of onward transmission of drug-resistant infections. The case here highlights the need for an improved and more integrated approach to HIV/TB prevention and care in prisons, as well as better linkage between prison health services and the public health system.

The incidence of TB disease in prisons worldwide has been shown to be more than 20 times that of the general population.[9] This is widely attributed to factors such as overcrowding, poor nutrition, insufficient ventilation and inadequate health services in prisons.[7,10-12] The problem is amplified in countries with a high HIV burden, as HIV infection is the strongest individual risk factor for developing active TB.[12-14] HIV prevalence is also often higher than that among the general population, with estimates of 40 - 45% in SA prisons.[15,16] Only 40% of SA correctional centres report segregating inmates on medical grounds, although drug-resistant TB has been cited as the most common reason for such segregation.[17] Ventilation is frequently poor;[6,11] our patient described small, slit-like windows high up on one exterior wall of his cell. There is a shortage of medical personnel in prisons and delays in accessing care are frequently an issue;[6,8,11,17] our patient stated that, during his second period of detention, he had reported his cough and night sweats to prison officials for 3 weeks before he was taken to the prison health facility.

The epidemiology of communicable diseases within and outside prisons is closely related; large numbers of prisoners and staff enter and leave prisons on a daily basis, acting as potential sources of transmission to the community at large. In SA in 2011/ 2012, over 80% of remand detainees[17] and 40% of those who received sentences were imprisoned for less than one year.[18] Thus, in SA, as elsewhere, prisons act as reservoirs of TB, and inevitably drug-resistant TB, that poses a threat to public health control.[12,14] Despite this, control measures for TB, HIV and other communicable diseases are often neglected, relative to measures directed at non-prison populations.[19]

Many of the same factors that enhance the spread of TB in prisons encourage the emergence of drug resistance and subsequent transmission of drug-resistant TB.[10,19] Moreover, the failure to ensure prompt recognition and appropriate treatment of drug-resistant cases results in a prolonged infective period, such that transmission risks may be even higher than those associated with drug-susceptible TB.[11] There are additional factors that may particularly promote the development of drug-resistant TB in prisons, such as: erratic drug supply and inadequate treatment; access to uncontrolled anti-TB drugs from staff and visitors; and chaotic lifestyles, including transfers between and within prisons. These enhance the likelihood of treatment interruption or default.[19]

While there is a paucity of data on antiretroviral drug resistance in prison populations, HIV-positive prisoners receiving ART in Brazil

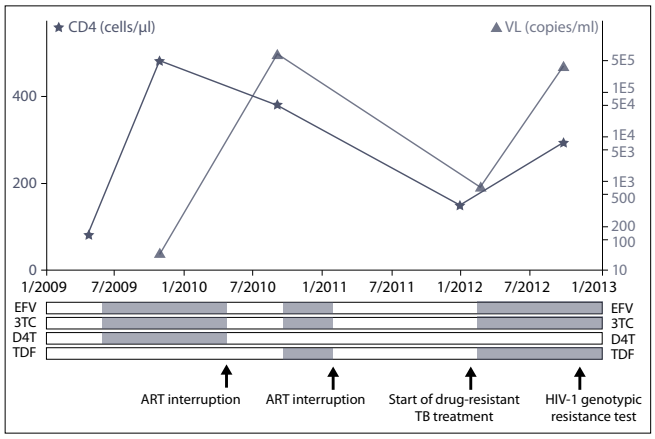

Fig. 1. Clinical course of ART with results of viral load (VL) and CD4⁺ cell count monitoring and timing of treatment interruptions.

have been found to have high rates of acquired HIV drug resistance;[20] and release from prison followed by re-incarceration has been shown to be associated with impaired virological and immunological outcomes while receiving ART.[21] Unplanned treatment interruptions are known to promote resistance;[22-24] and chaotic lifestyles,[18,19] fear of stigmatisation[18,25] and poor health services in prisons[6,25] are likely to increase the frequency of treatment interruptions. In SA, most prisons do not have dedicated HIV care programmes and those that exist are delivered by external service providers.[17] Our patient did not disclose his HIV-positive status or use of ART during either spell in prison, primarily due to fear of stigmatisation. While the timing of the development of ART drug resistance cannot be ascertained definitively in this case, it is plausible that the unscheduled interruption of treatment during the first period of incarceration could have led to the initial emergence of resistance. Certainly the interruption of ART, the emergence of ART drug resistance and the resultant drop in CD4⁺ cell count would have substantially increased the risk of developing TB disease.[26] We cannot definitively reject the possibility that ART resistance emerged prior to incarceration or that super-infection with a drug-resistant HIV strain occurred during incarceration.

The interdependence of numerous transmission risk factors necessitates a multifaceted approach to TB control in prisons, involving improvement in case finding, reductions in overcrowding and improvements in environmental conditions such as ventilation and airflow.[6,10-12,14] Robust evidence for action already exists: a modelling analysis based on conditions for inmates awaiting trial in Pollsmoor prison, Cape Town, suggested a potential reduction in TB transmission rates of 50% if active case finding and national minimum standards of cell occupancy were implemented; and a reduction of 94% if international environmental standards were adopted.[11] Screening and case detection in prisons worldwide has, until recently, been limited by suboptimal diagnostic tools and a lack of adequate laboratory facilities.[27] There is some evidence to suggest that screening prisoners using Xpert MTB/RIF could be a cost-effective means to reduce transmission of drug-resistant TB in settings with a high burden of drug resistance.[28] The recent announcement that correctional facilities in SA will now be prioritised for deployment of Xpert MTB/RIF offers strong encouragement.[29] However, research is needed to inform policies on the optimal use of Xpert MTB/RIF within prison health services, and any strategy must be linked to appropriate treatment programmes and proper segregation processes.

Furthermore, this case highlights that reducing the individual risk of TB disease should be as important, and optimising individual management of HIV disease, with the aim of virological suppression and prevention of antiretroviral resistance, should be a critical component of broader prison HIV/TB control strategies. No single intervention will adequately address the complex issues relating to TB and HIV in prisons. Ultimately, there needs to be the political will and funding to deliver sustained improvements to prison conditions and health services. Collaboration between the Department of Correctional Services and the Department of Health is necessary to facilitate better integration of prison health services within the public health system. The high costs of managing drug-resistant TB and HIV disease should be a powerful incentive to implement measures to reduce the emergence and spread of drug-resistant TB and HIV.[30-32] At a time when considerable progress is being made in the public health sector in SA,[3] the failure to address TB and HIV in prisons has the potential to seriously undermine the control of these infectious diseases in the community.

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Author contributions. KES and RJL looked after the patient. KES wrote the first draft of the manuscript. All authors contributed to revision of the manuscript and approved the final version.

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CASE REPORT

Native valve endocarditis due to *Candida parapsilosis* in an adult patient

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Candida endocarditis is rare, but associated with a high mortality. The most common species implicated is *Candida albicans*. The epidemiology of invasive *Candida* infections is changing, with a predominance of non-albicans species causing invasive disease. We describe a case of *Candida parapsilosis* endocarditis in an HIV-positive patient with pre-existing mitral valve disease and renal failure on haemodialysis. The patient presented with fever and malaise. Clinical examination revealed pulmonary oedema and severe mitral regurgitation. Blood cultures were positive for *C. parapsilosis*. β-D-glucan assay levels were elevated. An echocardiogram showed large, friable vegetations on the mitral valve. *C. parapsilosis* was cultured from the haemodialysis tip and the vegetations. The patient responded well to mitral valve replacement and antifungal therapy. A high index of suspicion and aggressive diagnostic modalities and therapy are essential in patients with candidaemia, to decrease mortality due to this condition.

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Fungal endocarditis accounts for 2 - 4% of all endocarditis cases. Of these cases, 25% are attributed to *Candida albicans*, other *Candida* species account for 25%, and *Aspergillus* species and other fungi account for the remainder.[1-3] Predisposing factors for *Candida parapsilosis* endocarditis include prosthetic valves, intravenous (IV) drug use, parenteral nutrition, abdominal surgery, immunosuppression, treatment with broad-spectrum antibiotics and pre-existing valvular disease.[4] Mortality for *Candida* endocarditis is high (67%), with a lower mortality in younger patients with a history of IV drug use.[5] We present a case of native valve *C. parapsilosis* endocarditis, which to our knowledge, is the first reported case in South Africa.

Case presentation

A 46-year-old HIV-positive man with a history of hypertension and renal failure presented with fever and malaise. The patient was receiving antiretroviral therapy (ART) and haemodialysis. Clinical examination of the patient revealed fever, pulmonary oedema and severe mitral regurgitation. Blood cultures, β-D-glucan assays and a full blood count were undertaken. The patient remained febrile after 48 hours and antifungal therapy was commenced.

Laboratory findings

Upon admission, white blood cell and $CD4^+$ counts were 11.37 x 10^9 cells/l and 435 cells/μl, respectively. The HIV viral load on admission was undetectable, as it had been for the previous 6 months. Blood cultures were positive for *C. parapsilosis*, which was susceptible to all antifungals tested (amphotericin B, fluconazole, voriconazole and caspofungin). Fungal identification and susceptibility testing were performed using the Vitek 2 (Biomerieux, France) automated system. The patient was treated with IV fluconazole in view of the impaired renal function and susceptibility of the isolate to this agent. Blood cultures taken 48 hours after commencing fluconazole were positive. The haemodialysis catheter was removed and replaced. Culture of the catheter tip revealed *C. parapsilosis* with susceptibilities corresponding to the blood culture isolate. β-D-glucan assay results were elevated (>523 pg/ml) on the day of the initial blood culture. The patient was referred for cardiology assessment. The echocardiographic examination demonstrated large, friable mitral valve vegetations, in keeping with fungal infective endocarditis (Fig. 1).

The patient underwent mitral valve resection and tissue was submitted for microbiological and histological evaluation. The tissue culture isolate corresponded to the admission blood culture and catheter tip culture findings. Histological evaluation showed fibrotic, hyalinised heart valve, with stromal neovascularisation, suggesting a pre-existing chronic valvulitis (Fig. 2a). Friable surface vegetations composed of fibrin, degenerating neutrophils and numerous fungal yeast forms were noted (Fig. 2b). Blood cultures performed 2 weeks after surgery were negative. Repeat β-D-glucan assays remained elevated 4 weeks after therapy. The patient was re-evaluated,

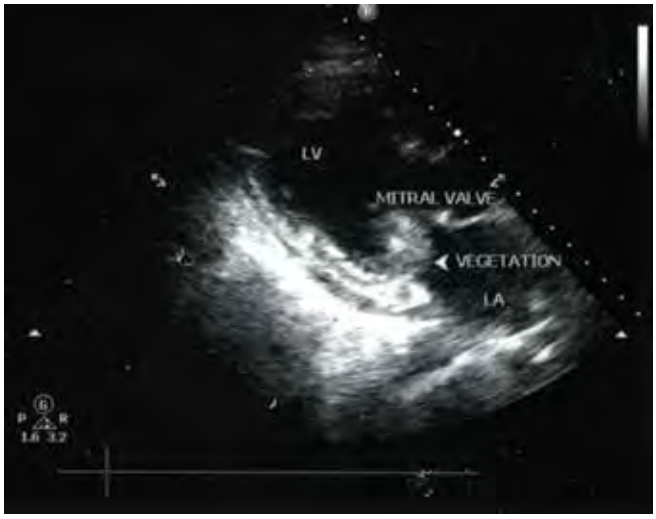

Fig. 1. Echocardiogram showing the size and position of the vegetation.

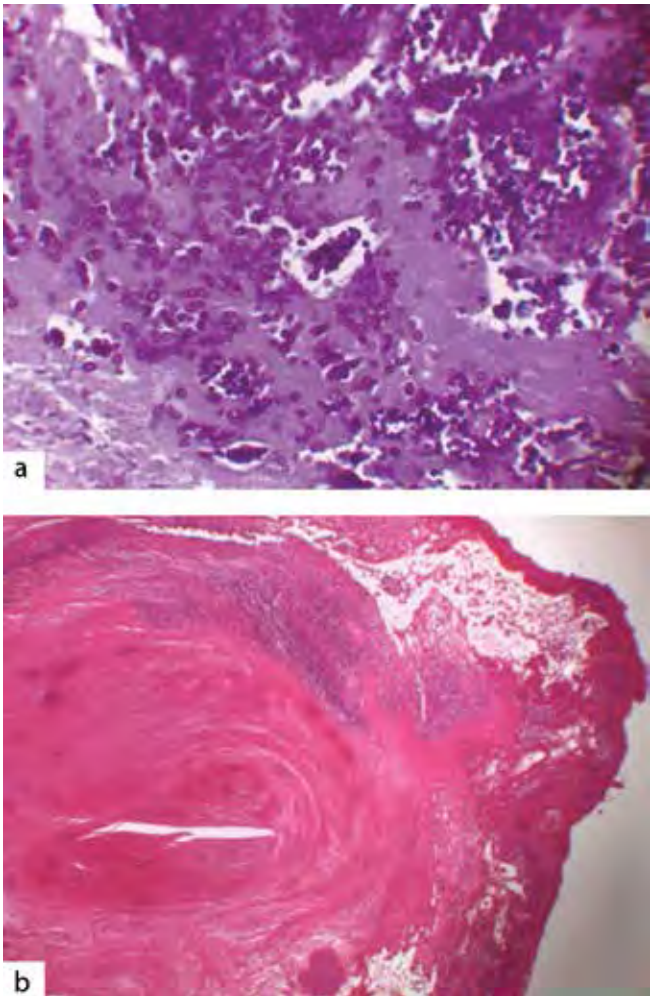

Fig. 2. Histological examination of the infected mitral valve with vegetations showing pre-existing fibrosis and infected vegetation.

but remained clinically stable. Treatment doses of fluconazole were discontinued after 6 weeks, and oral suppressive fluconazole therapy was continued. Two months following diagnosis, the patient remains clinically stable, and continues haemodialysis, fluconazole suppressive therapy and ART.

Discussion

This report presents an uncommon disease in a patient with several predisposing factors: renal failure, *in situ* IV catheter, admission broad-spectrum antimicrobial agents, pre-existing valvular heart disease and HIV infection. A catheter-related portal of entry has been reported in 80% of cases of *C. parapsilosis* endocarditis in one series of *Candida* endocarditis cases.[5] Other described risk factors include abdominal surgery, IV drug use and prosthetic heart valves.

Candidiasis is the most common opportunistic infection in HIV-positive patients with $CD4^+$ counts <200 cells/μl. The most prevalent presentation is mucocutaneous candidiasis, although invasive candidiasis has been reported.[6] Highly active antiretroviral therapy (HAART) has been shown to decrease the rate of candidiasis in this population.[7] Although this patient was HIV-positive, his disease state was controlled on ART at the time of diagnosis. Thus, the propensity for *C. parapsilosis* to adhere and form biofilms, together with the indwelling haemodialysis catheter, broad-spectrum antimicrobials on admission and chronic valvular disease, were more significant in the pathogenesis of endocarditis in this case.

The epidemiology of invasive *Candida* infection has changed. Improvements in medical therapy have resulted in increased survival of critically ill patients who are exposed to longer durations of broad-spectrum antimicrobial therapy. The incidence of non-albicans candidaemia has also increased, in some situations accounting for a higher percentage of isolates compared with *C. albicans* candidaemias.[8] This change is reflected in our local setting as well, where surveillance data from 2009 to 2012 from selected sites in SA were analysed. The data showed a predominance of non-albicans candidaemia in 4/6 sites, with *C. parapsilosis* being the most common non-albicans species (unpublished data, Dr N Govender, National Institute of Communicable Diseases, South Africa, 2012). This suggests a higher propensity for invasive disease, such as fungal endocarditis, to be caused by this species.

The clinical presentation of *Candida* endocarditis is non-specific. Fever and cardiac failure may be absent and embolic phenomena may be the presenting feature.[5] Most patients have a risk factor for invasive candidiasis. Documented predisposing factors in *C. parapsilosis* endocarditis present in this patient included *in situ* haemodialysis catheter, probable pre-existing chronic valve disease, admission broad-spectrum antibiotics, and immunosuppression mediated by HIV and renal failure. The aortic valve is most commonly affected.[4] Mitral valve involvement in this instance was likely due to pre-existing chronic valve disease.

Due to the non-specific clinical features, correct diagnosis requires a high index of suspicion in patients with known risk factors. Persistant candidaemia, as in this case, should prompt further clinical evaluation, as well as early transoesophageal echocardiography, as recommended by the European Society Clinical Microbiology and Infectious Diseases guidelines for non-neutropenic adult patients with candidaemia.[9]

The value of the β-D-glucan assay in diagnosis of invasive candidiasis has been reviewed.[5] The assay measures components of the fungal cell wall present in the bloodstream. This assay may be positive before the traditional culture results are available. It has a high sensitivity (77%) and specificity (83%).[10] The β-D-glucan assay levels were found to be significantly higher in patients infected with *C. parapsilosis, Candida tropicalis* and *Candida guilliermondii* endocarditis, than with *C. albicans* endocarditis.[5] There are no formal recommendations regarding the use

of this assay as a diagnostic tool; however, the β-D-glucan assay has a role in negating a diagnosis with a high negative predictive value and supporting a positive diagnosis where other clinical and laboratory features are in keeping with a fungal endocarditis.[3,9] Interestingly, the β-D-glucan assay remained elevated after commencement of treatment and following negative follow-up blood cultures. This has been described previously, where elevated levels during the early phase of the disease do not always return to baseline during the early stages of antifungal therapy.[5,10] This assay is also positive in patients with *Pneumocystis jiroveci* pneumonia. Thus, a positive assay must be interpreted with caution and correlated with the clinical picture in immunocompromised patients. This patient did not have any clinical features supporting a diagnosis of *P. jiroveci* infection. β-D-glucan assay levels may be elevated falsely in patients on haemodialysis where cellulose membranes have been utilised.[11,12] This patient's dialysis was performed using synthetic polysulfone membranes, which do not significantly elevate the assay.[12]

Treatment of fungal endocarditis includes medical or surgical interventions or a combination thereof. Although combined medical and surgical therapy has decreased the mortality of patients with *Candida* endocarditis, the mortality remains high.[1] Recommended first-line therapy includes early surgery plus liposomal amphotericin B or an echinocandin.[3,13] The source of *C. parapsilosis* in this patient was most likely the haemodialysis catheter. In patients with candidaemia, early removal of the catheter is recommended; however, this is not always possible. These situations require therapy with either amphotericin B or an echinocandin.[9] Individual case reports have shown successful medical treatment of *Candida* endocarditis using the echinocandins without surgical intervention;[14-16] however, there is insufficient experience with these agents to make a recommendation for medical management alone. The use of fluconazole in this patient was initially empirical and subsequently based on antimicrobial susceptibility results. Early aggressive surgical therapy combined with medical treatment resulted in a positive outcome. Long-term oral fluconazole therapy may be continued following IV therapy; however, the duration of suppressive therapy is not clearly defined, with some patients remaining on lifelong therapy.[3,16]

Conclusion

We describe a case of *C. parapsilosis* endocarditis in a patient with significant risk factors. The changing epidemiology of invasive fungal disease indicates that invasive disease due to this species may be more frequent. A high index of suspicion as well as aggressive diagnostic modalities and therapy are essential to decrease mortality due to this condition. The persistence of elevated β-D-glucan levels in the presence of negative blood cultures suggests that this test is not reliable as a marker for response to therapy. Although individual case reports suggest that the echinocandins offer promise as sole medical therapy, if surgery is not possible, then further evidence is required before this modality of therapy is pursued.

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CASE REPORT

Chylothorax associated with non-endemic Kaposi's sarcoma

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Chylothorax is a rare cause of pleural effusion, seen in approximately 2% of cases. In HIV-positive patients with Kaposi's sarcoma (KS), the development of chylothorax presents as a diagnostic challenge with an aggressive course and poor, often lethal outcome. In this clinical scenario, the aetiology of chylothorax may include infections and malignancy, while pleural fluid examination and computed tomography of the mediastinum may fail to establish a cause. We present a case of KS-associated non-traumatic chylothorax resulting in death, and a review of available literature on this condition.

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In HIV-positive patients with Kaposi's sarcoma (KS), chylothorax is a rare complication. KS is related to human herpesvirus-8 (HHV-8), and striking reductions in incidence and improvements in survival have been reported after the introduction of highly active antiretroviral therapy (HAART).[1] With prolonged survival, the sequelae as well as related complications of KS pleural effusions are increasingly being noted. However, in settings of high tuberculosis (TB) prevalence and limited clinical resources, patients with pleural effusions are typically treated empirically for TB, often with little consideration for KS. The limited availability of diagnostic testing in many settings to investigate unresolving pleural effusion despite TB treatment often presents a diagnostic dilemma. Chylous pleural effusion is an uncommon complication secondary to pathology of the thoracic duct; however, determining the aetiology of chylothorax in HIV-positive patients with KS and/or TB is a significant challenge. The contribution of infectious, malignant and iatrogenic causes needs to be investigated to determine the appropriate management strategy.

Case

A 40-year-old man sought medical attention for shortness of breath on mild exertion with dry cough of 1 month's duration. He had no significant past medical, social or family history. Physical examination revealed dullness to percussion at both bases, but no significant lymphadenopathy. A chest X-ray revealed bilateral pleural effusion without any infiltration. His sputum was negative twice for acid-fast bacilli (AFB). He tested positive for HIV with a $CD4^+$ count of 119 cells/µl (6%). He was started on emtricitabine, tenofovir and efavirenz as a fixed-dose combination, *Pneumocystis jerovii* prophylaxis, and 6 months of standard treatment for pulmonary TB.

After 2 months of this therapy, he reported with violaceous lesions on both legs and his chest wall. Skin biopsy revealed KS and he completed 6 cycles of chemotherapy with doxorubicin, bleomycin and vincristine.

After 6 months of ART, he was virologically suppressed; however, he had immunological failure with a $CD4^+$ count of 41 cells/µl (5%). Shortness of breath responded to this therapy, but he had radiological persistence of bilateral pleural effusions (Table 1). Repeated thoracocentesis revealed straw-coloured fluid with protein >3 g/dl, and inflammatory cells with a lymphocytic predominance without any atypical cells. Despite multiple attempts, no bacterial pathogens or AFB were isolated from the pleural effusion. His skin lesions decreased in size, but he developed woody oedema of the left leg that responded to lower-hemibody irradiation of 800 cGy in a single fraction. Table 1 presents a summary of the major investigations and findings.

Due to persistent bilateral pleural effusions, the patient received 6 cycles of 150 mg/m^2/day etoposide (injection) from day 1 through day 3 for treatment of pulmonary KS, with a temporary relief in his cough and shortness of breath. He still required repeated thoracocentesis to relieve his episodes of breathlessness. Three months after completion of chemotherapy, he developed a worsened shortness of breath and productive cough. The whitish sputum was negative upon Ziehl-Neelsen smear. Contrast-enhanced computed tomography (CT) of the chest confirmed bilateral pleural effusions with consolidation of the right lower zone of the lung, but no pulmonary nodules, mediastinal or hilar lymphadenopathy (Fig. 1). The patient underwent bilateral intercostal chest drainage, revealing thick brownish fluid (Fig. 2). Sputum and pleural fluid were negative for AFB cultures and *Mycobacterium tuberculosis* polymerase chain reaction (PCR) (GeneXpert), but bacterial cultures from pleural fluid grew *Staphylococcus aureus*. These were identified as methicillin-resistant *S. areus* (MRSA) and the coverage

Table 1. Summary: Results of key investigations

Investigation	Findings
Chest X-ray	• Bilateral pleural effusion without any infiltration
CT of the chest	• Bilateral pleural effusion with consolidation of the right lower zone of the lung without any pulmonary nodules or lymphadenopathy
Sputum examination	• Negative Ziehl-Neelsen stain (x 2) • Negative GeneXpert PCR for *Mycobacterium tuberculosis*
Pleural fluid examination	• Straw-coloured • Triglycerides 3.1 mmol/l, protein 2.2 g/dl, cholesterol 0.1 mmol/l and LDH 1 344 mol/l • Inflammatory cells with a lymphocytic predominance without any atypical cells • Cultures negative for bacterial pathogens or AFB

CT = computed tomography; PCR = polymerase chain reaction; LDH = lactate dehydrogenase; AFB = acid-fast bacilli.

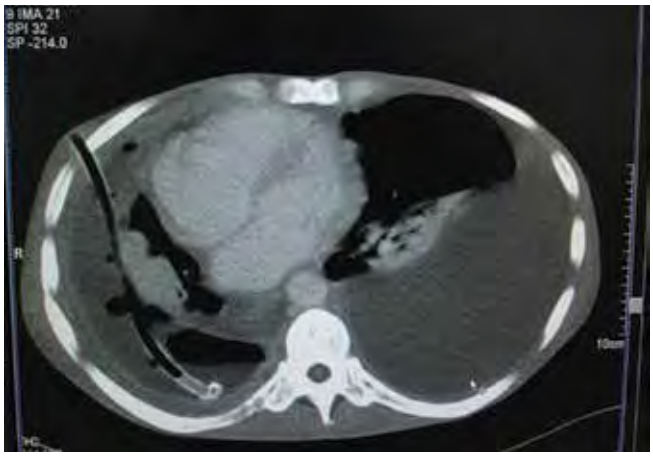

Fig. 1. Computed tomography scan of the chest showing bilateral pleural effusions with consolidation of the right lower zone of the lung with thickened pleura and intercostal drainage tube in place. No significant pulmonary nodules or lymphadenopathy are visible.

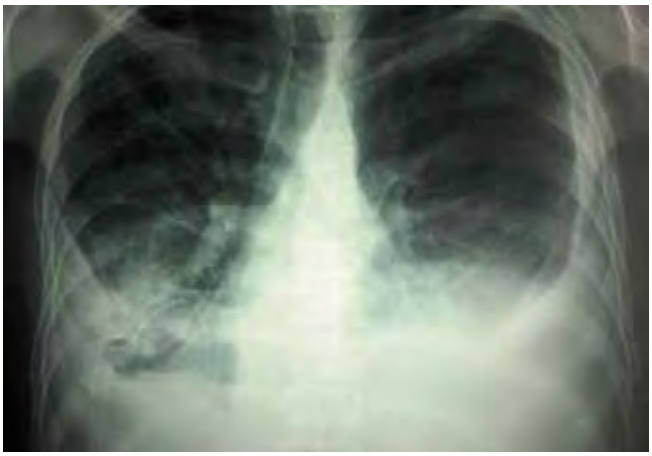

Fig. 2. Chest X-ray posteroanterior view showing bilateral pleural effusions with intercostal drainage tube in place.

was narrowed down to vancomycin only. After 5 days of vancomycin therapy, pleural fluid draining from both sides turned milky white in colour. The fluid triglyceride level was 3.1 mmol/l (247 g/dl), protein was 2.2 g/dl, cholesterol was 0.1 mmol/l and lactate dehydrogenase (LDH) was 1 344 mol/l. The patient was diagnosed with bilateral chylothorax and underwent blind pleural biopsy to rule out other aetiologies of persistent bilateral pleural effusion aside from KS-induced scarring of the thoracic duct. Diagnostic bronchoscopy revealed normal trachea and bronchi. The respiratory mucosa was inflamed and red, but visibly normal with no evidence of endobronchial lesions. There were profuse, whitish secretions in the trachea-bronchial tree, which were washed out and sent for microscopy, culture and sensitivity, as well as TB and fungal investigations. Bilateral thoracoscopy revealed empyema with loculations with beefy, inflamed, thick-walled visceral and parietal pleurae. In the presence of low $CD4^+$ counts, this was regarded as a relapse of pulmonary TB, and anti-tubercular treatment was started. The patient developed sepsis from extended spectrum β-lactamase (ESBL) gram-negative bacteria and died after several days in the intensive care unit.

Discussion

This patient was diagnosed with HIV with non-endemic KS and pulmonary TB manifesting as bilateral pleural effusion with *S. aureus* empyema with bilateral chylothorax. Bilateral pleural effusions persisted even after empirical anti-tubercular treatment for 6 months. The presence of advanced HIV disease, pulmonary TB and disseminated KS synchronously posed a difficult diagnostic scenario, and the aetiology of bilateral chylothorax in this patient was unclear. In the setting of HIV-associated KS, the underlying aetiology for bilateral chylothorax may include primary tumour (KS with involvement of pleura or thoracic nodes), infections (related to immunocompromised status and multi-agent chemotherapy) or an unrelated aetiology. Diagnostic bronchoscopy revealed no evidence of endobronchial lesions and ruled out pleuropulmonary KS as the cause for chylothorax.

Chyle consists of lymph of intestinal origin, which is a milky and opalescent fluid rich in lymphocytes, protein, triglycerides and chylomicrons. Chyle is conducted from intestinal lymphatics to the cisterna chyli, which eventually drains into the left subclavian vein via the thoracic duct through the posterior mediastinum. Disruption of flow in the thoracic duct results in mediastinal collection of chyle, which can leak into the pleural space resulting in chylothorax. This manifests as shortness of breath and chest discomfort due to compression of the lung by the collection of chyle. Drainage of milky-white pleural fluid suggests chylothorax that can be confirmed by pleural fluid examination. A level of pleural fluid triglycerides >110 mg/dl and a pleural fluid/serum cholesterol ratio <1 is diagnostic of chylothorax.[2] Normally, the

average flow of chyle is about 2 l/day; following meals it may increase to a rate of 4 l/day.[3] Continued loss of chyle leads to depletion of protein, fat and lymphocytes. The four main causes of chylothorax include: malignancy; trauma; idiopathic; and miscellaneous causes such as thrombosis of the superior vena cava or subclavian vein, cirrhosis and rarely, pulmonary lymphangiomyomatosis.[4]

KS is one of the most common causes of pleural effusion in patients with AIDS. The pathological diagnosis of pleural KS requires a characteristic architectural appearance and not a particular neoplastic cell type.[5] The sampled fluid (usually serosanguineous or haemorrhagic exudate) is unlikely to contain diagnostic cytological material. Since KS tends to involve only the visceral pleura, closed pleural biopsy is often non-diagnostic and the diagnosis requires thoracoscopy with the characteristic multiple cherry-red to purple appearance of the KS lesions on the visceral pleura.[6] In most cases, the clinical picture and the characteristic bronchoscopic appearance of the lesions help to make a presumptive diagnosis and may obviate the need for biopsy.[7] A study describing the clinical course and pleural fluid findings in patients with AIDS-associated pleural KS showed that 21/105 (20%) cases had pleuropulmonary KS involvement. Of these, 13 (62%) had pleural effusions and only 2 had chylothorax. Neither cytological examination nor needle biopsy of the parietal pleura was able to establish the diagnosis. At autopsy, patients with pulmonary KS have multiple cherry-red to purple lesions on the visceral, but not on the parietal pleural surface. The reported median survival from KS diagnosis to death was 205 days for patients with pleuropulmonary KS.[6] In another series, 29/53 (55%) patients had pleural effusions including 76% bilateral.[8]

Currently, the exact aetiology of chylothorax in patients affected by advanced HIV with KS is unclear, and few cases have been described in the literature.[8-10] Most cases reported evidence of lymphatic obstruction via KS involvement of the mediastinal nodes and/or prominent pulmonary KS, and the treatment included palliative measures such as pleural drainage, pleural sclerosis, fluid shunting and/or chemotherapy directed at KS. The treatment was largely unsuccessful, and patients in whom the outcome was noted, died within a few weeks to months. Average survival after diagnosis of KS pleural disease is around 4 months.[6] The potential cause of chylothorax in HIV-positive patients also includes TB, but chylothorax appears to be rare in patients with TB, and KS remains the leading concern in the differential diagnosis.[11] Chylothorax is also rare in patients with KS without HIV infection (endemic KS) and only a single case of KS-related chylothorax in an HIV-negative patient was reported in past years.[12] The pathogenesis of most effusions due to malignancy has been attributed to blockade of the lymphatic drainage system located in the parietal pleura, but this is unlikely in patients with KS-related pleural effusions, since their parietal pleura is not involved. The KS-related effusion may be due to the elaboration of vascular endothelial growth factor (VEGF). VEGF promotes angiogenesis and microvascular hyper-permeability to produce extravascular fluid that appears bloody.[13] In patients with KS, the pleural effusion is a chylothorax in about 2% of cases, which suggests involvement of the thoracic duct by the tumour. KS-related chylothorax is postulated to develop from metastases to the thoracic duct. More recently, however, it was demonstrated by the co-expression of HHV-8, CD34 and D2-40 on lesional cells, that chylothorax may arise due to the development of *in situ* KS in this region.[14]

The patient described here had no clinical, radiological or cytological indication of pleuropulmonary KS. There was no mediastinal lymphadenopathy, nor any history of chest trauma. Thus, the aetiopathogenesis of his bilateral chylothorax was not clinically or radiologically evident. In this scenario, the reason for chylothorax appeared to be involvement of the thoracic duct by KS, leading to obstruction and a resultant leakage of chyle from the thoracic duct. The process might have been exacerbated by post-chemotherapy fibrosis of mediastinal nodes and/or lymphatic involvement by mycobacteria. This can be evaluated by radioisotope lymphangiography, magnetic resonance imaging or positron emission tomography; however, these investigations are unfortunately not widely available. Further, thoracoscopy with biopsy of mediastinal nodes and a visceral pleural biopsy may help to differentiate KS from TB as the underlying aetiology.

Patients immunocompromised by HIV infection and chemotherapy are at high risk for infection-related effusions. A concomitant infection must be ruled out in patients with KS-related pleural effusion, as a failure to treat a concomitant infection carries a high short-term mortality. In this patient, isolation of MRSA from pleural fluid was probably related to pleurocentesis-related iatrogenic empyema.

Conclusion

KS-associated chylothorax may present a diagnostic challenge and carries a poor prognosis. Current literature is sparse and a congregation of such cases can provide more insight into the aetiopathogenesis of non-endemic KS-related chylothorax.

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CASE REPORT

MRSA bacteraemia complicating amphotericin B treatment of cryptococcal meningitis

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Intravenous amphotericin B is a key component of the antifungal therapy for cryptococcal meningitis recommended in South African and international guidelines. Unfortunately, its use is associated with significant toxicity including deterioration in renal function, electrolyte disturbance, anaemia and infusion reactions. Chemical phlebitis is common following administration via peripheral cannulae. This can be complicated by bacterial infection, resulting in localised cellulitis or bacterial sepsis. Here we describe two patients with cryptococcal meningitis who developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia during, or shortly after treatment with amphotericin B. These cases illustrate the dangers of line-related sepsis in hospitalised individuals and some of the difficulties encountered during treatment of this condition.

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Intravenous (IV) amphotericin B is a key component of the antifungal therapy for cryptococcal meningitis (CM) recommended in both South African (SA) and international guidelines.[1,2] Unfortunately, its use is associated with significant toxicity including deterioration in renal function, electrolyte disturbance, anaemia and infusion reactions.[3] Chemical phlebitis is commonly seen following its administration via peripheral cannulae. This can be complicated by bacterial infection, resulting either in localised cellulitis or bacterial sepsis.

Here we describe two patients with CM who developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia during, or shortly after treatment with amphotericin B. These cases illustrate the dangers of line-related sepsis in hospitalised individuals and some of the difficulties encountered during treatment of this condition.

Case 1

A 42-year-old, HIV-positive man presented to hospital with a one-week history of headache and vomiting. He was not receiving antiretroviral therapy (ART) and had a $CD4^+$ count of 23×10^6 cells/l.

CM was diagnosed following lumbar puncture (positive India ink, cryptococcal antigen test and culture) and he was treated with 1 mg/kg/day amphotericin B (IV) and 800 mg/day fluconazole (oral) for 14 days. During this time he had frequent episodes of phlebitis at peripheral cannula sites. On day 13 following admission, the patient deteriorated, developing fever and tachycardia. His right forearm was markedly swollen with frank pus discharging from an old cannula site. A diagnosis of bacterial sepsis secondary to drip-site infection was made, a blood culture was performed and IV vancomycin was administered. Within one day, *S. aureus* was identified from a blood culture. Resistance testing confirmed this to be methicillin-resistant, but vancomycin susceptible (minimum inhibitory concentration (MIC) 0.5 µg/ml). Vancomycin was continued with regular monitoring of trough levels. The patient's fever gradually settled, and a repeat blood culture after 7 days of therapy was negative. There were no clinical signs suggestive of complicated bacteraemia and the patient was discharged after 14 days of vancomycin therapy. He has since started ART and remains well 6 months later.

Case 2

A 50-year-old HIV-positive man receiving first-line ART (tenofovir, lamivudine and efavirenz) presented to hospital with a 3-week history of headache, vomiting and blurred vision. He was diagnosed with CM following lumbar puncture

Fig. 1. Cross-sectional computed tomography (CT) of the anterior chest (case 2). A lytic lesion in the sternum and overlying soft tissue mass is marked by the red oval. A needle aspirate of the collection grew methicillin-resistant Staphylococcus aureus *(MRSA), as did 3 blood cultures. Limited views of the lungs showed multiple lesions highly suggestive of septic pulmonary emboli (not shown here).*

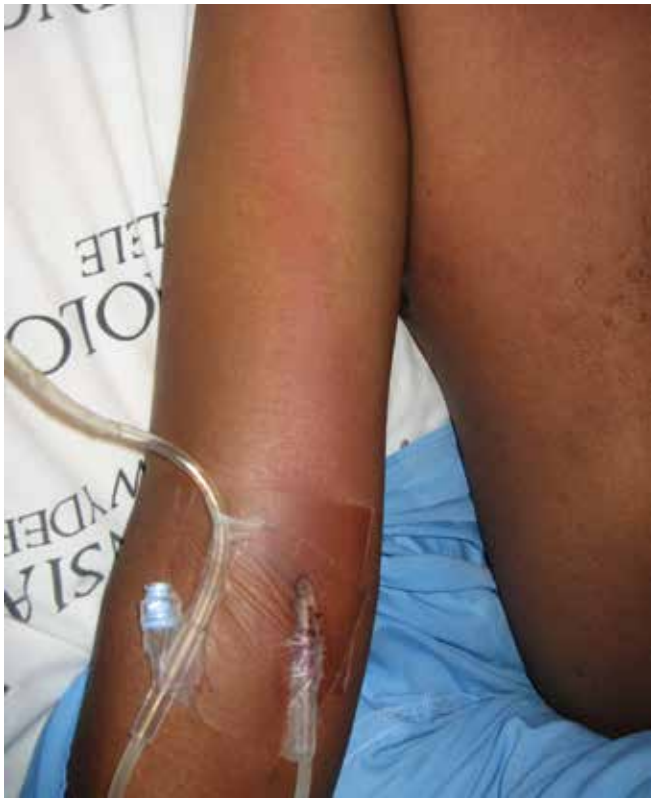

Fig. 2. 'Chemical' phlebitis complicating amphotericin B infusion (photograph courtesy of Dr T A Bicanic). This inflammation occurred during the 4-hour amphotericin B infusion and presented as redness and tenderness tracking up the cannulated vein. In such cases, the cannula should be removed once the infusion is completed and the site monitored closely for infection and the patient for fever. This is not an indication for immediate antibiotics.

(positive India ink, cryptococcal antigen test and culture) and treated with 1 mg/kg/day amphotericin B (IV) and 800 mg/day fluconazole (oral). Two weeks after discharge, he was seen in the infectious diseases clinic. Deemed to have failed first-line ART ($CD4^+$ count 2×10^6 cells/l, HIV viral load 60 414 copies/ml), he was switched to zidovudine, lamivudine and ritonavir-boosted lopinavir. He re-presented a further 3 weeks later with a recurrence of meningeal symptoms. Lumbar puncture was performed and raised intracranial pressure was noted (opening pressure 33 cmH_2O). Amphotericin B was re-started, but discontinued after 7 days when cerebrospinal fluid fungal cultures showed no growth. The patient was diagnosed with CM immune reconstitution inflammatory syndrome (CM-IRIS) and treated with 90 mg/day prednisone, with good resolution of symptoms. During both admissions, phlebitis was noted at amphotericin infusion sites, but this settled following removal of the cannula.

When seen in the outpatient clinic 2 weeks after his admission for IRIS, he complained of a 5-day history of fever and rigors. On examination, there was a tender, fluctuant mass over the inferior part of his sternum, but no signs of infection around any of his previous cannula sites. *S. aureus* was identified from a blood culture and needle aspirate of the mass; IV vancomycin was commenced pending sensitivities. A computed tomography (CT) scan of his chest revealed lytic destruction of the caudal end of the sternum with an adjacent soft-tissue collection (34 × 28 × 15 mm) (Fig. 1). Lung lesions suggestive of multiple septic emboli were also noted. A transthoracic echocardiogram showed no evidence of endocarditis, and a bone scan revealed no other areas of bone involvement. Antibiotic susceptibility testing demonstrated methicillin resistance, but susceptibility to vancomycin (MIC 1 µg/ml).

Incision and drainage of the chest wall abscess was performed and vancomycin was continued, but with little clinical improvement. Repeat blood cultures after 7 days of therapy remained positive for MRSA, and despite treatment, he deteriorated with ongoing fevers and worsening renal and respiratory failure. He died a week thereafter.

Discussion

S. aureus bacteraemia is a serious infection with significant associated mortality. The organism is highly pathogenic and should never be assumed to be a blood culture contaminant, even in a patient who appears systemically well. The infection seeds haematogenously to distant organs in approximately 40% of cases, leading to endocarditis, septic arthritis, osteomyelitis and other deep-tissue abscesses.[4] The second case presented here is an illustration of this.

In the cases described, both patients developed MRSA bacteraemia during, or shortly after treatment for CM; the likely portal of entry being peripheral venous cannulae used to administer amphotericin B and IV fluids. In the first case, the bacteraemia was accompanied by obvious signs of infection at a cannula site. In the second, no evidence of localised infection was found at the time of bacteraemia, but phlebitis (attributed to amphotericin B) had been noted during the recent admission.

Although studies from North America report the risk of bloodstream infection (BSI) associated with peripheral IV devices to be low (0.5 BSI/1 000 IVD days),[5] the risk could be higher in the SA setting, especially in this vulnerable group of patients, with advanced HIV infection receiving prolonged IV amphotericin B therapy.

Diagnosing bacterial infection at IV cannula sites in patients with CM can be difficult, especially given the frequent chemical phlebitis

seen following amphotericin B administration (Fig. 2). Both chemical and infective phlebitis result in erythema and pain, and in our experience, infective phlebitis may occur as a complication at the site of chemical phlebitis. Fever and systemic upset, or the presence of pus at the cannula site, are very suggestive of bacterial infection and should be investigated further. Blood cultures should be taken prior to the use of any antibiotics, and swabs sent for investigation if any exudate or pus is present.[6] In the absence of these features, it is reasonable to remove the cannula, elevate the limb, apply ice and observe. Bacterial infection should be considered if there is no significant improvement in 24 hours, or it there is an expanding area of cellulitis.

If signs of systemic infection are present, then once blood cultures are taken, empirical IV antibiotic therapy should be commenced. Antibiotic choice should ensure adequate coverage of *S. aureus*.[6] Given the high rates of methicillin resistance among nosocomially acquired isolates in SA (30 - 60%),[7,8] IV vancomycin should be used until microbiology results are available. If blood cultures are negative, antibiotics can be stopped after 5 days.

If blood cultures are positive for *S. aureus,* then more prolonged antibiotic treatment is required. The Infectious Diseases Society of America (IDSA) recommends treating *uncomplicated* MRSA bacteraemia for at least 2 weeks with IV vancomycin, with target trough levels of 15 - 20 µg/ml. Due to high rates of unrecognised endocarditis, the IDSA recommends echocardiography in all patients – an impractical option in many SA settings.

A pragmatic approach is to risk stratify patients by taking repeat blood cultures after 2 - 4 days of antibiotic therapy. Patients with no implantable prostheses, no clinical evidence of endocarditis or metastatic infection, who have a negative repeat blood culture and resolution of fever within 72 hours of initiating effective therapy, can be treated for 2 weeks with IV vancomycin (monitoring trough levels and creatinine). Patients at high risk of complicated infection, such as those with prosthetic cardiac material, should be investigated with echocardiography (transoesophageal is preferred over transthoracic). If neither is available, high-risk patients should be treated as having complicated bacteraemia, with careful clinical follow-up to exclude a relapse of infection or complications of prosthetic-valve endocarditis.

Patients with persistent fevers, positive repeat blood cultures or clinical features suggestive of metastatic infection, should be considered as complicated cases and investigated for endocarditis, osteomyelitis and deep-tissue abscesses.[4,9,10] The management of *complicated* MRSA bacteraemia should be discussed with an expert wherever possible. Surgery may be required to drain an abscess or remove a focus of infection, and antibiotic therapy should continue for approximately 4 - 6 weeks depending on the extent of the infection and response to treatment.[10]

With regard to patients with CM, it is important that clinicians are aware of this additional complication of amphotericin B treatment. Cannula sites should be monitored regularly and any patient who develops a new fever should be evaluated carefully for signs of drip-site-related infection.

Finally, efforts should be made to reduce the incidence of nosocomial infections as a whole, through increased emphasis on infection-control practices such as handwashing and aseptic technique. Although it is now more than 100 years since the pioneering work of Semmelweis, his lessons remain pertinent today.

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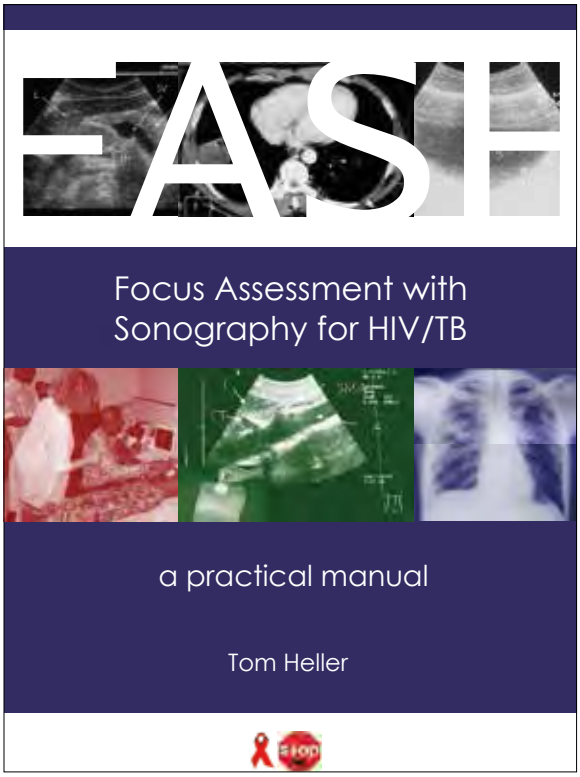
BOOK REVIEW
'FASH – Focused Assessment with Sonography for HIV/TB – a practical manual'

by Tom Heller. London, UK: Teaching-Aids at Low Cost (TALC), 2013. ISBN: 978-0-9558811-8-3.



The emergence of high quality, yet affordable portable ultrasound devices during the past decade has brought the ultrasound examination out of imaging services to the patients' bedside. Point-of-care (POC) ultrasound is increasingly practised throughout various medical disciplines. Simplified and targeted ultrasound protocols, applied by the attending clinician or medical staff, allow instantaneous assessment of clinically relevant questions. Time to diagnosis can be shortened, referrals can be avoided, and resources can be saved. POC ultrasound requires little training and is a safe and effective tool, with particular value for resource-limited settings where imaging modalities are often restricted.

Extra-pulmonary tuberculosis (EPTB) is common in HIV-infected individuals, but diagnosis is a challenge, especially where access to adequate imaging diagnostics is limited. The value of ultrasound for diagnosing EPTB has long been recognised, but its availability in primary care settings, where most HIV/TB-infected patients are seen, often remains restricted by the absence of appropriate equipment and/or radiological expertise.

In 2010, infectious diseases physician and ultrasound expert, Tom Heller, developed 'Focused Assessment with Sonography for HIV/TB (FASH)' as a POC ultrasound protocol to improve the diagnosis of EPTB in HIV-positive patients. It evolved on the basis of multiple years of experience in a rural district hospital in Hlabisa, South Africa. FASH was a success thereafter: throughout the world, and especially in Southern Africa, FASH was taught in short courses for practitioners working in the field. By now, Heller's method is an integral part of the emergency POC ultrasound curriculum for Emergency Medicine trainees in South Africa and one of the most frequently taught modules in the country.

The practical manual, *FASH – Focused Assessment with Sonography for HIV/TB*, comprises 84 pages and includes a CD. The book is organised in 13 chapters. The first three encompass a concise introduction to POC ultrasound, the HIV/TB pandemic, as well as the basics of ultrasound physics and ultrasound anatomy of the abdomen. Seven core chapters address the bedside ultrasound evaluation of the main areas of interest in the context of HIV and TB: effusions, lymphadenopathy, spleen, liver, chest, EPTB and the heart. Three final chapters deal with other HIV-related pathologies, deep vein thrombosis and interventional ultrasound.

Chapters are well structured, allowing easy orientation through the sections of anatomy, normal ultrasound findings, pathophysiology of HIV/TB, differential diagnoses, diagnostic tests, clinical implications, tips and pitfalls, and references for further reading. All chapters are illustrated with ultrasound images that include probe positions, corresponding X-ray, computed tomography and/or magnetic resonance imaging findings, and coloured schematics to simplify learning. Besides a digital copy of the manual, the CD provides video clips of both normal anatomy and pathological findings. The latter is a particularly useful addition for learners, as visual memory is the most helpful aid at the bedside.

In summary, this low-cost manual is a comprehensive guide for practitioners in the field, providing very helpful instruction on bedside ultrasound evaluation even beyond the context of HIV/TB. Applying FASH on an everyday basis in the hospital, I wish to encourage practitioners to adopt 'the concept of ultrasound as the stethoscope of the 21st century'. The manual will be a very useful companion!

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HIV risk behaviour among primary care patients with tuberculosis (TB) in South Africa (SA)

1. When counselling TB patients, condom use and alcohol/substance use risk reduction need to be considered as HIV-prevention measures.

Child privacy rights in HIV-prevention research

2. While children are entitled to privacy, in some cases, their expectation of privacy may be limited and may not be deemed reasonable by the healthcare provider.

Chylothorax associated with non-endemic Kaposi's sarcoma (KS)

3. Chylothorax is a common complication in patients infected with HIV and with KS.
4. The most common cause of chylothorax in and HIV-infected patient is TB.
5. KS-associated chylothorax carries a poor prognosis.
6. Treatment of chylothorax in patients affected by advanced HIV and KS is best considered a palliative measure.

Analysis of HIV-related mortality data in a tertiary South African neurology unit from 2006 to 2012

7. Neurological complications of HIV infection are rare in SA.
8. After bacterial and fungal meningitis, encephalitis is the most common neurological presentation in HIV-infected patients requiring hospitalisation.
9. The incidence of neurological diseases such as HIV-associated dementia and central nervous system opportunistic infections may be decreasing due to antiretroviral therapy (ART).

Combined ART/anti-TB drug resistance after incarceration

10. SA is responsible for a quarter of the world's burden of HIV-associated TB.
11. Prisons act as reservoirs of TB, including drug-resistant TB that poses a threat to public health control.
12. In settings with a high burden of drug resistance, screening using Xpert MTB/TIF has little role in reducing the transmission of drug-resistant TB.
13. Patients receiving ART and/or TB treatment who become incarcerated may be at high risk of defaulting treatment and/or developing treatment resistance.

Management of drug-induced liver injury (DILI) in HIV-infected patients treated for TB

14. DILI occurs in <0.1% of patients receiving TB treatment and ART.
15. Some of the individual risk factors for DILI in patients receiving TB treatment or ART are younger age, children, hepatitis B surface antigen positivity, malnutrition and use of alcohol.

Starting ART following cryptococcal meningitis (CM) – the optimal time has yet to be defined

16. Patients with CM in Southern Africa typically present with $CD4^+$ counts >100 cells/µl.
17. There is clear evidence that ART should be initiated no more than 2 weeks after initiation of CM treatment.

Native valve endocarditis due to *Candida parapsilosis* in a an adult patient

18. A high index of suspicion as well as aggressive diagnostic modalities and therapy are essential in patients with candidaemia to decrease mortality.
19. Candidiasis is the most common opportunistic infection in HIV-infected patients with $CD4^+$ counts <200 cells/µl.
20. The most prevalent presentation of candidiasis is invasive candidiasis.

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